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OUTSOURCING LABORATORY BASED SERVICES

Inventing a new future for R&D and Testing

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G. Sudesh Kumar Ph.D

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"To the Best Measure of Success—The unconditional love shared with my wife Padmaja and son Vaibhav

Preface

Inspiration for writing this book came from reading numerous articles on outsourcing of IT-enabled services and increasing visibility of India's evolution as knowledge-based economy. The economic underpinning of the outsourcing philosophy is that value creation activities tend to relocate to where there is a comparative advantage. Globalization and increasing speed to market are causing many manufacturing-based industries to review all aspects of their business processes including R&D and regulatory testing.. India and China, favored destinations for business process outsourcing, are attracting outsourced research and development projects and offshore R&D units of major global pharmaceutical and engineering companies. Outsourcing is a tool that offers benefits ranging from lower cost, reduction in capital investments, and conversion of fixed costs to variable costs to increased quality, efficiency, and technical expertise. The focus of the first chapter is to differentiate research process outsourcing from business process outsourcing and the laws of migration which govern laboratory-based services.

Research and development outsourcing had historically been viewed inside the company as a short-term 'resource gap filler' rather than an innovation lever. The second and third chapters examine the key drivers impacting the trends in outsourcing and/or offshoring design and discovery components. Both India and China, which offer benefits of low-cost R&D, strong scientific base together with a large and skilled (and in India's case English speaking) labor pool, are attracting foreign investments. As many as 150 R&D centers have been established in India. Major pharmaceutical and biotechnology companies are beginning to explore these emerging markets, which offer a low cost structure along with other potential benefits such as a sizeable domestic market and opportunities for clinical and pre-clinical trials and long-term regulatory studies. The rise of laboratory-based services, either as off-shore units or as contract research organizations, is propelled by availability of trained scientific manpower, growing emphasis on laboratory infrastructure and quality management systems. It is not MNC outsourcing work alone that

is contributing to the surge of demand for laboratory testing services. A number of companies are also involved in sourcing products like medical devices, chemical intermediates, textiles, herbal medicines and minerals. As global sourcing of raw materials and components is increasing, quality inspection and testing services are on the rise. Many of these companies would like to ensure that the materials conform to the requirements of the global markets and meet all regulatory requirements and are heavily dependent on certified laboratories in host countries.

Science-based marketing has advantages with consumers around the world. Public confidence in consumer products is boosted if they are 'scientifically tested' or 'scientifically proven.' The fourth chapter presents the scenario of private testing laboratories in India and a few examples from a broad spectrum of contract testing services. The list of domestic companies that are making products of everyday use and testing them for performance, quality or compliance and safety is growing day by day. Likewise, World Trade Agreement provides excellent opportunities to the export of manufactured goods and farm produce. Residues of toxins, contaminants, pesticides, antibiotics and trace metals are a major concern to the food regulators. The toxic residues in food commodities can easily become trade barrier in WTO regime and the issues related to the residues have led to the major changes in international trade. Independent laboratories have grappled consistently with the issue of providing their services in a cost effective way with required speed and quality, due to lack of economies of scale for expensive instrument-based services. Market-driven laboratories are now uniquely placed to gain opportunities and grow their businesses. By partnering with laboratory service providers, companies can reduce large investments in lab instrumentation, minimize expensive overheads, and enable in-house laboratory staff to focus on value-addition and problem-solving.

International trade and commerce would not be possible in the absence of globally accepted measurement and accreditation systems. Independent laboratories provide their services in many fields such as chemistry, microbiology, nutrition, food science, pharmaceutical, agriculture, environmental science and materials testing. In all of these areas, it is necessary for a laboratory to generate robust data, meet

client's needs and satisfy required quality standards. The need for laboratories to demonstrate competence through adoption of quality systems and recognized accreditation is widely established within the industry. Globalization of R&D is also bringing the need for reliable measurements and validation of methodology into the center stage. A brief overview of the quality management systems specific to each activity such as ISO 17025, GLP, GMP, GCP etc are discussed in Chapters 4 and 5.

The final chapter is about path forward for laboratory-based services. Economic success accrues increasingly to those societies that are most capable in identifying, educating, developing and exploiting the talents of their people. Successful laboratory-services strategy requires building and exploration of competencies in a given field of specialization and the ability to harvest market opportunities from a wide array of choices. Going forward intensity of global competition will only increase. The challenge for low-cost countries and for multinational corporations who are using them is to achieve clear benefits of global free markets while seeking to offset their inherent imperfections. All countries will continue to make their business climate attractive to global innovation leaders, and low-wage countries will retain a labor-cost advantage in the near future The long-term success of laboratory services industry is critical component for building Asia as the knowledge hub of new millennium.

G. SUDESH KUMAR

JULY 2005

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Many of the trends and insights that I present in this book came through my two decades- long career experience of leading knowledge teams in corporate laboratories at ICI Research and Technology Center at Thane, ICI Paints, Hyderabad , GE India Technology Center and GE Silicones at Bangalore, GE Plastics, Bergen op zoom (Netherlands) , and developing growth-orientation and implementation of quality systems for contract research and testing laboratories—Shriram Institute for Industrial Research, Bangalore, Shiva Analyticals Ltd., Bangalore, and Vimta Labs Ltd, Hyderabad. This book is the result of practical and personal insights, shared memories of many collaborative hours with colleagues, customers and consultants over the years.

I would like to record my gratitude to late Dr. J.K.Nigam, who initially led me "down the path less travelled by" i.e., career in testing laboratories. I owe my initiation into analytical quality assurance and metrology to Dr. G.V.Iyengar, who was at National Institutes of Standards and Technology, USA. I am inspired by the visions Mr. Krishna Chivukula, Chairman of Shiva Technologies Inc, and Dr. S.P.Vasireddi, Chairman and Managing Director of Vimta Labs Ltd. who created benchmark world-class laboratory-services organizations in their respective fields and walk the talk that the "amount of unfinished work is independent of finished work and always remains constant."

The book would still be an eclectic set of notes scattered across several hard drives, white papers and neurons without hard encouragement from friends and family. Dr. Savio Sebastian was kind enough to allow me to use his laboratory orchestra picture in the book. My special thanks Ms. Deepa Varadarajan of Tata-McGraw Hill for great editorial inputs.

G. Sudesh Kumar

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Chapter 1

Global Outsourcing in a Knowledge Economy

The dawn of the new millennium has been met with creative chaos triggered by globalization and knowledge-based economies. The foundation for a new economic world order is being laid based on knowledge, innovation and international collaboration. The demands and opportunities of an interdependent global economy bear implications on the private and public decision-making of enterprises and communities whether local, national, regional or global. Globalization is not an option we can choose but rather an imperative we cannot ignore. If anyone is asked to characterize world affairs of the late 20th century, globalization would be, for many, the first word that comes to mind. Much has been written about this ongoing phenomenon, particularly over the last decade, and bitter debates continue to rage over its positive or negative effects on political, social and economic progress. Many eminent scholars would argue that globalization is not a new phenomenon at all, but an ancient one, dating back to the first days of long-distance trade, exploration and conquest. All these activities, economists argue, brought new ideas, cultural influences, goods and technologies to distant lands where they were assimilated and adapted to fit local conditions and tastes, much the same as happens today. Economists point out to none less than the father of modern economics, Adam Smith, as having foreseen globalization as a natural extension of his "invisible hand" theory of capitalism outlined in *The Wealth of Nations*. However, his view of globalization interprets the phenomenon more as an effect than as a driver of long-distance trade as well as

economic and technological transformation, which is how most would characterize the concept today.

Also, what sets the current phase of globalization apart from earlier periods is today's universal and almost instant dissemination of information, technology and know-how that is a driving force in every country's economy. The information and communication revolutions that sparked the hi-tech boom of the 1990s have broken down traditional borders and barriers to trade. Even the world's poorest nations can now access—in virtual if not physical form—much of the world's most advanced technological know-how. What has made such unprecedented technological diffusion possible has been the development of more sophisticated, as well as steadily less expensive means of communication, transportation and trade. The driving forces are digitization, the Internet and high-speed data networks that girdle the globe. The 'death of distance' that is intrinsic to information networking is one of the most important forces shaping society. The result is that economic and technological development today, depends less on where one resides than on how well connected and ultimately how intelligent, responsive, innovative and inventive one can be. It is this increasingly transnational nature and technological capacity that is critical in distinguishing the current wave of globalization.

Globalization is a process by which production of goods and services are carried out on a level of magnitude that supersedes the boundaries of nations. The large movement of labor, capital and entrepreneurial ability characterizes it and it is spurred on by further liberalization of markets and advances in technology. The business world today is boundaryless, a constantly shifting marketplace that overcomes barriers of place, time zones and cultures. Business leaders characterize today's global market landscape as high-velocity and hypercompetitive. It isn't just change, but accelerated changes that is the watchword to understand this new landscape. Industry and business are no longer about maintaining the status quo—it is essentially a race, where every enterprise is out in front controlling its destiny. The race goes to the swift but also to the sure-footed and it is the achievement of balance between these two characteristics, plus achieving the right balance between the new trail and beaten track that leads to success. Globalization has fuzzy frontiers. Success depends on how

confidently a business can create and navigate a road map in unfamiliar territory. Establishing the direction of business with clarity is like playing three dimensional chess, the extra dimension being where you look at inputs and outputs of the business processes from geographical locations affecting the outcome and success of the business. Every organization is trying to stay on top of this chaos and is positioning itself to maximize profits, enlarge market share and put a check on ever-increasing costs.

> *"It has been said that arguing against Globalization is like arguing against the laws of gravity."*
>
> —KOFI ANNAN, UN SECRETARY-GENERAL

INTELLECTUAL CAPITAL GAINS

Perhaps one of the most remarkable developments of the last decade is the discovery that knowledge is key, not just for economic and social progress, but also for business and corporate success. The discovery, in many ways, is merely a rediscovery. While there has been a small group of academicians and others consistently beating the drum as to the importance of knowledge assets, widespread realization that this is the main game is barely a decade old. In a world where markets, products, services, regulations, technologies, competitors and, of course, CEOs change rapidly, continuous innovation and the knowledge that enables such innovations have become important sources of sustainable competitive advantage. The knowledge economy has brought our attention to the human being, where it belongs. Peter Drucker described the knowledge worker as the "new majority" even before the knowledge movement had diffused worldwide, especially into those communities previously excluded from worldwide economic action.

One measure of the importance of knowledge is the value of intellectual property. For example, in 1999, copyright became the United State's number one earner of foreign currency, outstripping clothes, chemicals, cars, computers and planes! The United States produced $414 billion worth in books, films, music, television programs and other copyright products.

"We are now living in a knowledge-based society, where knowledge is the source of the highest quality power."

—ALVIN TOFFLER (1990)

Traditional factors of production—land, labor and capital—have become less important. The current emphasis is not on physical or tangible assets but on intangible assets like knowledge, skill sets, enabling services and intellectual property. These non-replicable, unique and proprietary intangible assets are providing companies with the competitive edge. The nature of intangible assets will vary from industry to industry, but they will include several commonalties such as research and development, patents, proprietary technologies, trademarks, copyrights and, of course, people. The value of intellectual capital and value added services will determine an institution's rank and competitiveness. The world's major growth industries such as microelectronics, biotechnology, designer materials and telecommunications are already brainpower industries. These knowledge industries stimulate other industries, in turn, to become knowledge based.

The manufacture of drugs and pharmaceuticals is one of the world's largest and most profitable businesses. Modern biological discoveries, particularly in the area of genetics, are providing drug chemists with vastly more information on how drugs operate and how new molecules may be designed. The old ways of making promising molecules and filling pipelines have become leaky and grossly expensive affairs. The average cost of a chemical compound when it pops out of the pipeline is now over $600 million.The new paradigm is to produce more effective drugs for a wider range of diseases to make R&D less expensive and to speed up the whole process and benefit from patent protection. We are witnessing a paradigm shift to *open innovation* from the traditional do-it-yourself approach through knowledge networks. Thus are emerging embryos to help create new ways of doing business in industry.

The human genome sequence was announced in 2003, capping off years of hard work. Benefits of the sequence were prophesied to include 'magic bullet' therapeutics, individualized medicine and the prediction of disease long before symptoms surface. Genomic sequence data are enabling clinical genome investigation, in which the characteristics of

human patients are explored using comprehensive inventories of biomolecules. Now that the flash bulbs have dimmed, scientists are taking a hard look at the results. Such projects will increasingly rely on fully integrated multidisciplinary teams spread across the world, demanding new organizational models even in universities and research institutes.

The transformation in the pharmaceutical and biotechnology industries is illustrative of what is underway to a lesser or greater extent in many other industries. IT and biopharmaceutical industries will probably be the leaders creating the roar of tomorrow.

The Rise of Services

A powerful new wave has hit an already turbulent business world. It is a wave of service, or, more specifically, a new and intense preoccupation with the quality of service. We now live in a service economy, where relationships are becoming more important than physical products. The new service imperative will mean that the old customer service department will remain an appendage as leaders transform entire organizations into customer-centric business entities. Service is no longer an industrial by-product, a sector that generates no wealth but "simply moves money around", as one economist scoffed. Service has become a powerful economic engine in its own right, a staple of the advanced economy. *Newsweek* columnist George F. Will summarized the look of the American economy, the beauty queen of the world, succinctly when he observed that, "McDonald's has more employees than US Steel. Golden arches, not blast furnaces, symbolize the American economy." We are only beginning to understand the significance of this change in the way we live and work.

Cross border trade in business services, especially in the so called IT-enabled services, is today among the fastest growing areas of international trade. While the industrial countries are the largest exporters of such services, some of the most dynamic exporters are developing countries. Three factors are responsible for this phenomenon:

1. Advances in high-speed networks have made cross border trade possible in a number of services that were previously tradable only through physical movement of providers.

2. Substantial investments in education in a number of developing countries have created a relative abundance of skilled labor, and the absence of commensurate employment opportunities have ensured its availability at a relatively low wage.
3. Finally, innovations in business practices have led to the out-location of non-core services in both manufacturing and service industries to offshore operational units or their out-sourcing to foreign third-party service providers.

It is not just major corporate conglomerates which are solely steering the forces of globalization and single-handedly reaping the rewards of a global economy. Perhaps the real driving influence and the key to the future integration and success of international markets are small businesses. While big businesses often gain attention for spreading their tentacles overseas, their smaller compatriots are going global in record numbers. Even in the US, 97% of the companies that export services are small businesses, according to the US Small Business Administration. In the last decade that number has tripled.

Perhaps this trend is not so surprising considering the web of technological forces spun in the last decade. Technology has rapidly broken down barriers and led to the development of a global economy in which many can participate. The information revolution in particular has significantly lowered the costs of doing business for new entrants and has increased competition. With changes in communication and information technology, it's easier to get into the game. The advent of the Internet and the e-commerce revolution is at the heart of smaller companies thinking global. Technology is moving so fast it is all too easy to be either too early or too late. In such a world, the timing of an investment or a service launch is critical, and how companies deal with this factor determines who falls by the wayside and who moves through to the next round. The aim is to stay ahead of one's competition, however fleeting the lead may be.

Down to the Core

Marketing, Research & Development and Manufacturing constitute the core of a manufacturing business as primary value adding activities

in the value chain and are streamlined by logistical management. The development of global sourcing strategies across different markets has become a central issue for many multinational firms. The other activities are considered to be supportive of the primary activities in global strategy development.

There are five continuous and interactive steps involved in developing such a global sourcing strategy along the value chain.

1. Identify the separable links (R&D, manufacturing, marketing) in the firm's value chain.
2. In the context of these links, determine the components of the firm's competitive advantages, considering both economies of scale and scope.
3. Ascertain the level of transaction costs between links in the value chain, both internal and external, and select the lowest cost mode.

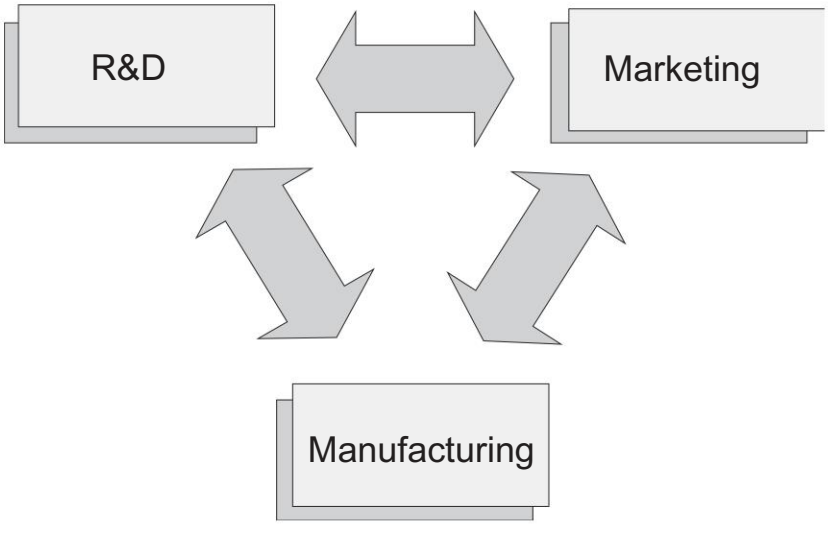


Figure 1.1 Links of a value chain in a manufacturing company

4. Determine the comparative advantages of countries (including the home country) relative to each link in the value chain and the relevant transaction costs.

5. Develop adequate flexibility in corporate decision-making so as to permit the firm to respond to changes in its competitive advantages.

Globalization has triggered 'outside-in thinking'. There is a growing realization of the advantages to be acquired by co-ordinating and integrating operations across national boundaries leading to strategic mobility along the value chain. Even international companies have always constrained their thinking that it is incumbent to carry out all the steps of a manufacturing process by themselves. Earlier, the twin siren songs of forward integration and backward integration led most large companies to do everything by themselves, from manufacturing their own plants and spares to sometimes even owning their own retail outlets. Once such a chain is established, even if the firms are aware of the weak links, they are tuned to believe that the whole lot is interdependent. It is only when the possibility of buying, the price and delivery and the actual consequences are tested and tried that new opportunities take shape. Big companies of yesteryears, which had operations in dozens of countries had some advantages. The economic cycle hit different parts of the world at different times and their spread gave these companies some degree of stability but as the world became increasingly interdependent that ceased to be the case and new strategies had to evolve.

Outsourcing—A Perfect Storm Brewing Overseas

Management gurus are undertaking every effort and every possible mantra is being applied to rethink and readopt new processes, especially the buzzwords like "off-shore outsourcing" and "smart sourcing." Outsourcing of all kinds of services is a growing trend among companies. Outsourcing is the process of procuring services or products from an external service provider with a view to curb costs, replace in-house capabilities and thereby reduce the time period of projects. There is little that cannot be outsourced including the manufacturing of goods. Outsourcing basically breaks down into two categories, tactical

Figure 1.2 Globalization hierarchy

and strategic. Tactical outsourcing is a short-term solution. The need for this type of outsourcing can result from a fluctuation in demand for products or services due to seasonal variation, one-time large orders or other factors. Tactical outsourcing can also provide temporary relief in bottleneck situations when an organization or a department is overwhelmed by a large volume of work or slow output. Strategic outsourcing, on the other hand, involves a long-term partnership. By utilizing this type of outsourcing, a company can reap many long-term benefits, including decreased overhead costs and the ability to advance projects of even lower priority. Outsourcing is an umbrella term to cover the whole spectrum of possibilities of how and where selected business processes, core and non-core, are migrated and includes new words and phrases like right sourcing, smart sourcing and insourcing not to mention in-shoring, off-shoring, near-shoring, right-shoring, etc.

Outsourcing is not new. It is really just a variation of the division of labor, a defining feature of capitalism. But what is new is its geographical and technical reach. Earlier it was in the manufacturing sector, now it has affected the services sector, which accounts for almost 60–80% of all jobs, dominating the economies of most

developed countries. Outsourcing has migrated from a tactical, primarily manufacturing, perspective to the more strategic philosophy of contracting out any functions, especially services, that have not been identified as core competencies of the company. The strategic move began with Information Technology (IT) functions and today it has had a ripple effect on a wide spectrum of other knowledge-based services.

We are dealing with a phenomenon of outsourcing which is too amorphous to define and classify, not to mention of quantify. There is no correlation between services that are being traded and the existing service sector classifications of Import-Export Laws. Furthermore, this trade, by its very nature, is hard to measure—no customs officials record the passage of IT products and keeping track of the financial transactions is very difficult.

Outsourcing as a business practice in the US economy became a political hot potato in the 2004 presidential elections and received a lot of coverage even in the general press and not just in the financial pages. The outsourcing debate in the US and the resulting job losses to low-cost countries or to low-cost labor from developing countries has even inspired a freelance TV filmmaker, to make a documentary on outsourcing titled, "American Jobs" which was released as a DVD on Labor Day 2004. It is not surprising that comic strip characters, Dilbert, a known cynic of business practices, and Cathy, who satirizes social mores, both parody the concept of outsourcing.

In many ways, outsourcing has changed not just the face of the workplace but also social attitudes towards work and employment. Price/cost differentials favor less-developed countries. For some companies and entrepreneurs, it has created new avenues and opportunities for growth. In various cases, it has afforded companies to secure goods and services at a lower cost with higher quality. To others, who have experienced its adverse effects (layoffs and decline in service levels) outsourcing is not the comical situation some portray. To many, it carries a negative connotation associated with companies who put profits above all else. Amid growing competition, companies are being challenged to harness the benefits of outsourcing while simultaneously minimizing its detrimental effects.

Figure 1.3 A Dilbert cartoon on outsourcing

According to the International Data Corp's US and Worldwide Outsourcing Markets and Trends,1998–2003 report, outsourcing services is a $100 billion industry worldwide. The outsourcing services being provided include software development data entry, wealth management, legal services, payroll services, patent writing, competitive analysis etc. Besides these, there are inbound call centers, inbound customer support, animation, programming, audio tape transcription, book conversion to digital formats, market research, customer interaction, banking, financial and insurance services, healthcare and welfare services, content development, courseware development, data conversion, e-commerce, internet marketing, multimedia, telemarketing, web development and writing. A brief compilation and classification of these services through the familiar 'lumping and splitting' process into different silos is attempted in Table 1.1.

The most dynamic area of the services trade and the bulk of increased trade involving developing countries is in Information Technology (IT) and Business Process Outsourcing (BPO) services. Table 1.1 provides a list of the most common outsourced or off-shored IT and BPO service activities and brief sub-divisions.

Economics of Knowledge

This widespread outsourcing of non-core business processes by companies in industrialized countries is likely to have profound implications.

A random browsing through the net on off-shore outsourcing throws up news items in plenty with every major international player declaring their intentions to join the party. Preliminary estimates suggest that the efficiency gains made possible by this global division of labor are remarkable. Glaxo Smith Kline (GSK) plans to outsource all its global IT operations and expects around 35% in savings a year on its IT budget. General Electric Co. saves about $350 million per year through the 18,000 off-shore employees it has in India. Reports suggest that the US banking industry alone saved as much as $8 billion in the last four years due to outsourcing and estimates on future gains (until 2009) for the overall US industry range to $390 billion, with $138 billion in annual cost savings for the world's top 100 financial institutions. All in all, the projected savings figures are usually in the range of 30–60%. Through off-shoring some of its customer-service activities to India, Prudential, the British insurance company, plans to save $26.2 million through the creation of 1,000 customer service jobs in India. The stories of off-shoring to low wage countries is a weekly feature in business headlines these days.

Most industries have started to outsource operation because it allows them to significantly cut labor costs and additionally achieve significant productivity gains, ranging from 15–25%. As only around 5% of US firms with revenues from $100 million to $4 billion have begun to outsource, much untapped potential for this sort of cost saving and productivity gains remain. The size of the outsourcing market will certainly grow when smaller and medium sized enterprises seek similar efficiency gains. A survey by Deloitte Research found that the world's 100 largest financial services firms expect to transfer $350 billion of their cost bases abroad by 2008. The value of medical transcription outsourcing in America alone is expected to double by 2005 to $4 billion. The US market for contact centers alone has an estimated turnover of $100 billion.

Given the enormous size and rapid growth of the BPO market, the economic implications for developing countries could be enormous. For example, if half of India's 50 million English speakers were to eventually earn $10,000 per year in IT-related services, this would more than double India's current GDP of $450 billion. Given that IT-enabled exports tend to be associated with high levels of foreign

Table 1.1 IT-based, BPO-based and lab-based services

1. Information Technology-related Services	
Software Development and Implementation Services, Data Processing and Database Services, IT support services, Application Development and maintenance, Business Intelligence and Data warehousing, Content Management, E-Procurement and B2B market places, Enterprise secuity, Package implementation, System Integration, SCM, Enterprise Application Integration, Total Infrastructure Outsourcing, Web services, Web-hosting and Application service providers	
2. Business Process Outsourcing	
Customer Interaction Services	Sales Support, Membership management, Claims, Reservations for airlines and hotels, Subscription Renewals, Customer services helpline, Handling Credit and Billing problems etc. Telemarketing and Marketing Research Services
Back-office Operations	Data entry handling, Dataprocessing and database services, Medical transcription, payment services, Financial processing, Human resources processing services, payroll services, Warehousing, Logistics, Inventory, supply chain services, ticketing, Insurance claims adjudication, Mortgage processing etc.
More Independent Business and Professional Services	Human Resource Services (Hiring, benefit planning and payroll etc), Finance and Accounting services (including auditing, bookkeeping, taxation services etc), Marketing services, Intellectual property. Services like patent writing etc
3. Laboratory-based Services	
Contract Research & Development	Development of new drug molecules, Advanced materials research, New Process/method Development, Product Design and Development
Testing Services	Clinical trials, Analytical services, Stability studies, Testing for regulatory compliance, Diagnostic Services, material testing as per QC methods and International Methods

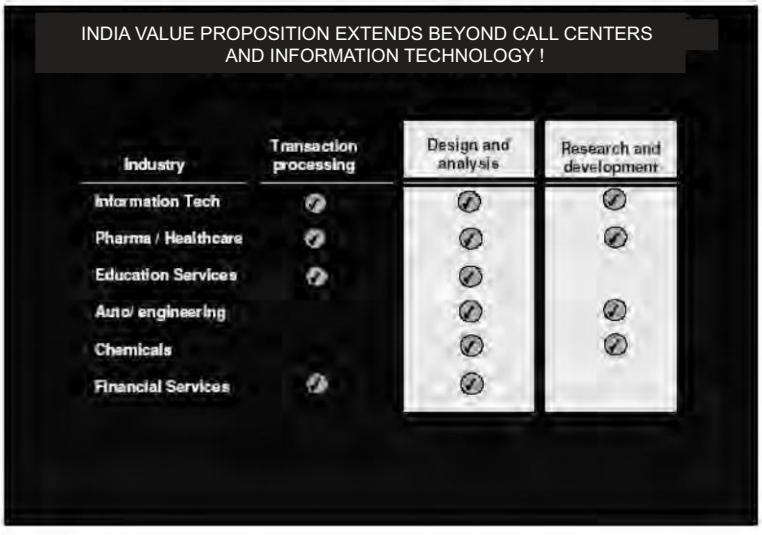


Figure 1.4 Beyond call centers

direct investments, human capital formation, demonstration effects and knowledge-spillovers, the indirect benefits might also be substantial.

There is every reason to believe that the comparative advantage of developing countries will not be limited to standard back office services. Already, cross border service exports have evolved from lower end, disentangled BPO services to more integrated, export-based and web-enabled services. Companies have started to move up the value chain by focusing on innovation, consulting, branding and increasingly integrated services. In addition, more sophisticated cross border trade activities like Training/online education, Product Design and Development services and Technical testing are already being exported. Further changes in technology, the developing country skill set and business practices are bound to lead cross border trade in ever more sophisticated services.

Laws of Migration

The best way for managers to get the most effective outsourcing solution for their business is to separate the *what* from the *how* and *where,* when they are planning a change.

Table 1.2 Offshore solution: Stepwise IDEA

1. **I**dentify which processes need to be migrated
2. **D**etermine the full range of off-shore alternatives for implementation and subsequent operations
3. **E**valuate each alternative against strategic, financial and organizational criteria
4. **A**gree on preferred model to deliver in terms of management commitment, capital, capabilities and time

The organization's first task is to identify what processes and activities should be migrated, irrespective of how or where the migration will be executed. Their second separate task is to determine the full range of in-shore/off-shore alternatives for both implementation and subsequent operations. Third, they should subject each alternative to rigorous, objective evaluation against strategic, financial and organizational criteria. The right off-shore business model provides the most appropriate trade-offs between ownership, operating flexibility and economics, both at points in time and over time. The final task is to identify what the preferred model will take to deliver in terms of managerial commitment, capital, capabilities and risk assessment.

What?

The capital implications for those going it alone depend largely on what activities are being moved off-shore. A pharmaceutical research lab will clearly require a much higher investment than a back office processing or call center. Capital requirements even for the latter can be significant with $20–30 million typically needed to establish a 1000 seat facility.

In the early days of off-shore outsourcing, companies tended to migrate activities such as software development and IT support that

could be isolated from day-to-day operations and were not deemed business critical. This was due in part to a reluctance to expose the company to unknown risk such as lack of local skills in more demanding activities and unreliable communication links between the host and home country. Today, the delivery risks have become well understood, the local skill base has broadened and the communications infrastructure is robust, for the most part, in many low-cost countries.

As a result, companies are increasingly moving core activities such as scientific research, new product development, finance and accounting and internal audits to off-shore locations. These activities require ongoing involvement and accountability of senior decision makers within the company. As such there may be inherent benefits in retaining some of these activities in-house (either in the on-shore or off-shore environment) rather than passing on management control and decision rights to a third party. When quick decisions are required to sustain a competitive advantage, the response times are likely to be shorter from a wholly owned subsidiary than from a third party provider.

How?

Given the sheer scale of activities that companies are moving off-shore these days, decisions on how to configure operations can have an unprecedented impact on shareholder value. Global outsourcing may not always be a better alternative to going it alone off-shore or teaming up with a partner overseas. On the contrary, companies that set up their own operations in low-cost regions increasingly generate returns comparable to or higher than companies that outsource. What is more, the delivery risk of putting a viable operation in place may actually be lower than that of outsourcing. Only after rigorously evaluating alternative off-shoring business models and understanding the true wing-to-wing economics of each alternative can managers answer for increasing their company's long term value in outsourcing. But, there are often sound strategic, operational and economic arguments for going off-shore for a captive facility and retaining at least partial control and/or ownership of operations. The key challenge to making the right move is to separate the off-shoring decision from the outsourcing one.

The capital investment necessary to establish an in-house operation in a foreign country is often cited as a key reason to outsource. Companies can exploit their vendor's in-place assets (property, staff, IT/telecommunications) rather than make significant investments of their own. That said, most off-shore operating costs (the majority of which relate to labor, property and telecoms) are essentially variable with the number of staff, particularly if property is leased rather than bought outright. In the IT industry, while the outsourcing provider's size may give them lower unit operating costs than a company can achieve on its own, the third party typically captures a significant share of the end-to-end cost savings. Keeping a bigger slice of such operating savings may well offset any incremental set up and unit operating costs incurred by the do-it-yourself alternative. These considerations are different for a non-IT-based activity like laboratory-based services. A do-it-yourself approach may also allow the firm to capture one-off duty waivers on imported capital equipment which would otherwise go to the third party provider.

Where?

There are innumerable case studies showing that outsourcing is the quickest and safest way to migrate operations off-shore to attractive low-cost countries with a talented pool of skilled workers. Many of the world's leading MNCs have successfully outsourced major pieces of their businesses, customer services, manufacturing, IT development, tech support and even product engineering to these firms in India and elsewhere. The meteoric rise of specialist service providers such as Infosys and WIPRO has fuelled the growth of India as the world's outsourcing hub. As IT off-shoring has flourished, it has also become more manageable. The political and regulatory environments of host countries have eased considerably. At the same time, the flexibility and skill level of local labor markets have increased without losing cost competitiveness. Finally, shareholders and lenders have become less nervous about major investments in remote emerging markets.

Western managers wary of establishing new operations in foreign environments can choose from a range of pretexts to avoid in-house off-shore solutions. A common argument against outsourcing is that

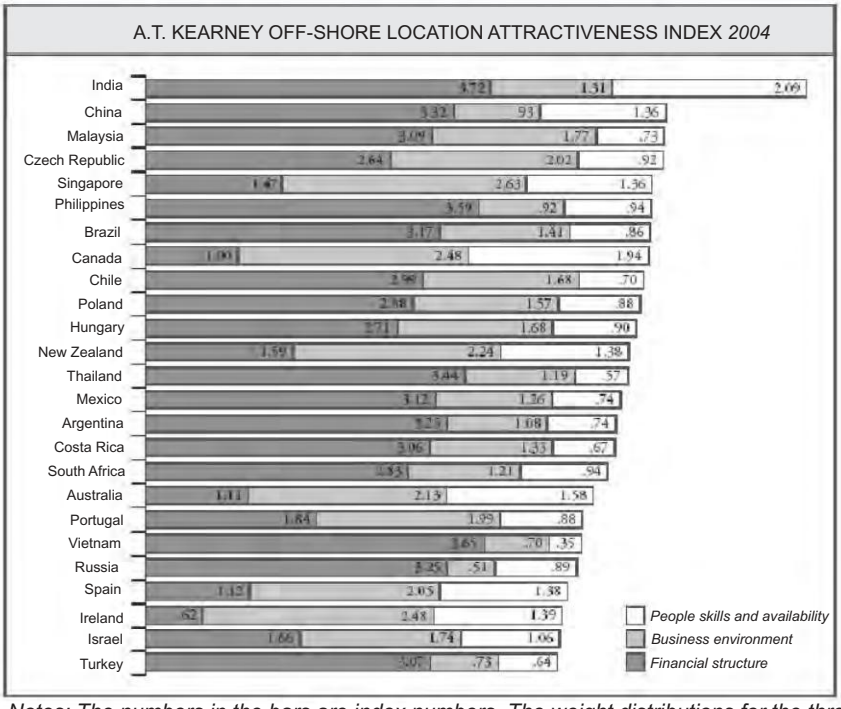
shifting operations off-shore is simply too complex, time consuming and risky to be done. However, there are now plenty of case studies of companies that have successfully established their own off-shore facilities. An entire industry has emerged in host countries to provide almost turn-key set-up assistance for BPOs.

Of course, establishing an owned facility in an emerging market such as India or China is not without risk. The major external factors are geopolitical (political instability, etc) and these are equally applicable to outsourced and in-house operations. Another risk both models share is the threat of sudden adverse changes in the regulatory tax regimen. However, rising financial contributions of off-shoring units to the host nation's economic policies acts as a natural hedge against this threat. Most business risks, on the other hand, are more easily managed internally through adherence to strict compliance procedures and rigorous staff training processes, a benefit companies transfer when using third party providers. In fact, a wholly owned facility is configured to provide off-shore back up and disaster recovery in the event of an on-shore failure. Moreover, third party providers seek to minimize their own business risk, often demanding contracts with lengthy lock-in periods and lenient service agreements.

And the Winner is...

A study by A.T. Kearney has compared the attractiveness of different countries as outsourcing locations (Figure 1.5). It confirms that while India remains overall the most attractive business location, other countries are not far behind. Latin American countries offer low labor costs, proximity to the US and are in the same time zone. Brazil's strengths include its large investments in information technology and telecom infrastructure and a large skilled labor pool. Companies such as Xerox and Unisys have committed to Brazil. Mexico offers the advantage of Spanish, a vital language for many businesses. In the US, AOL Time Warner services its Spanish-speaking customers from a call center in Monterrey, Mexico with estimated cost savings of 25–40%. The Philippines is an attractive destination due to its cultural affinities with the US, especially in terms of familiarity with US standards of service. For example, to take advantage of the large number of Filipino accountants trained in US accounting standards, P&G moved the

accounting services for its global operations to the Philippines. Other companies that have located to the Philippines include AIG, American Express and Citibank. From the perspective of a multinational that operates in Europe, it is the central European countries that offer cultural and linguistic similarities, greater ease of ensuring compliance with European regulations, e.g pertaining to privacy, as well as high levels of technical ability. GE has become one of the largest investors in Hungary over the past 12 years, moving a number of business processes to that country, in particular to support GE units across western Europe. Russia, too, has a large pool of technical talent but needs to overcome difficulties created by weak infrastructure and language barriers. Boeing was among the first companies to locate to Russia. Today Russian aeronautics specialists in several cities are designing parts for the Boeing 777 aircraft.



Notes: The numbers in the bars are index numbers. The weight distributions for the three categories is 40:30:30, meaning that the financial structure is noted on a scale of 1 to 4, and that business environment, and people skills and availability are on a scale of 1 to 3.
Source: A.T. Kearney

Figure 1.5 Kearney's analysis

The optimistic scenario confronts one possible problem, political opposition in importing countries and pressure for trade barriers. What looks like a healthy job creation process in India and other developing countries may be seen as a white collar job outflow in the industrialized economies. The figures referred to above and other examples (forecasts that as many as 3.3 million jobs in the US and 2 million jobs in western financial services will be lost over the next decade and 200,000 in the UK by 2008, as well as more specific episodes, e.g. British Telecom announcing the creation of 2200 jobs in India at the expense of the British call centers) are alarming some unions and politicians in the industrialized economies and political opposition is visible.

One of the key economic arguments in favor of off-shore outsourcing is that it allows global companies to save money and create new opportunities at home for higher-wage, higher-skill jobs, which fuel growth. But, higher skilled professional jobs like computer chip design, information technology services, programming, architecture, engineering, consulting, automotive design and pharmaceutical research are beginning to migrate globally.

Namaste! Welcome to the New Frontier of Indian Outsourcing!

Indian companies have discovered that there is money in doing the same work others are doing abroad that global and domestic companies are willing to let go and outsource at lower cost. While Indian programmers used to write simple computer codes, they now design and build the software themselves. While its people used to sell credit cards over the phone, Indian financial analysts now do brokerage reports for Wall Street clients. Some companies are beginning to provide 'patent writing' services, wherein its people analyze inventions coming from countries like Russia and China. The purpose is to evaluate their commercial prospects where the client can think of ways in which to sell the product. IT companies have led the way in cultivating India's strength in crunching software code and staffing call centers for companies based far away from the subcontinent. Now manufacturing-based companies like GE, GM, Honeywell and Intel

are taking outsourcing to a new level—snapping up India's scientists and engineers to work on next-generation chips, X-ray machines and nanomaterials. Another key driver is the number of Indians already doing research in US companies and the Indian scientists in such highly visible federal government agencies like NASA and a staple pool of temporary research workers in US and European Universities.

India always debated 'make' or 'buy' options, which often got converted to 'indigenous' and 'import' discussions and the country did pursue, in the closed economy, a more defensive *make* approach. Technology companies of today faced with the same situation are opting for the more aggressive *buy* approach and India is actually benefiting from that surge. Ironically, it is the same *make* (in-house) or *buy* (outsource) debate in the advanced economies which is driving the outsourcing wave in favor of low-cost countries. The discussions of the past were based on tangible assets, while today's trends are on intangible assets. For India, the emergence of the knowledge industry is good news. But harnessing the full potential of the knowledge industry requires an aggressive and visionary policy framework, creative planning, global benchmarking and risk abatement.

India has unquestionably been the leader first developing a reputation as a premier location for software development, still its main cross-border IT-enabled service export. Two-fifths of the Fortune 500 companies outsource requirements to India and the work related to the year 2000 alone earned Indian companies $2.5 billion. In 2002, India's IT industry grew 29% faster than the growth of this industry in any other country. More recently, however, BPO services that provide intermediary inputs throughout the production process (for both goods and services) have grown much faster. While classical IT services, such as software development, grew last year by a "mere" 22%, IT-enabled services such as outsourcing expanded by 65%. The latter typically involve India-based service operations providing an input or support service to the core activity/organizational functions of the importing company, e.g. WIPRO or GE provide payroll and customer care functions to the headquarters and affiliates of GE.

While such a transition is already underway in India, other developing countries with a similarly well-educated and relatively cheap

workforce will undoubtedly enhance their participation in this market. Wages in Vietnam or China are already said to be lower than Indian wages for comparable work—and the movement of Indian service suppliers to higher value analytical tasks is expected to bolster the trend. More generic, commodity processes will eventually move to lower cost environments.

Knowledge industries such as software development, pharmaceuticals, biotechnology, engineering services etc. operate in a highly competitive environment with great demand on the speed of response in dynamic market conditions. A high operational efficiency and functional flexibility is crucial for such industries. Government policies, therefore, have to be conducive to providing these requirements. For example, knowledge work cannot be governed by using the laws meant for physical labor. Knowledge-based companies that employ knowledge workers may require compensations with attractive schemes to create and share wealth. Several other changes in foreign exchange regulations etc. and export and import of materials, i.e. to facilitate easy material logistics across boundaries, will be needed to cater to export intensive industries. Moving from straightforward IT outsourcing to high-level research requires a 'leap of faith' and does not happen automatically. India is a clear leader on that front.

India's Innovation Infrastructure

The practice of science and technology in India is mainly divided amongst three major classes of institutions. The strategic departments, the Defence Research and Development Organization (DRDO), the Department of Atomic Energy (DAE) and the Indian Space Research Organization (ISRO) are largely insulated from public review and budgetary fluctuations. The national laboratories, with the Council of Scientific and Industrial Research (CSIR), the Indian Council of Agricultural Research (ICAR) and the Indian Council of Medical Research (ICMR) being the most visible, constitute a second category.

CSIR has a network of 40 laboratories and 81 field stations/extension centers/regional centers all over India to undertake research in several disciplines. It currently employs more than 22,000 highly

qualified multidisciplinary professionals. CSIR is the national R&D organization providing scientific industrial research for India's economic growth and human welfare. ICAR promotes science and technology programs in agricultural research and education and carries out research directly through ICAR institutes and national research centers, project directorates and also in association with the State Agricultural Universities (SAUs) through the all-India co-ordinated research project systems. The vast network of ICAR has a manpower of about 30,000 personnel, out of which nearly 7000 are engaged in active research and its management. The 30 SAUs employ about 26,000 scientists for teaching, research and extension education. Of these, over 6,000 scientists are employed in the ICAR supported co-ordinated projects.

The ICMR formulates, co-ordinates and promotes biomedical research. Its network consists of 21 permanent research institutes/centers (national institutes) located in different parts of India and six regional medical centers. The ICMR national institutes offer opportunities for research in the areas of medical biotechnology. Many of these institutions that come under this group struggle with problems of limited research outputs, aging scientific workforce and management practices that are an anachronism in the present context. All the research organizations under these agencies are gearing up to face the new challenges ahead, not only the new regulatory policies but also competition from the emerging private sector. Publicly funded R&D institutions are being used as idea generators and providers of new concepts by the industry.

The third category is the large body of academic institutions like the Indian Institute of Science (IISc), Indian Institutes of Technology (IIT) and Universities funded centrally and at state level. The academic ambience and the scientific excellence vary widely. While a few institutions, notably the IITs and IISc are international role models because they are able to graduate a galaxy of scientists and technocrats, many other institutions are in different shades of despair and indifference to scientific research.

Another significant block of technical capability, often overlooked and invisible in Indian debates and discussions on scientific talent, but contributing significantly to industry and trade, are laboratories involved in enforcing the regulatory compliance. Globalization has

created a pressing need for a quality assurance system that protects all international consumers in an effective way. The level of consensus that transcends national frontiers provided by ISO standards and other international bodies propels them forward as actors on an international stage. They are challenged to creditably support national policy goals and the relevant regulatory test requirements in the increasingly busy international bazaar.

The Bureau of Indian Standards is the National Standards Body (NSB) of India and covers product quality certification, consumer affairs and development of technical standards. The network of eight BIS laboratories, spread throughout the country, provide conformity testing of BIS certified products against relevant Indian Standards. The central laboratory near Delhi and the laboratories at Regional Offices are engaged in testing primarily for operation of the BIS Certification Marks Scheme (ISI mark, Hallmarking etc).

There is also an impressive nexus of laboratories with several ministries—like the Ministry of Textiles, Chemicals and Fertilizers, Ministry of Mines, Ministry of Environment, Ministry of Public Health etc, at both the central and state levels. These ministries have a network of laboratories implementing existing policy guidelines and facilitating domestic and international trade. These laboratories called test laboratories/field stations/technical centers etc., implement a regulatory framework and enforce the quality of manufactured goods thus ensuring public health and safety. Many of these bodies enforce specific regulatory guidelines and certification schemes either through their in-house testing or collaborations with private laboratories through laboratory recognition/certification schemes. These government laboratories and independent test laboratories are a critical link in a chain of quality assurance that the public and trade have to count on. These laboratories are an integral part of an enabling technological infrastructure that delivers food, medicine, fuel and materials that are the hallmark of modern life and trade. Industry is looking at contract research institutions and test laboratories for off-the-shelf services critical to business processes.

The fifth category is industrial research, mainly carried out by in-house laboratories of private companies, corporate research laboratories and several private non-profit laboratories like Shriram Institute for

Industrial Research, Delhi. The spectrum of activities carried out is closely linked with the company objectives, is subject to confidentiality agreements and is largely outside the public domain.

The chain of concept to commercialization necessarily crosses transnational boundaries today. In an era of global connectivity, the concept of a virtual laboratory is gaining ground. Basic science and engineering skills are gaining importance and the new paradigm is skill-based competition. High technology companies are asking as to which skills, capabilities and talents they should build up, rather than a stereotypical question, as to which markets they should enter, and with which products. These global customers can use the virtual real-time management and operation of laboratories in any part of the world. Thus, companies are seeking to gain a competitive advantage by using global knowledge resources and working with a global time clock. Many major multinational corporations in the US and Europe, whose R&D budgets are larger than even India's R&D budget are developing global partnerships. CSIR's partners today include giants such as Mobil, General Electric, DuPont etc.

India's Resources

India's current 2.5–3.0 million college graduates a year figure is expected to double by 2010. During the past half century the number of colleges and universities across the country has multiplied from 565 and 25 in 1953 to 15,600 and 311 respectively in the fiscal year 2003–2004. The number of engineering colleges is slated to grow by 50%, to nearly 1,600, in four years. Of course, not all are good enough to produce the world-class grads of elite schools like the IITs, which accepted just 3,500 of 178,000 applicants in 2004. Simultaneously, the number of students availing tertiary level education has risen from 0.23 million to 9.28 million, while the number of faculty employed in higher education has zoomed from 15,000 to 4.62 lakh currently. According to a study by US-based consultancy firm Goldman Sachs, which is bullish about the sustained growth of the Indian economy in the 21st century, the reality that India produces over 2.5 million university graduates per year has heavily influenced its backing of this nation as a winner in the new millennium.

Table 1.3 Scientific manpower of India

India's position in Human Development Index	127
India's Global Competitive Index	53
India's position in Growth Competitiveness Index	56
India's ranking in Business Competitiveness Index	37
Annual science Ph.Ds in India	3896
Annual Engg Ph.Ds in India	696
Ph.Ds of Indian origin in US	30,100
Indian recipients of US Science and Engg. Ph.Ds (1985–2000)	16,029
Foreign-born people with Science & Engg Degrees in US (India Rank 1)	164,600

Sources:
National Science Foundation: S&E Indicators 2004
The Global Competitiveness Report 2003 by the World Economic Forum

However, the picture may not be as rosy as the numbers suggest. While India has a large strength of scientific and technology personnel of over 6.3 million, the number of scientists actually engaged in research labs is only about 150,000. The annual student enrolment in post-graduate courses in science and engineering is on the decline. A clear drop in enrolment in basic sciences is visible. The percentage of those students who opted for basic science as their course declined from 30% to 19.6% in a matter of three decades. This decline has a lot to do with the lack of investment by the government and industry in R&D and education in engineering and science in the last one and half decades. The strength of R&D manpower can grow rapidly if industry makes its contributions through the induction of R&D personnel in substantially large numbers. It is quite clear to observers of the R&D scene that in the immediate future the industry is not going to come forward to meet this expectation unless there are large inflows of research dollars into the country.

Outsourcing Laboratory Services—the Cont®act is just the Beginning

India's foray into the global scenario comes at a time when the whole idea of competitive advantage is changing. Global acceptance is linked

to leveraging *mindware* and *hardware embedded with mindware*. The notion of conquest has changed today. The power of products, services, brands and the intellectual property they hold are the modern day tools of warfare for global dominance. In 1998, the share of Indian pharmaceutical companies in the US generics business was 0.4%. In five years, it rose to 3.4%, while the US market doubled to $16 billion. And by 2008, our share is expected to rise to 7.7%. At that figure, India's incremental market share over the decade will be 12%.

Laboratory-based services are the theme of this book and R&D investments in experimental sciences and engineering fields, as of today, really constitute only a minor proportion of the revenues. But R&D has gained high visibility because of its strategic and knowledge-based nature in the innovation chain of any manufacturing firm. Like in other categories of services, laboratory-based services encompass the whole spectrum of industries from biotech, pharmaceuticals to herbal medicines, fibers to fabrics, food processing industries to cosmetic industries.

Until a few years ago, R&D managers in large organizations regarded using outside contractors as a short term activity, designed to overcome

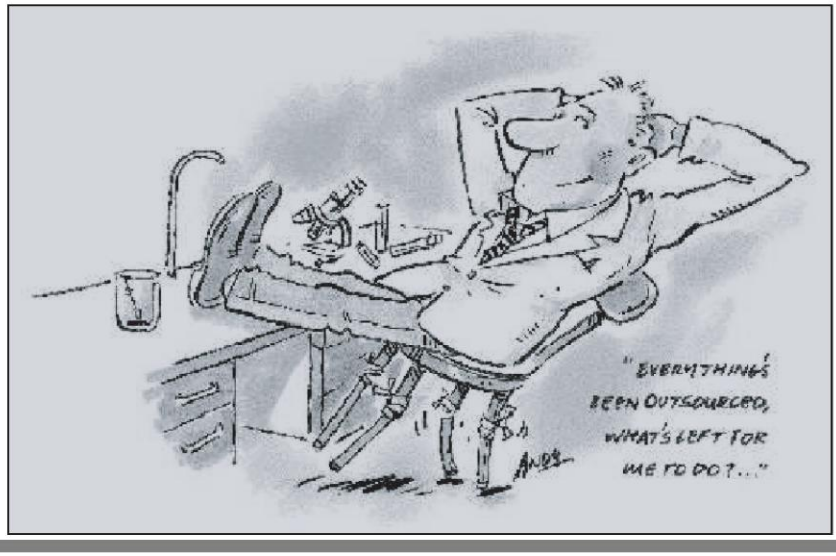


Figure 1.6

a temporary constraint on their resources. Typically, a company would use a small laboratory to provide a specialized analytical service, hire a piece of equipment for trial, or employ a toll manufacturer to make the initial quantities of a new intermediate. It was a tactical option—if the service was going to be needed regularly, the managers would recruit the staff, buy the equipment and then build up the resource. If sales of a new product grew significantly, the firm would build a plant to make the intermediate and terminate toll manufacture.

But all this changed in the 1990s. R&D organizations are being downsized, delayered and demerged. No longer are technology organizations allowed to increase staff numbers but are told to concentrate on core activities and build on core competencies.

The Rise of Global R&D

A growing indicator and important effect of this new transnational technological environment is the rise in overseas research and development. Until fairly recently, the vast majority of R&D work conducted by American hi-tech firms was performed within US borders or, in select cases, in allied nations abroad, primarily Great Britain, Germany, and Japan. The same held true for most other western nations whose industrial R&D activities were concentrated at home or, if abroad, were frequently located in the US. However, beginning with the latest wave of globalization and acceleration in the 1990s, a growing number of multinational firms have begun to explore opportunities to expand and outsource R&D work to the developing world. While still making up only a small fraction of overall industrial R&D, the emergence of hi-tech R&D investment in far corners of the world is a rapidly growing phenomenon.

Beginning in the 1920s and continuing into the 1950s, the US gradually earned a dominant position in science and engineering. These gains were made in part through the influx of foreign-born scientists from Europe and later from the developing world, who were attracted to their extraordinary research institutes, universities and industrial research laboratories. The *New York Times* carried an article in June 2004 by veteran science correspondent William J. Broad on US dominance in research and development. Drawing from a number of

sources, Broad concluded that many nations, particularly in Western Europe and Asia, are catching up with, and in some cases even surpassing, the US in various measures of scientific and technological accomplishment. The US no longer dominates the world as it once did in the number of scientific papers published, patents awarded or Ph.Ds conferred. The US share of scientific papers, according to NSF, fell from 38.1% of the total in 1988 to 30.9% in 2001 with the share from Western Europe rising from 30.9% to 35.3% and the share from Asia up from 11.1% to 17.5% over the same period.

Experts believe that the shift of the R&D scene is due to widespread change in the source of funding for most R&D activities. Between 1860 and 1920, individuals invented, with an eye on commercial success. From 1920 to 1980—the period that covers the First and Second World Wars and the Cold War—the governments funded much of R&D, even though their funding was supposed to be for defense purposes. In reality, they were funding the commercialization of R&D. Presently, industry investment far outpaces government funding for R&D. In the US, this shift first emerged after 1980, as the latest wave of globalization was just getting under way. By the turn of the century, US industry was funding more than two-thirds of all domestic R&D and performing almost three quarters of this work, while the share of government-funded R&D had declined across the board. Over the past decade, a similar trend has emerged in many other western economies. As industry became the primary source of R&D funding, more of this investment and activity began to flow overseas looking for *hired to invent* talent, where MNCs seek to exploit new markets throughout the developing world. Multinational firms are playing a central role in the internationalization of hi-tech R&D.

As in earlier waves of globalization, overseas R&D is also being made easier by the enhanced mobility of both human beings and financial capital. Today, talented individuals and foreign investors face few international barriers while seeking innovative opportunities across the globe. In fact, these investors are likely to be drawn to wherever supportive ecosystems for technological innovation exist. For this reason, numerous countries are attempting to replicate the success of California's Silicon Valley by developing new "Science Cities" or "Technology Parks" designed to attract researchers, entrepreneurs and

venture capitalists from around the world. For their part, high tech firms often find that R&D conducted in foreign locales can inspire new ideas and uncover unique sources of innovation. Moreover, conducting R&D abroad can at least temporarily reduce labor costs where firms are able to tap into local, and increasingly high skilled, multidisciplinary scientific expertise of the developing world.

In turn, this growing global dispersion of skilled engineers, scientists and researchers has helped promote the rise of international research consortiums. Due in part to the decline in public funding for R&D, scientists from around the world are collaborating to tackle a number of difficult areas of fundamental and applied research, working together to more rapidly achieve a shared scientific objective. Projects such as the international space station, Antarctic field research, human genome project and efforts to find a cure for HIV/AIDS, to name a just few, have all benefitted from co-operative international R&D. Newly formed global technology alliances among corporate partners are also growing in number, with hundreds more created each year. These inter-firm projects are designed to accelerate commercial advances in fields such as pharmaceuticals and biotechnology, information communications, aerospace and defense, advanced materials and the automotive industry. Scientists and researchers from less-developed countries are increasingly participating in, and contributing to, these scientific and technically ambitious efforts through government-to-government (G2G) and government-to-business (G2B) initiatives.

Another factor driving global R&D is the extremely competitive nature of hi-tech industries such as computer software development and wireless telecommunications. Increasingly, the race for product innovation has led multinational firms to seek the competitive advantage gained from round-the-clock R&D, while working anti-clockwise in some parts of the world. Having researchers located across different international time zones that, as a team, are able to work continuously on a specific problem or project allows a virtual 24/7 development cycle.

Finally, an important driver facilitating the globalization of R&D is the move toward normalization of international trade through the World Trade Organization (WTO). As more emerging countries like India and China become members of this international forum, their

economies will become substantially more attractive to foreign hi-tech investors concerned with fair trade measures and effective enforcement of intellectual property rights. Even the expectation of China's pending membership in the WTO had a palpable effect on investor confidence, leading many corporations to expand their investments there long before China's entry into the WTO became official in December 2001.

After two decades of pursuing hi-tech investment, China is now home to dozens of multinational R&D centers. Almost all the global giants in automobile, telecommunications technology, computers, software, machinery, electronics, biotechnology, pharmaceuticals and other major industries have made such hi-tech investments in China. These companies include General Electric (GE), General Motors, P&G, Unilever, Microsoft, Intel, IBM, Motorola, Siemens, Ericsson, Nortel, AT&T, Lucent Bell and Samsung.

What was a tactical option for the previous generation of R&D managers, is now an essential component of business strategy in many companies. There has been a sudden explosion in R&D outsourcing and off-shoring, especially by drug and biotechnology companies as they try to shorten development times. So what are the different types and levels of outsourcing R&D available, and how best can we ensure success with this activity in industry? Perhaps the scenario is a little different from one industry segment to another and considerations are different for the IT industry, but there is enough cheer to pass around the table.

Outsourcing R&D?

It is easy to understand why small and medium-sized enterprises (SMEs) use outsourcing. New products and developments come along at more irregular intervals in the SME sector than they do in larger companies. Additionally, some R&D skills required for product development are missing in smaller companies but because of the peaks and troughs in R&D requirements they cannot justify recruiting more staff. These companies have no choice but to use outside expertise if they are to make progress, contracting these resources only when they are needed.

But why should a large company, with all the resources it needs to develop a product in-house, choose to contract some of these activities to an outside agency? After all, managers have control of their resources, can maintain their quality, limit their cost, plan their future activities and resolve potential conflicts of interest between competing projects. Yet, it is just such companies that are increasingly resorting to outsourcing. Basically, there are three reasons for this change: cost, time and technological complexity.

1. R&D managers are under constant pressure to control costs, especially fixed costs, and to do more work with fewer people. No one wishes to cut resources at the sharp end of R&D, and the only way to avoid this is to put all other activities under the microscope. One answer is to stop any irrelevant support and to consider outsourcing of certain non-core, but essential, *services.*
2. Everybody wants to get their products to market as quickly as possible—time is money. A shorter time to market means that income arrives sooner and the residual patent life left for protected sales is longer. Using smaller, less bureaucratic, contract companies to carry out some of the key development activities is one way to speed up product development.
3. R&D has become increasingly technologically complex and multi-disciplinary. Consider the number of different skills needed to invent and put a new drug on the market or to develop a new engineering plastic. Few companies, if any, can afford to have all the necessary technical expertise under their direct control. Outsourcing or joint collaborations is one way around this problem.

Briefly, outsourcing a strategically selected subset of testing requirements will enable an organization to positively impact speed, budget, quality and credibility in the following aspects:

- Optimize product/time to market
  - o Enable internal technical and engineering resources to focus on core business drivers and other critical test initiatives.
  - o Minimize management overheads.

- Alleviate capital budget requirements
  - Remove capital expenditures for expensive test equipment.
  - Eliminate the need to plan, build and operate a laboratory environment.
- Maintain and track product quality
  - Allow regression testing to continue for widely deployed products.
  - Utilize database trending information from historical data to assist design teams in product development.
- Gain Third-party credibility
  - Outsourcing tests will provide customers with even greater levels of confidence in the products provided to them.

What, When and Where?

In theory, companies can outsource almost every laboratory activity related to R&D, manufacturing (quality control), process engineering and marketing (producing data sheets, regulatory tests etc). However, very few major companies still haven't taken the plunge and allowed its key research activities to be totally outsourced. Where the company's core and strategic interests are to be guarded, major global players are setting up captive R&D facilities and technology centers in low-cost countries. These off-shore captive facilities offer the same advantages as off-shore outsourcing companies, as discussed above, with tighter management control. There are many examples of successful outsourcing of laboratory services and there is no doubt that companies can save fixed and capital costs and deliver projects faster by the intelligent use of contract research organizations (CRO).

Companies regularly outsource many steps on the critical path to introducing new products. Custom manufacture of key intermediates has gone on for many years, but over the past decade the growth in this area has been very fast. More recently, companies have begun sourcing products as well as intermediates from contract manufacturers.

Additionally, other key services for product development that are regularly outsourced are all aspects of safety, health and environment, including toxicology and product safety testing etc.

More sophisticated than any of the preceding activities, and more prone to risk, is the shift to outsource key steps in the discovery phase of R&D. This is at the centre of the debate as to how far companies should go with outsourcing and when does a technological company cease to be one. Many managers think that it is very unwise to outsource technologies that are critical to achieving the business strategy. Outsourcing of selected research activities and technologies is still the preferred option. Companies prefer to form strategic alliances or collaborate with other companies through confidentiality agreements when essential technological in-house core competences required to carry out research programs is unavailable.

There is no engineering blueprint on outsourcing and information is more like recipes in a cookbook. They tell us what ingredients to use, in what quantities and in what order but they do not provide a complete and accurate plan of the final result. To date no detailed study has been published on outsourcing of laboratory activities but the following guidelines need to be applied to off-shore R&D.

Outsourcing Guidelines

These elements, presented in order of importance, are essential to an outsourcing venture.

1. **Critical, core technologies:** This is dangerous territory which requires a cautious approach. Without these core skills, companies have little to differentiate themselves from others in the field.
2. **Confidentiality and intellectual property ownership:** These issues must be addressed and formalized from the outset of any relationship.
3. **Management time:** Do not under-estimate the amount of management time that is required to monitor outsourced activities.

It has been suggested that if more than 25% of a manager's ongoing time is spent on an outsourced service it is probably more cost effective to have an in-house resource

4. **Enabling technologies, longer term and/or fundamental research:** These can all be outsourced but companies need to retain enough internal intellectual capacity to be intelligent purchasers.
5. **Planning and project management:** These cannot be left to chance. The contract should cover all eventualities and have shared benefits, the supplier being treated as a partner. All parties should be aware of what is to be delivered and on what time scale
6. **Commodity services and non-core technologies:** These are suitable for outsourcing and there are already established testing labs providing these services to a wide range of industries.
7. **Suppliers:** Companies have to ensure that service providers have the right skills, necessary facilities and can control quality and costs to the desired standards. They should preferably be chosen from previous or existing relationships. Geography, language and culture are important secondary considerations.

Reluctance of companies to move into wholesale outsourcing has not prevented a massive expansion in the number of CROs over the past decade. A whole range of CROs have sprung up to service the development requirements of drug companies, including carrying out Phase I, II and III clinical trials in every country. More than 600 CROs are now believed to be touting for business worldwide in the pharmaceutical field alone. This is hardly surprising since calculations show that every 1% move into outsourcing by international pharmaceutical companies produces $200 million in extra business for CROs.

It is not R&D work from overseas multinational corporations alone that is creating the surge in demand for laboratory-based services. A larger number of companies are involved in sourcing a number of products like chemical intermediates, textiles, herbal medicines, automobile components etc., out of low-cost manufacturing bases like India. As global sourcing of raw materials and components increase from countries like India and China, the need for quality laboratory testing becomes an absolute necessity. Many of these companies

would like to ensure that the materials conform to the requirements of the global markets and meet all regulatory requirements and are heavily dependent on private independent laboratories in the host countries from where the materials are being sourced.

Which products need special warning labels to help prevent injury or instructions on how to treat accidental exposures? Which materials in workplaces will require special handling to prevent injury to workers? Which materials are safe to introduce into our environment, our air, soil, and water? Scientists working in specialized laboratories answer these and many other important questions through product safety research and testing. The product list is long and practically covers all the products that we see around us.

Now's the Time

Identifying, establishing and supporting, and leveraging outside/foreign competencies are the essential building blocks in the globalization process. In the last decade, MNCs have eagerly embraced globalization and have strived to develop and implement worldwide strategies. Numerous barriers stand in the way of successful globalization. Some companies have been spectacularly successful in taking their proven approach and replicating it. From re-engineering to downsizing to Total Quality Management (TQM), the emphasis has shifted internally, leading to the goal of finding and developing core competencies. In globalizing, MNCs need to be able to transfer their most critical capabilities within and between their networks of international operations and also to their innovation partners like CROs.

India is on the verge of a new outsourcing wave. This story is not the often-heard story about IT companies locating their R&D centers or using Indian BPOs. That story is well-known. The focus of the book is exclusively on pharmaceutical, biotechnology, electronics and materials manufacturing companies who require laboratory-based services and scientific talent—in other words, experimental science and engineering talent. That is what makes this movement stand apart from the IT software revolution. There's a huge amount of activity taking place even in areas outside software. As goes the title of the old Charlie Parker bop classic: 'Now's the time'.

Chapter 2

Research Process Outsourcing: The Beginning of Pharma Cont®acts

"There is nothing more powerful than an idea whose time has come."

—VOLTAIRE

In the early 1500s, Italian Renaissance sculptor, painter, architect and poet, Michelangelo, organized what may have been the first truly virtual company. He developed a network of trusted suppliers, artists and stone masons to supply the materials he needed for his masterpieces. The comprehensive records he kept for his projects detail the excellent guidance he provided his vendors and his careful monitoring of quality and costs. Subsequent leaders were slow to follow Michelangelo's outsourcing lead. In pursuit of new blockbuster drugs, the pharmaceutical industry is following in his footsteps with their global sourcing strategies for raw materials, intermediates and services to refine their rather long and complicated drug discovery process.

For years, Wall Street declared that big pharma companies need to roll out at least two to three major drugs annually to build valuations. Even with their mega merger strategies, which brought their best brains together, pharmaceutical companies have not been able to reach that level of production. Drug companies have been building up their discovery chemistry units, but not quickly enough to catch up with the proliferation of "targets"—the site of attack for drug molecules. They can't get to as many targets as they need to, and they simply can't

buy in all the laboratory capacity, because many targets may turn out to be not worth pursuing. Thanks to genomics, there are plenty more targets out there. Thus, the market for drug discovery service providers, Contract Research Organizations, turned bullish.

The largest driver for outsourcing in the pharmaceutical industry is the need to bring down costs and trim developmental cycle times. The drying pipeline of blockbuster drugs on the one hand, and the increasing cost of taking a New Chemical Entity (NCE) through development and clinical trials on the other, are forcing large companies to look for cheaper alternatives to sections of research and manufacturing processes. Players within the industry contend that the annual market for outsourcing drug discovery chemistry may exceed $1 billion. Several industry figures contend that 15–18% of total pharmaceutical R&D budgets are devoted to chemistry, so a comparable 50/50 split with outsourcing could create an enormous opportunity for CROs. Outsourcing has become so important in the industry that there is a professional organization, the Pharmaceutical Outsourcing Management Association, for managers specializing in outsourcing, and a publication, *Bio/Pharmaceutical Outsourcing Report,* covering outsourcing by pharmaceutical and biotechnology firms.

Successful discovery and marketing of new medicines is a very profitable business, with annual sales of blockbuster drugs often in excess of $1 billion and carrying a high profit margin. Such returns are always transitory as there will always be a competitor coming along with a similar medicine willing to undercut their price. The pharmaceutical industry relies heavily on patents to protect its products, which prevent a competitor from selling the same medicine, but a competitor can market a similar product that lies outside the scope of the original patent. Also, patents also have finite lives of twenty years. The period of patent protection starts when the parent compound is registered with the patent office, not when it appears on pharmacist's shelves (which may be 5–10 years later). After the patent expires, any company can copy the drug and market it as a so called *generic product.* This has created a secondary tier of companies that specialize in the production and marketing of generic medicines. As they do not have to incur the expensive costs of R&D, generic drug companies can market the product much cheaper than the original discoverer. For an average

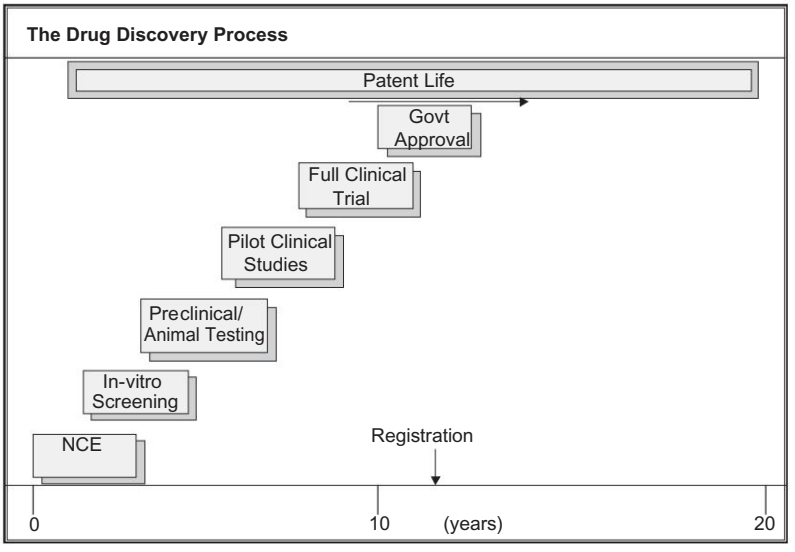


Figure 2.1 The making of a new medicine

drug, every day's delay after a patent has been applied for costs $1 million in protected sales. Since 20 years of protection provided by a patent is often substantially eroded during the long process of research and development needed before a product can move to market, the major companies must keep looking for the next generation of medicines, preferably new blockbusters. How this is done has become an extraordinarily complex and hi-tech process.

> *"Science (of life) is a superb and dazzlingly lighted hall which may be reached only by passing through a long and ghastly kitchen."*
>
> —CLAUDE BERNARD

THE DRUG DISCOVERY PATH: PIPE DREAMS

Drugs are organic chemicals either derived from natural sources or man-made molecules. The compounds of natural origin may be extracted from plants, animals or microbes. But most modern drugs are synthetic, man-made chemicals designed to act on some biochemical targets.

Whatever may be the route of delivery, oral, injected etc., the drug molecule must either end up in the bloodstream from where it will be transported to the target organ or delivered to the target organ locally. In the target organ, the drug is recognized by 'receptors'. These receptors are large protein molecules to which the drug binds tightly and precisely with a high degree of specificity. Molecular biologists are trying to figure out the molecular architecture of such receptors and chemists are designing newer molecules which fit more and more precisely with known receptors.

All drugs act on specific receptors and most innovative companies seek to discover new receptor targets that offer a novel approach to the treatment of a particular disease. According to pharmaceutical scientists, all contemporary drug therapies are based on a total of 500 targets. The range of new targets available is extended greatly as our knowledge of the human genome is complete. Humans have around 30,000–40,000 genes, each of which encodes the information for making a protein. Clearly, not all of these will be suitable as drug targets, but many new targets will emerge. The problem for companies is how to decide which of the many possible novel receptors offer the greatest chance of providing effective new treatments, and which are the ones to invest in. The choice of a new drug discovery target is thus now associated with an embarrassment of riches. Once a target has been chosen, the human target protein can be made or expressed in immortalized cell cultures and tested for new drug candidates.

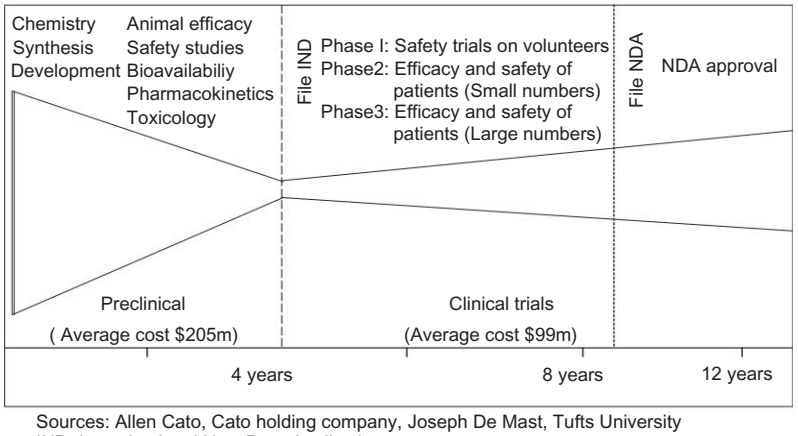
Screening for a Lead Role

The synthesis of new molecules as drug candidates for activity screening is a laborious and slow process. The traditional process of drug discovery starts by screening a library to see if any of the compounds it contains have properties that could plausibly be harnessed to the cause of medicine. But, substances emerging from this initial screening carried out in a tissue culture are rarely powerful enough to be effective as they stand. The next step, therefore, for synthetic chemists, is to fiddle with the chemical structure of promising compounds and tinker with the active sites in order to increase their potency. Each new molecule, NCE, was traditionally individually synthesized through a

multi-step synthetic route by expert synthetic organic chemists, who, on an average could produce one or two new compounds each week. Since the 1990s, this process has radically changed by the intro-duction of robot chemistry, which allows the assembly of various chemical combinations that make up new drug molecular structures. Using such combinatorial chemistry techniques, a single chemist can produce thousands of new compounds each week. Specialized companies have emerged that synthesize chemical libraries containing hundreds and thousands of new chemicals and sell them to pharmaceutical companies for their own particular screening projects.

The screening of large numbers of new chemicals has become possible because of the parallel development of new high throughput screening technology. By using advanced laboratory automation tools to handle a very large number of tests and using computers to process data, it is now possible for a company to screen as many as a million chemicals in less than a month against given targets. Often these chemical libraries are made up of a random selection of many different types of molecules, but sometimes more selective libraries are prepared based on molecules that resemble the natural receptor or enzyme substrate or mimics already available drugs. The process of mass screening should generate a number of lead chemicals with some activity at the target receptor.

Large-scale screening involves simple tests on the human receptor target in a test tube or cell culture model. The next stage will involve testing the best drug candidates in more complex biological systems, often using the isolated organs or tissues of experimental animals whose receptor proteins are usually similar to their human counterparts. The shortlisted candidates may then be tested *in vivo* on living animals. The initial screening may involve hundreds of thousands of chemicals, but this will have been reduced to a short list of 10–100 candidates for assessment in all the animal tests. From these, a handful of possible development candidates will emerge. Each of these candidates needs to be assessed for toxicity to see if it is likely to provide a useful and safe medicine. Further animal experiments will be needed to establish bio-availability, i.e. how well the compounds are absorbed into the blood circulation and how long their actions last. A compound that is not well absorbed when taken orally will be troublesome unless another route of administration can be devised.



Sources: Allen Cato, Cato holding company, Joseph De Mast, Tufts University
IND: Investigational New Drug Application
NDA: New Drug Application

Figure 2.2 Funneling money for new medicine

Once well absorbed, if it rapidly degrades or is eliminated it will not be attractive for human use, as this would mean that the patient would need to take several doses each day.

To obtain approval for the introduction of a new medicine, the company needs to satisfy various government regulatory agencies on the issues that the compound is effective in treating the condition for which it is intended and that it is unlikely to have any side effects on the patient (Figure 2.2). The safety of a new drug can never fully be predicted by tests on animals, but these can at least eliminate many potentially toxic substances. All governments require extensive animal safety testing. This involves, for example, testing the new medicines by administering it to animals in various doses, including at least one high dose greatly in excess of planned human use. The drug is administered everyday for periods up to 12 months. During this period, the animals will be weighed regularly and blood samples taken to see whether any biochemical or blood abnormalities are triggered. At the end of the test period the animals are killed and their various internal organs are examined in detail under the microscope to detect any adverse changes. These safety tests will be repeated in two mammalian species to maximize the chance of detecting any toxicity. Special animal tests in pregnant animals will be needed if the drug is to be

used in women of child-bearing age, to detect any possible adverse effects that the compound might have on the developing foetus. Any drug that is to be used over a substantial period of time in humans will have to be tested for cancer liability in animal tests lasting two years in two different animal species. The saga of synthesizing, screening and animal testing continues with several twists and turns.

The Final Round of Trials

If the lead compound passes these tests, it can then be administered to human subjects. The initial Phase I clinical trials involve a small number of healthy volunteers. They receive the drug under carefully monitored conditions to make sure that it does not cause any unpredicted unpleasant or dangerous side effects. Monitoring drug levels in blood samples from such volunteers will also provide valuable information on how well the drug is absorbed in humans, how long it persists in the body, and what the main breakdown products are. This information will help the selection of the most suitable dose regime for the next stage (Phase II) of clinical tests which involves patients. These trials are usually done with a small number of patients and the aim is to test whether the drug actually works, i.e. does it improve the patient's symptoms? In the case of drugs that target a novel human receptor for the first time, this proof of concept is particularly vital, as it may not always work out the way scientists predicted.

In the happy event that the results of the Phase II trials are positive, the compound can enter the much larger Phase III clinical trials. These trials commonly involve thousands of patients, recruited at a number of different medical centers. Because of their complexity, and the need to treat patients over extended periods of time, these trials can often take years to complete. At every stage, detailed records need to be kept of each patient and, wherever possible, objective methods are used to measure improvement in their clinical state.

A study released in April 2004 by Tufts Center for the Study of Drug Development (Boston) indicates variations in the cost and time for development of drugs for different indications. Therapeutic class, a critical determinant of drug development time and cost, analyzes data for 68 drug candidates from ten pharmaceutical companies that

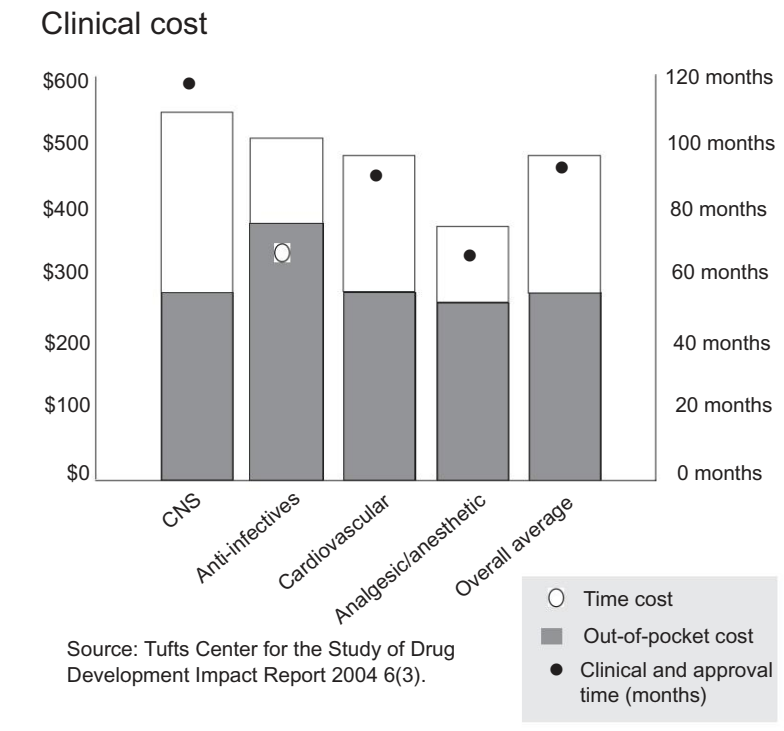


Figure 2.3 Tufts Report on Cost of Development

first entered clinical testing between 1983 and 1994. Clinical costs averaged $466 million (in year 2000 dollars) in this sample, exclusive of the preclinical and post-approval research costs included in Tufts' widely cited figure of $897 million per drug. Analgesic/anesthetic drugs were the least costly at $375 million and Central Nervous System (CNS) treatments were the most expensive at $527 million. The exorbitant price of the CNS candidate is because it requires 9.5 years of clinical research and approval, 2 years longer than the overall average, and 4.3 years longer than analgesic/anesthetic drugs.

Registration: The Finish Line

If all goes well with the Phase III trials, the company will be ready to assemble a massive package of data. This will include a detailed

description of all the results obtained on the compound in the clinic, in animal safety and in the laboratory, together with information on how the compound can be manufactured and what quality control measures exist. Such a package of data will occupy many volumes. It will be submitted to a government regulatory agency for detailed scrutiny and, after expert assessment, the agency will inevitably come back to the company with a list of questions that need to be answered, often involving the need for the company to undertake further tests for efficacy or safety. After this process is completed the agency may hold a public meeting at which a panel of experts can interrogate company representatives on the fine points of their submission. The panel then votes to advise the government agency on whether to approve or decline the submission. The review process by the regulatory agency, like the FDA, can take years to complete, although for some diseases, (e.g. AIDS) there are fast track approval procedures.

Once a new medicine has been given official registration, the company is free to market it, but it can only be recommended and advertised for the particular disorders for which official approval has been given. Any additional new medical uses will need further clinical trial data and government approval before the company can promote these. Since new medicines represent entirely new chemical molecules to which humans have never been exposed, their safety is never going to be completely predictable. After marketing, post-marketing surveillance requires doctors to alert the authorities on any adverse drug effects for them to take corrective action.

Drug companies are fond of talking about their pipelines—the compounds they have in various stages of development in their laboratories—ready to take over as money-making machines when the patents on their existing products expire. However, there is no law equivalent to Moore's Law (the doubling of transistors per integrated circuit), i.e. exponential growth indicating when the next improved version might come up. For every approved drug that comes out of a pipeline, about 10,000 molecules would have gone in and got lost somewhere along the way. The complex and exacting process of drug discovery and development takes many years to complete and involves company scientists and outside experts from many disciplines. The whole process, from initial screening to final product takes ten years

or more and the costs involved continue to escalate as regulatory agencies set more and more demanding criteria for drug approval. On an average, for every 100 promising drug candidates discovered in the research laboratory, only 10 will get as far as being assessed on human subjects. And only one of these will become a registered new medicine. Even then, less than half of the new medicines will make a profit for the company. Since each new medicine costs several hundred million dollars to develop, pharmaceutical companies use the high cost of R&D to justify the high process and profit margins they obtain for new products. Remarkable success of the pharmaceutical industry in discovering innovative new treatments for human diseases depends on the ability to spend heavily on R&D. Pharmaceutical companies reinvest more than 10 % of their income on R&D, a far higher proportion than most other sectors of the industry. For an industry that depends heavily on products with limited patent life, there is an intense pressure to find the next blockbuster drug.

The buyers, governments and health maintenance organizations are now putting pressure on processes, particularly where patented blockbusters are subjected to competition from out of patent generic drugs or me-too compounds. The industry, to stay ahead of generic drug producers, needs to come up with new drugs that either treat what was previously untreatable or offers better treatment than before. Recent advances in genomics promise a quantum leap in providing drug targets. The genomic sequence allows 'designer drugs' that can attack the underlying genetic cause of the disease rather than the 'one-size-fits-all' synthetic drugs that are currently in use. But pharmaceutical and biopharmaceutical companies are in a bind when it comes to validating targets and optimizing leads. This has created a market for outsourced drug discovery chemistry.

Advantage India: Target Site

A number of CROs in India have evinced interest in working on different parts of the discovery chain. Even small companies are claiming a piece of the pie because they too are armed with the relevant credentials—trained analytical and development chemists, a record for innovation and manufacturing facilities approved by the FDA.

These strengths enable Indian companies to offer between 30 and 50% in cost savings.

Kiran Mazumdar Shaw, CEO of Biocon India, realized the potential of research outsourcing early on and launched Syngene, India's first contract pharma research company in the early 1990s. Today, Syngene earns over Rs 40 crores annually, partnering with some of the biggest drug companies, including Glaxo Smith Kline Beecham, Bristol Myers Squibb and Astra Zeneca on research projects. Syngene performs contract research in custom synthesis and recombinant DNA technology and wants to move into cardiovascular, diabetes and anti-infective drugs by developing its own intellectual property.

Aurigene, a subsidiary of Dr. Reddy's Laboratories, is also pioneering CRO in NCE research. The Indian lab offers a range of support services to the research done at its sister laboratory in Boston on structure-guided generation of hit molecules for early-stage novel targets (if the target is validated), synthesis of drug-analogs and drug library or early stage discovery candidates.

GVK Biosciences has setup an R&D team of 275 scientists. The company is extending beyond contract research to lead optimization, lead validation, target validation and preclinical and clinical development. Suven Pharma, a Hyderabad-based company, started by following the custom synthesis route as well. Suven follows a business model that Venkat Jasti, Chairman Suven Pharma, calls CRAMS, for Contract Research And Manufacturing Services. Beginning with custom synthesis and contract manufacturing, it now develops its own pipeline of molecules for the central nervous system segment. Suven, which employs about 30 research staff, has supplied about 180 intermediates so far. Another company, Avra Laboratories, founded by eminent organic chemist, Dr. A.V. Rama Rao, is offering contract research services by providing compounds and intermediates that are used in the production of new chemical entities.

China is also in the race. Shanghai-based Wu Xi Pharma Tech, which started as a CRO in 2001, tripled its revenues in the year 2002–2003 and expects a repeat performance. Pharma Tech's rented labs in the Shanghai Free Trade Zone are like an R&D mall of the

Table 2.1 Pharma CROs

Synthesis/Process	Preclinical	Clinical
• Aurigene Technologies, Bangalore • Syngene, Bangalore • GVK Biosciences, Hyd'bad • Suven Pharma, Hyd'bad • AVRA, Hyd'bad	• Jai Research Foundation, Ahmedabad • Rallis Research Center, Bangalore • Vimta Labs Ltd., Hyd'bad • Sipra Labs, Hyd'bad • Shriram Institute, Delhi	• Quintiles Spectral • Clingene • Vimta Labs Ltd. • GVK Biosciences • Lambda Research, Ahmedabad • Wellquest

world's most famous drug companies offering dedicated facilities, space and scientists to companies like Sumitomo, Merck & Co etc. In three years, the firm is expected to complete construction of its own premises in two different locations in Shanghai, investing $18 million. One of the new facilities will provide ingredients in kilogram or ton quantities for customers who want to initiate toxicology studies or clinical trials on samples generated by Pharma Tech. The Shanghai firm is thus moving downstream from contract research and provision of milligrams or grams of samples to the scale-up level. Ge Li, founder of Pharma Tech, says the firm has been so successful because of its customer focus and 24/7 contact with customers around the world. Pharma Tech has designed a live tracking system that allows customers to follow the progress of their projects.

Sources of revenue for Indian CROs vary according to the way the firms interact with their foreign customers. Prasad, of Dr. Reddy's Lab, says it makes very little sense for Indian research firms to be paid simply for time and effort. "At Aurigene, we are bringing intellectual content to the process, and it is not time alone that we are bringing," he points out. The same sentiment is expressed by S. Sivaram, Director, National Chemical Laboratory, Pune. Sivaram stresses that foreign companies should compensate their Indian partners fairly when they come to India to develop intellectual property. "There must be a sense that some of the benefits from the R&D flow back into the country," he says. Until now, most of these companies have been doing simple work that needs modification and iteration. But that is the only way to move up the value chain till a company can

grow in core expertise and build its own intellectual property and then become licence-sharing partners in development, where returns come as royalties and milestone payments, rather than transactional fees.

Kilo Labs

All commercial pharmaceuticals start out as little more than an idea in a drug company lab, with a few milligrams of wonder molecules made and fingerprinted by the scientists. To test the concept, the company needs small quantities for *in vitro* and toxicological studies. Next, it needs slightly larger batches for Phase I and Phase II clinical trials, then even larger quantities for Phase III trials and, finally, full scale, long-term supplies for the commercial launch. Traditionally, the early stage quantities were either made in-house by the drug company or supplied by small, independent outfits known variously as process development or *kilo lab* firms. Small quantity supply is a good business in its own right where CROs can utilize the lab scale facilities to the fullest.

Pharmacopoeal Testing

Besides custom-made organic synthesis of novel molecules, there are almost unlimited opportunities for outsourcing regulatory or compliance-related testing for commercial drugs. The laboratory service can be as simple as drug identification through an Infrared Spectrophotometer (IR) or as complex as method development using High Performance Liquid Chromatography (HPLC) for impurity profiling. Many laboratories specialize in certain techniques or analyses, whereas others provide a more general spectrum of testing. The list of analyses and testing available through external providers is long and covers every aspect of analytical, pharmaceutical and microbiological testing. The list can range from standard United States Pharmacopoeia (USP), BP (British Pharmacopoeia) and Indian Pharmacopoeia (IP) protocols to new method development/validation, and drug product tests for identification and potency to microbiological testing for sterility.

Stability Studies

In a long list of tests carried out during development, stability of the formulation is a critical and mandatory requirement. Many laboratories in India are equipped to do these studies. Handling stability programs is often extremely time-consuming work involving a number of responsibilities, including initiating and maintaining stability studies, tracking pull dates, testing samples and reporting results. Managing thousands of stability samples and timelines requires a solid stability-sample tracking system to ensure that all samples are handled appropriately.

Reliable stability software makes a significant difference when tracking pull dates and sample locations and quantities. When using either off-the-shelf or customized sample-tracking software applications, it is important to comply with FDA regulations. Auditors today are increasingly concerned with the integrity and security of stability software, preferring programs that comply with regulatory guidelines.

All Indian CROs would not add up to even 1% of the market. Opportunity exists for Indian companies to be part of the drug development chain. The breadth of experience of a contract laboratory can actually be equal or superior to in-house capabilities because of the expertise developed from dealing with several types of pharmaceutical compounds. Outsourcing can be taken one step further by using the one-stop shopping option. The CRO is granted the complete project starting from formulation support and manufacture of clinical materials to analytical support of the drug product. However, R&D in most major pharmaceutical companies is highly segregated. Different development groups usually govern each function and these groups make decisions about what will be done in-house, what will be outsourced and by which CRO. Therefore, a successful initiation of a one-stop shopping project takes a tremendous effort of collaboration between different functional groups.

Preclinical Testing: Animal Rights and Wrongs

Animal house facilities are critical for any CRO as they can't move to the next phase of clinical research—Phase I trials on humans—without

them. Animal experiments, so crucial in pharmaceutical research, stir controversies the world over. Scientists and animal welfare activists are pitted against each other in almost every nation. To address the domestic debate, the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) was formed in 1998 under the Ministry of Environment and Forests with the mandate that all the animal houses would be registered with the CPCSEA. Animal houses also need to have Institutional Animal Ethics Committees (IAECs) with representatives from CPCSEA, who are vested with veto powers.

Even after permissions, clinical research takes a complicated route. A molecule has to prove its efficacy at every stage. Details and observations are noted in a preclinical dossier. After the *in vitro* tests are successfully completed, IAEC grants permission to test it on animals. At the first level, rats or mice are used for toxicology tests. After this,

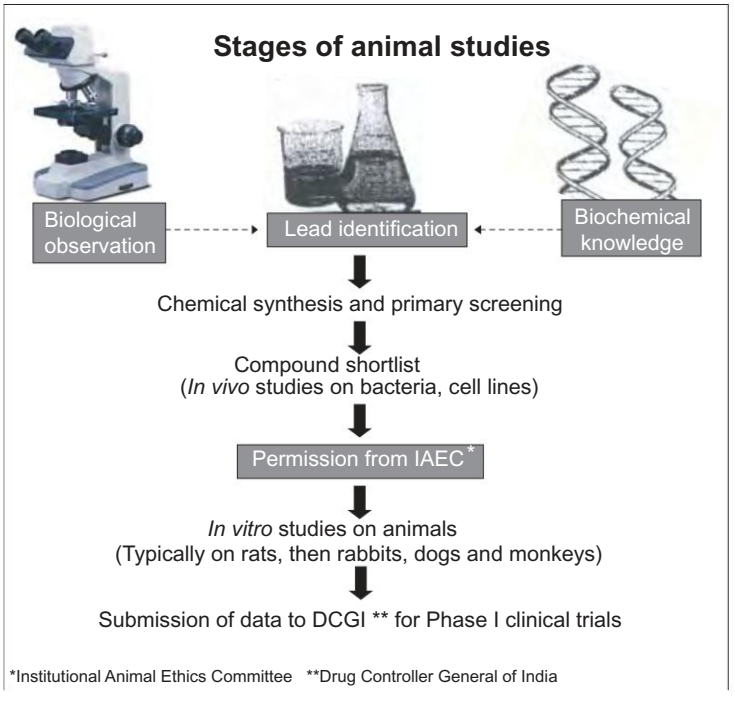


Figure 2.4 Stages of preclinical studies

the product moves on to other animals like rabbits, guinea pigs, hamsters, etc. The most important stage is when the molecule is given to dogs and primates. At this stage, animal modeling is carried out to ensure that the animal fits the disease and the profiles being researched.

The CPCSEA has 615 animal houses registered with it, including those run by pharmaceutical companies, research hospitals and laboratories. Companies contend that CPCSEA responds to their request to import dogs and monkeys very slowly at best, and often stalls the process, while CPCSEA argues that not much original research takes place in India and animal imports should not be encouraged for clinical trials of overseas pharma companies. These policy debates contradict economic wisdom. Ninety-day trials on dogs cost about $100,000 in India, while they cost three to four times that amount in the West.

India's loss can be a quick gain for others. If permission is not granted in India, companies can move to other countries, says Ranjan Banerjee, Director, Toxicology, Jai Research Foundation (JRF), an Ahmedabad-based preclinical CRO. It is not easy breaking into the pharma research market. But the inability to carry out full clinical studies blunts the edge. Most of the preclinical studies done by private CROs like Rallis Research Center, Bangalore, JRF and Intox, Pune and Sipra labs in Hyderabad have been on rats, mice, rabbits or hamsters and rarely on higher animals such as dogs and primates. CROs feel constrained and find it tough to offer integrated services.

The government is trying to help. ICMR is setting up two large facilities. The first is an animal breeding facility in Mumbai with technical and financial assistance from the National Institutes of Health (NIH), USA and the second at Hyderabad will work as a CRO and undertake contract research from pharma and biotech firms. These labs plan to stock transgenic and knock-out (in which parts of genes have been knocked out to induce a disease profile) models of animals.

Clinical Trials: Challenges and Opportunities

This is currently the most attractive area of outsourcing. Big international players like Quintiles, Parexel, Covance and PPD Inc. provide

clinical testing, laboratory services, clinical trials and data management, biostatistical analysis, regulatory consulting and medical writing for drug companies around the world. Though these large players are based in North America, where approximately 60% of their revenues are generated, many are looking to Asia for growth opportunities. CROs' clients for clinical trials include the world's top 50 pharma companies.

As stated before, clinical testing of experimental drugs is normally done in three phases, with each successive phase involving a larger number of participants. Phase I assesses the drug's safety, Phase II tests for efficacy and Phase III is the large-scale human testing, involving hundreds or thousands of patients, to thoroughly understand the drug's effectiveness, benefits and possible adverse reactions. Once a New Drug Approval (NDA) is granted Figure 2.2, companies follow up by performing post-marketing or Phase IV studies. *80% of the total cost of drug discovery goes towards development—taking the drug through clinical trials*. Trials for Phases I, II and III account for the maximum amount of time and cost. The additional problem of delayed development time is also causing new drug introductions to lose incremental revenues. One of the major factors for delay is unsatisfactory patient recruitment rates. This dual challenge of accelerating clinical development and reducing costs has forced major players to look at alternate destinations for sourcing patients for their global studies. Exploration on these lines would then take companies to selected countries in Latin America, Eastern Europe, Commonwealth of Independent States (CIS) countries and Asia.

Among potential Asian countries, India stands out prominently with its large pharmaceutical industry presence that has dominated world markets due to cheap generics. India has a large pool of treatment-naïve patients who are willing to participate in clinical studies. With large geographic coverage, fast recruitment of patients at major sites in all major metropolitan cities can have a positive impact on global patient recruitment plans. English is the main language of communication in the hospitals of all major cities and the majority of patients can understand English. Telecom facilities in India are suitable for data transmission (for example, the medical transcription industry has used India as the base for sending and receiving data for overnight transcription output).

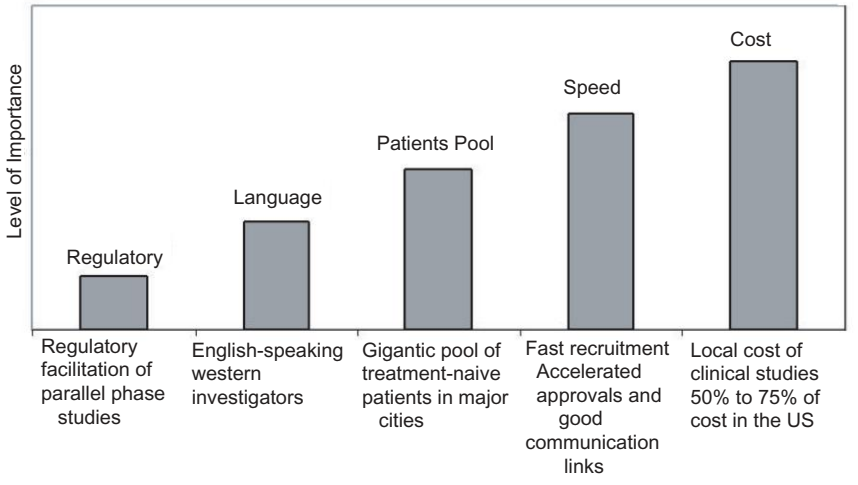


Figure 2.5 The India advantage

India is a signatory to Intellectual Property Rights (IPR) protection from 2005. However, due to the current lack of protection, a few companies believe that they are morally bound not to place their developmental activities in an environment with lax protection for intellectual property. Others suspect that data on their early phase molecules will not remain in safe hands, resulting in an earlier introduction of their generic competitors, who could benefit from their Investigational New Drug (IND) applications to the Indian authorities.

Regulatory Regime: Lagging behind Schedule Y

India has taken a relatively long time to evolve regulations to facilitate global clinical studies. In 1988, the government legislated a law stating the requirements for the approval of new drugs for import and manufacture. This was inserted in the Drugs and Cosmetics Act and was called *Schedule Y.* Schedule Y stipulated that the first applicant for any new drug should generate data in local clinical trials conducted on about 100 patients. This schedule also dictated that permission for such clinical trials would be given for 'one phase behind' the

developmental status in the rest of the world, meaning that, if the compound was undergoing Phase III in its source country, India would grant permission for only Phase II in India. Thus, if the product is already marketed in the US/EU, the first applicant would be asked to carry out a Phase III study. Interestingly, for a second applicant with the same compound, no clinical trials would be required since the second applicant could show bioequivalence* to the first product approved and introduced in the market. These two provisions taken together discouraged research-based multinational corporations from carrying out global clinical studies by their local subsidiaries, which preferred to wait for their innovator brands to be approved in source countries and then carry out limited bridging studies for local approvals. This law created a lag of few years between the introduction of new products in India and the rest of world.

In the interim period, some Indian research-based companies which started their discovery programs unveiled their new molecules and started Phase I and Phase II programs that were allowed under the same Schedule Y that made Indian discoveries exceptions for a phase lag. Thus, the discrepancy in the rules that existed on the basis of the source of NCEs became more apparent. This phase lag is now being removed as per the amendment to the Schedule Y that has been endorsed by the Drug Technical Advisory Board and is awaiting release of notification.

Good Clinical Practices (GCP)

For many years, ICMR had issued guidelines on GCP and ethics were adopted by various organizations conducting clinical trial studies in India. Various proposals of the pharmaceutical companies were referred to the ICMR for review whenever drug control authorities could not decide on the outcome. However, there was a need for GCP guidelines that conformed to the latest World Health Organization (WHO), ICH, FDA and Committee for Proprietary Medicinal Products (CPMP) standards. The Drug Control Authorities in India

* Bioequivalence: Studies to prove that the drug acts in the body in the same way as the patented drug it seeks to replace

then formed an expert committee to draft Indian GCP guidelines with a view to making it legally mandatory for all sponsors of clinical studies. In December 2001, the Directorate General of Health Services released guidelines with a public announcement that it would be necessary to follow them for all clinical trials. The scope of any error is very limited and involves a high degree of ethics both personal and professional. If these guidelines are implemented seriously for all clinical studies on investigational products, India 'could emerge as a new power for clinical development'.

There is already some controversial news on the clinical trials front. WHO has withdrawn some AIDS drugs made in India from the list of approved medicines. Reason: The contracted labs or CROs that conducted trials on these drugs did not comply with WHO standards. According to WHO Co-ordinator, Dr. Lembit Rago, "The irregularities found in CROs were serious enough to cause concern about the efficacy and safety of these products. These are products that meet quality criteria but are not necessarily safe or effective. In the case of generics, safety and efficacy is proved through bioequivalence studies."

Quintiles, which entered India in 1997, has already worked on 90 international Phase II and III projects. Ferzaan Engineer, CEO Quintiles India, says the cost of a trial in India is 40% less. However, others point out to as much as 80% lesser costs. SIRO is the largest local CRO with a good track record and many global studies to their credit. Pfizer, Eli Lilly, Novo Nordisk and Aventis have been conducting their global studies according to GCP for many years. Therefore, there are several sites that are familiar with ensuring high quality data for submission to the FDA and CPMP.

The contract research and clinical business in India during 2002–03 was estimated to be Rs 135 crore. Quintiles Spectral, SiroClinpharm and Syngene are the three key independent CRO players here. These three alone account for 71% of the market. The Indian CRO market is currently growing at 20% per annum and has excellent growth opportunities. As on date, clinical research is still a sunrise industry in India and constitutes just 0.7% of the global market, but this scenario is soon expected to change. Analysts estimate that by the year 2010 India would contribute 20% of the global

clinical research industry's revenues. The global market for such services in 2002 was estimated to be $1.2 billion and may grow to $3 billion by 2008. By 2005, India will have full patent protection, removing the last barrier. While the power of promise has raised huge expectations, it is the power of performance that will decide if India is to enter the big league of countries that turn pharmaceutical R&D opportunities into breakthrough therapies.

Another segment which would boost clinical trials is the burgeoning biotech hopefuls pursuing clinical trials of their fledgling products. Different issues surface when providing outsourced clinical trial services to biotechnology companies when compared to drug companies. Pharma companies have large capital bases and infrastructure, and can withstand negative outcomes of research activities. By contrast, biotechs have few resources, limited background experience, very limited cash reserves and restricted capacity to withstand failures. CROs will have to understand these differences and build relationships with customers for this outsourcing industry to grow.

In the 2003 budget, the government took a big step in the right direction by allowing clinical trial samples to be imported without having to pay customs duties. This has significantly reduced the burden on the local affiliates/partners. Customs duty had been a serious deterrent to attracting more studies from sponsors for many years. Resolution of this issue has shown that the government is serious about attracting foreign investments into the country by way of clinical trials.

Medical Dignostic Services: *Path*-finders

The diagnostic industry grew wings when the winds of liberalization started blowing. These services are emerging as yet another outsourcing opportunity for Indian pathology laboratories looking to take on work from overseas hospitals and agencies. The business of pathology has gone through the first phase of corporatization in the last few years and a few players have emerged as clear path-finders.

Pathology is a business with high margins and low entry barriers. A conservative estimate would put the gross margin at about 50%.

There is no licensing requirement and one only needs to follow the Shop and Establishment Act. There are an estimated 30,000 pathology labs in India, more than enough to serve the hospitals in Europe and North America but lack uniform quality standards. A possible downside is that only a few of them have international accreditation like NABL or CAP (Certificate of American Pathologists) that instills confidence about them among foreign hospital chains.

Quest Inc., US, leads the global industry with a topline of $4.8 billion. The six major players who have come out on top riding the first wave in India are SRL-Ranbaxy, Metropolis, Dr. Lal's Pathology, Pathnet India, Wellspring and Thyrocare. SRL-Ranbaxy and Wellspring were promoted by pharmaceutical companies who got interested in this segment. These companies have brought in streamlined quality systems and company processes and have also expanded the reach and menu of tests offered. Most of them have earned quality accreditations from national and international accreditation bodies.

SRL-Ranbaxy reportedly has 20,000 disease profiles and epidemiological data of regions and claims its own intellectual property—it now markets its own tests for an ailment like pyrexia of unknown origin, a low grade persistent fever. The company recently concluded a pilot project for a UK-based hospital and is looking to expand its scope of work in Europe, says Vidur Kaushik, CEO, SRL-Ranbaxy. Kaushik bets that the next big pathology CRO will be from South Asia. SRL-Ranbaxy supports a diagnostic laboratory network across 362 towns in the country. Logistics companies bring in the samples from foreign markets and the reporting is done from India online. Most of these labs use the web-server model to spread their services.

Their services include sophisticated tests for cancer-related diagnosis, auto-immune disorder, cytogenetics or diseases related to abnormalities in chromosomes, infectious diseases and Hepatitis B and C. To import blood samples for testing purposes, laboratories have to acquire a license from the Drug Controller General in addition to approval from the Director General of Foreign Trade. As part of the National Pathology Grid, some of these labs have a network of collection and processing centers across the country connected through an IT backbone and results can be checked by the patient on the internet.

As in the case of clinical trials, laboratories are dealing with critical and often confidential health information. This requires accredited labs and processes that are comparable to the world's best. It may work out about 25% cheaper for the hospitals and agencies outsourcing diagnostic work to India. Given that everything is linked to insurance, quality should be of the highest degree. Dr Sushil Shah, Founder-Chairman of Metropolis Health Services, echoes caution, "Hospitals based in West Asia have been outsourcing their diagnostic work to Indian laboratories, since it works out less expensive in comparison to sending samples to France or Germany. But increasingly, hospitals in markets like the UK are outsourcing their diagnostic services to local path-labs." From the earlier trend where outsourcing was done in radiology, sending across X-rays or images to India for interpretation, foreign hospitals and agencies now outsource jobs such as tissue typing, drug advisory or hormone analysis. But the trend is still nascent and no data is available regarding the opportunity that it opens up.

Monitoring Medical Devices

The global medical device market is worth more than $100 billion, according to a Frost & Sullivan 2004 survey. About one-third of the expenditure on healthcare worldwide is attributable to Asia, and spending here is expected to increase by additional 45% by 2005. The industry is driven by an aging population, increased life expectancy, growing incidence of major diseases such as diabetes, coronary heart disease and stroke, the needs of health-conscious populations and higher disposable incomes. With a total population of more than 3 billion, Asia accounts for about 60% of the world's population and includes highly advanced markets such as Japan, Singapore and Hong Kong.

Although both the idea and the reality of outsourcing medical devices from Asia has taken shape, the practice has been limited to manufacturing thus far. Despite the cost benefits of leveraging the hi-tech capabilities of Asian contract manufacturers by the global companies, outsourcing still poses a substantial logistical feat. Asian-made products must be transported back for sterilization and testing before they are released for worldwide marketing. There is a growing need for medical

device testing support services in Asia. This demand is prompted in part by the growth of medical device manufacturing in the region. The increase in medical device R&D in Asia is also an important driver behind the need for safety testing. A medical device requires evaluation for its quality, efficacy, reliability and safety after manufacture. If the device is implantable, it would further require systematic and rigorous preclinical and clinical studies much like a drug. While performance evaluation remains part of a company's product development efforts and tends to stay in-house, many other testing functions such as material analysis, sterility testing and biocompatibility evaluation are increasingly being shifted to outside labs. The use of contract labs is growing across the board, with large and small device makers turning to outside help. Whether they are seeking expert opinion or just need fast turnaround service, many companies view testing providers as an integral part of their quality systems.

Medical device products must be manufactured, sterilized and tested according to accepted standards and regulatory requirements. Contract manufacturers and sterilizers have been investing heavily in implementing and upgrading quality systems to comply with the latest international quality system standards, such as ISO 13485. Such certification is especially important to those who are venturing into the medical device field. Certification enables them to demonstrate competency, credibility, reliability and knowledge in the area.

Asian contract manufacturers face demands from global clients to exhibit vigilance and take responsibility for both production and sterilization processes, including validation and testing. These changes are likely to be driven by the cost benefits of localizing all aspects of device production in Asia. In addition, testing in Asia would enable original equipment manufacturers (OEMs) to avoid the logistical complexities of delivering time-sensitive device samples to overseas laboratories. Unfortunately, most microbial testing laboratories in Southeast Asia serve the food and petrochemical industries; they are not familiar with medical device requirements and Indian CROs can grow to get a share of this growing market. Contract manufacturers are increasingly turning to laboratories that have a history of testing medical devices. Preferred laboratories are able to provide scientific consultancy and testing recommendations, as well as being widely

knowledgeable in the appropriate testing standards and regulatory requirements for medical devices.

Testing requirements include biocompatibility tests, raw-material characterization, performance tests and microbiological tests for sterilization validation.

Currently, there is a dearth of support services in India to cater to these needs. Consultancy enterprises that assist in the preparation for quality system certification often have little or no experience with medical device manufacturing and provide only generic solutions. Laboratories from the United States and Europe that have comprehensive testing services are appointing Asian representatives to gain a share in the potential market for medical device testing in Asia. These representatives perform marketing and customer management tasks, and samples are submitted to the parent laboratory for actual testing. Besides the standard physical and microbiological tests, chemical characterization is likely to become an important issue in the near future as Part 18 of ISO 10993 (Biological Evaluation of Medical Devices–Chemical Characterization of Materials) moves closer to approval. This standard will cover a wide variety of issues such as measuring the level of leachables, screening of new raw materials, assessment of product safety and detection of batch variation. If widely adopted, the standard would force device manufacturers to provide more laboratory data to regulatory bodies. At the same time, there may be differences over which types of tests would satisfy the standards. Contract labs could play an important role in interpreting the requirements, working with regulators to establish guidelines and even developing new protocols.

The Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, is working towards establishing a national testing center for a whole range of biomaterials and biomedical devices. The institute's existing facility has been certified by COFRAC of France as complying with ISO/IEC 17025 standards with respect to testing services for medical devices. This is perhaps the first laboratory in Asia to be assessed in this manner. Recently, Bhat Biotech India received ISO 13485:1996 certification and is believed to be the first diagnostic and biotech company in India

to receive this certification. ISO 13485 is the certification specifically for medical devices and is the prerequisite for getting CE marking and US FDA approvals.

Although the potential for medical device work is high, there is very little work coming into the country. India lacks any kind of regulatory framework for certification, quality assurance, safety evaluation and post-market surveillance of both imported and indigenous medical devices. Even the Drug Controller of India does not have any mandate to regulate the medical devices market and the use of devices. In the absence of any regulatory framework in which these devices are monitored, it is difficult for private laboratories to develop competency in this area and carve out a market share in device testing.

BIOTECH R&D: THE *GENIE* IS OUT

> "*It seems almost a miracle to me that 50 years ago we could have been so ignorant of the genetic material and now can imagine that we will have the complete genetic blueprint of man.*"
>
> —JAMES WATSON

Biotechnology is a fast emerging sector and is expected to play a key role in the new economy. India has many comparative advantages in terms of knowledge, skills, R&D facilities and costs in this sector. Biotechnology, as an application science, has taken firm footing in countries abroad where a number of transgenic crops, genetically modified food and recombinant therapeutic molecules for human and animal health are available. There has been an emergence of companies like Biocon, Aesthagen, Bangalore Genei, Cytogenomics, Magene Life Sciences, Metahelix, Reliance Life Sciences, Bharat Biotech, Shanta Biotech, Panacea Biotech etc, besides bioinformatics companies. A look at the financial support provided by the Department of Biotechnology (DBT) and other agencies over the years in biotechnology, reflects the majority of the support that has gone into national laboratories and universities. The result is the generation of a good R&D infrastructural setup in public-funded institutions pursuing biotechnology research.

Biotechnology can be divided into three broad areas—human and animal health care, agricultural and industrial biotechnology. Outsourcing of R&D in biotechnology represents a tremendous opportunity for Indian companies to do contract research for overseas corporations. The current global spending on outsourced R&D is approximately $7 billion and is expected to grow at 30% per annum for the next five years. The growing interest in outsourced research and the emergence of start-ups has led to a demand for industrial parks containing a large number of shared facilities for research and development most suited to start ups and contract research activities. Key facilities include clean rooms, gas pipelines, filtered air, wet labs, high-end computers for bio-informatics and protein modeling studies, besides customs clearing, patent facilitation and knowledge centers.

Indian pharma companies possess competitive skills in chemical synthesis and process engineering, which they are leveraging to develop new chemical entities and, with the application of bio-informatics tools, tap into the high potential biogenerics segment. Under the new IPR regime, synergies in pharma-biotech relationships are being successfully turned into opportunities for undertaking international contract research in segments of new drug discovery, clinical trials and bio-informatics related services. Indian bio-informatics companies are playing a significant role in critical areas such as data mining, mapping and DNA sequencing, besides functional genomics, proteonics and molecule design simulation.

While outside India, private institutions are actively engaged in taking up contract research in multi-stage activities towards the development of a transgenic/vaccine/drug or therapeutic, in India the strength is still largely in public-funded institutions. Though some Indian biotech companies have undertaken contract research for American and European labs and industries, they are executing only small modules for them. Globally, major pharmaceutical companies like Abbott, Alza, Cambrex and Genzyme Transgenics are working as contract services and outsourcing companies. Their contracts include:

1. Competence in molecular biology, biochemistry and bioprocessing, mouse genetics and assay development;
2. Bench top R&D;

3. Discovery of new molecular modifications and improvement of existing drugs;
4. High throughput screening for therapeutics;
5. Stability testing, analytical development and validation;
6. Provision of testing facilities including testing in human cell lines;
7. Drug delivery research;
8. Clinical trial services;
9. Clinical trial management, data management, biostatistical analysis; and
10. Designing of facilities for commercial production.

According to Kiran Mazumdar Shaw, MD, Biocon, the biotechnology industry in India will hold a $9 billion market potential by 2010 across various industry segments. "India is fast emerging, not only as a destination—the prime source as well as the market for new generation pharmaceuticals and biotech products—but also as an international hub for contract research and manufacturing," she says.

Bangalore Genei Co. operates in the space of product manufacture for genetic engineering and molecular biology but started undertaking R&D contracts for leading biotech companies and is the mainstay of Sanmar Chemicals, which acquired Genei. Hyderabad-based Magene Life Sciences is aiming to make its mark in the niche bioservices sector. It offers testing services for companies which have developed new molecules. With a lab capacity to test 96 molecules at a time, the company is focusing on generic protein therapeutics.

Reliance Life Sciences (RLS) has been the cynosure of the scientific community since it hit the headlines in August 2001, when the National Institute of Health (NIH), US, approved seven of its embryonic stem cell (ESC) lines for US federal funding. Till date, only about 70 lines from various companies have been approved for funding. Essentially, the embryonic stem cells are akin to nature's blank slates capable of developing into any of more than 200 cell types that make up the human body. Such stem cell research offers the potential to replace "faulty" and "malfunctioning" tissues and pave the way for

curing hitherto incurable diseases. Stem cells, usually retrieved from the core of five- to seven-day-old human embryos, can grow into virtually any kind of tissue in the human body when nurtured properly

Globally, countries are divided on whether ESC research should be allowed to enter the realm of cloning, with the likes of UK, France and Sweden taking the liberal view. But there is no debate on research for development of therapy using ESCs. So private companies are going full steam ahead even as regulators try to keep pace with them to lay down the guidelines for taking laboratory research through animal and human clinical trials. Currently In India stem cell research is carried out at the National Centre for Biological Sciences, Bangalore; National Centre for Cell Science, Pune; L.V. Prasad Eye Institute, Hyderabad, National Brain Research Center, New Delhi and Reliance Life Sciences, Thane.

Dr. William A Haseltine, founder and CEO, Human Genome Sciences, is looking at opportunities to work together with Indian pharmaceutical and biotechnology companies for the discovery and development of new pharmaceutical products. Talking about partnerships with Indian firms he said, "We use collaborations for the development of gene therapy products, small molecule drugs and diagnostic products discovered using our genomics-based technology."

Traditional Medicine: Back to the Future

Public interest in attaining or maintaining health with 'natural' remedies has steadily increased in the last few decades. The demand for phytopharmaceuticals, otherwise known as herbal or traditional medicines, to treat diseases has become a worldwide phenomenon. With the rising popularity of Yoga, acupuncture and the New-Age lifestyle, the Western appetite for traditional or alternative medicine seems insatiable. According to the 2003 WHO report on traditional medicine, 70% of Canadians, 48% of Australians and 42% of US citizens have tried traditional medicine at least once. Such remedies also remain widely prevalent in the majority of developing countries. Eighty percent of Kenyans and 65% of rural Indians, for instance, continue to resort to natural cures according to a WHO report which estimates the global market for herbal medicines to be $60 billion annually. In Europe, the market for botanicals is well developed and involves prescription sales

in some countries. China and Japan also have long traditions of using herbal drugs. In the US, interest continues to rise as more Americans choose alternative medicines and self-treatment approaches to health.

Historically traditional medicines in the US market have been regulated as dietary supplements under the 1994 Dietary Supplement Health and Education Act (DSHEA). Unlike the standard used for prescription drugs, DSHEA puts the onus on the FDA to prove that a supplement poses significant or unreasonable risk rather than on the manufacturer to prove the supplement's safety. The caveat for manufacturers is that, unlike pharmaceuticals and recombinant drugs, dietary supplements can only claim to prevent a disease's symptoms, not cure the disease. The European Union regulates supplements in a similar manner to the US, though the process is faster because a substance's historical use can be used to document its safety and efficacy in the absence of scientific evidence to the contrary.

Manufacturers that opt to designate their products as supplements can bypass expensive and time-intensive clinical trials, thereby getting products to the shelf quicker and cheaper. However, the absence of adequate evaluation and safety monitoring systems for supplements did have serious repercussions in the global market for traditional medicine. In 2000, for instance, the FDA stopped imports of Chinese herbs in the genus *Aristolochia*—used in the manufacture of slimming agents—after reports of kidney failure among users in UK, Belgium and Singapore. More recently, the FDA banned the sale of products containing *ephedra*. Derived from the Chinese herb *ma huan* (*Epheda sinica*), ephedra is an amphetamine-like herb used to promote weight loss and enhance athletic performance. Although the principal active ingredient of ephedra, ephedrine, was banned by the FDA in the 1980s when it was marketed as a drug in combination with caffeine, dietary supplements containing ephedra and caffeine remained on the shelves. Over a hundred reports of ephedra-related deaths, including that of athlete Steve Belcher in 2003, prompted the FDA to ban ephedra.

In December 2003, the European Parliament adopted a new legislation that makes it easier for traditional medicine makers to show efficacy to the EU member nations. For limited therapeutic indications,

and in the absence of adequate clinical data, companies have the option of demonstrating the safe use of a traditional medicinal herbal product for 15 years within Europe, and for at least 30 years in its community of origin. Canada also opened the doors of its new Natural Health Products Directorate in January 2004. In the absence of clinical data, the directorate will now consider entry of a natural remedy if traditional references like translated Sanskrit texts or anthropologically validated oral traditions can prove its use for at least 50 years. While Western regulatory agencies are rethinking their regulatory practices, developing countries are inching closer to Western style laboratory testing and documentation of scientific data.

As regulations change in the West, authorities in developing nations, such as China and India, are introducing regulations to ensure higher safety standards so that consumers will not be deterred from the traditional medicines market. Under the new regulations, Chinese traditional medicine practitioners and herbal pharmacists must have licenses, and manufacturers and herbal farmers must comply with international manufacturing standards (GMP) starting this year. Clinical trials will also be more rigorous, modeled after western regulatory protocols. China's ministry of Science and Technology has dedicated an entire technology park in Houzhou to the scientific study of traditional Chinese medicine.

Hong Kong also intends to become an international center for Chinese medicine before the end of the decade. Its government is funding at least 18 Chinese medicine research projects that include clinical trials, development of quality standards and basic pharmacological studies. Hong Kong is also building a new laboratory devoted to Chinese medicine and has one of the region's only screening centers to identify promising drug leads within Chinese medicine.

The Kanglaite Injection, produced by a Chinese company, has come farther than any traditional medicine towards earning drug approval in the west. Kanglaite is an extract produced from the oix seed (*Semen coicis*), a Chinese food staple. An injectible form of the extract was approved by China's State Drug Administration (SDA) Beijing. Kanglaite has now been used by over 50,000 Chinese patients for lung, liver, breast and several other cancers.

A Himalayan Task

Seventy-four years ago, on a visit to Burma, Mohammad Manal saw restless elephants being fed with a root to pacify them. He found out that the plant from which the root was taken was *Rauwolfia serpentina*. Fascinated by the effects of the plant on the elephants, Manal had it scientifically evaluated. After extensive research *Serpina*, the world's first anti-hypertensive drug, was launched in 1934 by the Himalaya Drug Company founded by Manal. His vision was to unravel the mystery behind the 5000-year-old system of medicine and bring *Ayurveda* to society in a contemporary form. Today, the Himalaya Drug Company has a turnover of Rs 350 crore and is the modern face of *Ayurveda* and is investing Rs 165 crore to set up a new 200 acre state-of-the-art manufacturing and R&D facility at Bangalore. Other companies attempting to reformulate age-old remedies into modern medicine include Avestha Gengraine Technologies, Bangalore which is beginning to clinically validate Ayurvedic cures targeted at obesity and diabetes.

Dr. R A Mashelkar has emphasized the importance of scientific rigor in validating the traditional Indian Ayurvedic and *Siddha* systems. Studies have shown that acetylcholine receptors may serve as receptors for the rabies virus and provide validation for the traditional Indian remedy of *Datura strammonium* as a prophylaxis for rabies mentioned in *Sushruta Samhita*, the ancient Indian classic on the science of life. Under the New Millennium Indian Technology Leadership Initiative Program, CSIR scientists have been collating pharmacokinetic, pharmacodynamic and epidemiological data on Ayurvedic medicines and developing standardized herbal formulations. Randomized, controlled clinical trials for rheumatoid arthritis, osteoarthritis, hepatoprotectives, diabetes, hyperlipidemic agents, asthma and Parkinson's disease are underway to establish clinical efficacy.

A recent article in *Nature Biotechnology* (22, 263) *2004* highlights the renewed interest in herbal products, the world market for which is expected to be $62 billion. The recent boom in research and herbal products is mirrored by an exponential increase in related patents at the US Patent and Trademark Office (USPTO), Washington DC. Between 2001 and 2003, 1,359 patent applications were filed at

USPTO compared with just 1,968 patents on botanicals granted over the past 28 years (1976–2003).

A survey of the 1,359 botanical inventions recently filed at USPTO reveals that around half relate to pharmaceutical products/formulations/compositions. About 55% of these applications originate in the US alone, with other major players being Japan (8.8%), France (5.9%), India (5.1%), South Korea (3.8%), UK (3.6%), Canada (2.9%), Germany (2.5%) and China (2.7%). The most prominent application areas are cosmetics (skin care and sunburn compositions), health protectants (nutritional supplements, antioxidants, laxatives and weight loss agents) and medicines (anti-ulcer agents, antidiabetic agents, antivirals and antifungals, anticancer formulations, anti-allergics and osteoporosis treatment). Significantly, about 13% of the published patents include *in vivo* and *in vitro* validation data, several making use of data based on administration of herbal medicines on volunteers.

In most cases, a pharmaceutical company will purchase raw material from a supplier. For botanical raw material, a company needs a well characterized material with an established supply chain. The herbal raw material can be a specialty item, USP/NF material or a commodity

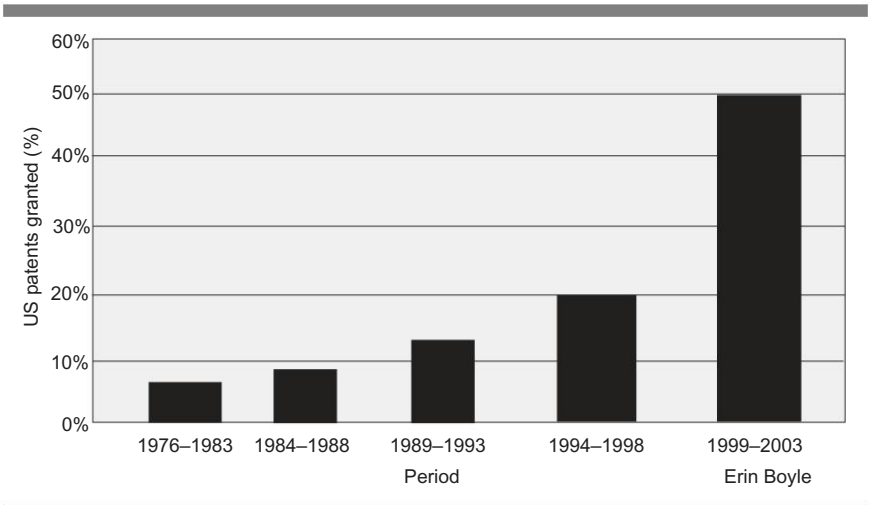


Figure 2.6 Herbal medicine patents granted by USPTO between 1976 and 2005

item. Regardless of whether the supplier is a domestic or foreign company, it is important to determine that the supplier can provide details on how the product was processed, along with a complete certificate of analysis with evidence of written and validated methods. Raw material needs to be traceable, measurable and of pre-determined acceptable quality. Issues that need to be considered include raw material characterization, product uniformity and product shelf-life.

Raw material is authenticated using macroscopic, microscopic, organoleptic and chromatographic techniques. The use of different marine/plant species and/or different parts of the plant (e.g. root versus aerial) can result in significantly different pharmacologically active components. Crude raw material handling such as drying, crushing, storage and preservation conditions need to be considered to ensure product reliability. Common pharmacologically active components of interest consist of the following class of compounds: alkaloids, flavonoids, fatty acids, steroids and terpenoids, to name a few. These active components need to be isolated from the plant matrix.

Analytical experience and state-of-the-art instrumentation is a key component for the analysis of natural products. When dealing with natural products, test laboratories must contend with a complex sample matrix that contains similar chemical compounds. The pharmacologically active compounds are usually present in small amounts. With the increased development and use of natural drug systems, it is necessary to develop highly sophisticated analytical methods to ensure that the natural drug is uniform and pure. It is critical that the integrity of the natural drug components are preserved during manufacturing and that the resulting natural drug product does not contain toxic impurities. Bio-assays are used to determine the biological activity and determine the efficacy of the formulated product. Several types of assay tests are available, including enzymatic, cellular, microbial, metabolic and gene expression. The challenge is choosing the test that will most accurately represent the biological activity of interest. Natural product contract laboratories usually do not have the in-house expertise to perform these tests. They routinely outsource this work.

High standards are necessary to ensure that a high-quality product gets to the consumer. High product quality drives brand strength

which is based on product integrity, safety and efficacy. A testing program should include instrument IQ/OQ, calibration, documentation, review, approval and archival processes for methods, data and studies. Presently, there are few standardized industry methodologies for herbal product testing. The United States Pharmacopeia (USP) has developed monographs for some of the more common herbs; however, these methods are limited in the degree to which they have been validated. The Institute for Nutraceutical Advancement (INA) is an industry-sponsored program that has 12 analytical methods that have been validated by several laboratories for some of the more popular botanicals. The American Herbal Pharmacopoeia (AHP), a not-for-profit educational corporation, currently has 10 critically reviewed monographs that include validated analytical methodology.

This Is Just the Beginning...

Compared with the global CRO market, the Indian CRO market is very small because companies are offering low end services—bioequivalence studies, bioanalytical studies and Phase II and Phase III studies. The industry is divided when it comes to estimating the market size. But most of them believe that the present Indian pharma CRO market is in the range of Rs 200–250 crore. There are about 25 CROs working in India with many pharma companies having their own clinical research units conducting trials in about 80 government and privately owned hospitals.

The awareness about the mega CRO opportunity is a familiar topic these days. But this does not mean that the industry is not confronted with hurdles. Indian companies have their own share of woes while conducting trials on human beings. This, the industry says, is mainly because there is no clear regulatory framework that supports and encourages companies to take up human trials in a proper manner. The implementation of GCP guidelines is uneven. Regulatory (DCGI) approval timelines are high against those in the US. While it takes about 30 days in the US, over here it is about 90–120 days. This puts a crimp in project timelines. However, more often than not, this is made up by the enrollment timelines as the enrollment rates in India are higher than in most developed nations. The challenges

confronting this segment are the unstructured environment in hospitals and lack of CGCP awareness among the large institutions, and a regulatory environment which is not well defined.

The industry is still in its infancy and the challenges are many. The most important selling quality of a CRO, regardless of its geographic location, is its reputation for quality and thoroughness of data. Since flawed data can lead to product approval delays or disqualifications, data quality is a prime consideration in the selection/success of a CRO. The speed at which a project is completed is almost as important since trials are complex and can take years. Wide variations exist in the capabilities of different CROs. This has made it difficult to recruit large numbers of staff and patients for clinical trials.

Pharmaceutical companies have limited experience with natural products chemistry. Their expertise tends to lie with synthetically designed drugs developed in a highly controlled environment. Natural products chemistry is quite different from traditional pharmaceutical work, both from a chemistry as well as a regulatory standpoint. Consequently, pharmaceutical companies have found it advantageous to develop working relationships with contract laboratories that specialize in natural products chemistry. Scientific studies and clinical trials to support claims of efficacy will be essential for the long-term success of any herbal or natural product. Research will separate the winners from the losers. Performing clinical studies, patenting products and developing proprietary or trademarked products are some of the best ways to achieve market protection.

Chapter 3

Off-shore R&D Labs: From Citadels to Clusters

"The best way to a good idea is to get a lot of ideas."

—LINUS PAULING

Much of R&D folklore is built on stories of unexpected discoveries and maverick inventors. Successful R&D in the 21st century is not only judged by what companies discover but how they do so, whether by applying themselves to customer problems, compressing innovation timescales through globalization or allocating research budgets through systematic prioritization of ideas etc. Developing new products, services and business models is the fuel that fires corporate growth in good times and bad. In a world of dwindling natural resources, there is no shortage of human ingenuity—just ask the overworked US Patent and Trademark office. It registered over 350,000 patent applications in 2003, while granting over 180,000 patents for inventions deemed "new, useful and not obvious". But there is often a yawning gap of time, investment and energy between an initial bout of inspiration and a product's entry into the market. The level of uncertainty and risk unnerves executives, who know that new products are the life-blood of their company and that the marketplace is increasingly unforgiving of delay and deficiencies in product development.

Off-shore laboratories are not only exploring areas of research in the domain of expertise they focus their efforts on, but they also reflect

the parent firm's planning, execution and exploitation of human capital in the most innovative ways to increase their global competitiveness. The challenge for low-cost countries and for multinational corporations is to achieve the clear benefits of global free markets, while seeking to offset their inherent imperfections. Success comes not by chance. It is the result of the right thinking, sustained hard work and a systematic and logical approach to any problem. Here is an opportunity for global companies and for those companies aspiring to be global, to create, again, a fresh wave of post-genome and post-internet breakthroughs using global human capital. Asia is bound to play a major role in this fresh wave of globalization.

Houses of Magic

Industrial research was born out of the German dye industry in the 1870s when scientists and engineers were hired into companies to change the prevailing hit-and-miss existence. Finding new colors was necessary for survival. By institutionalizing the hunt for these new colors, German companies were able to ensure their future stability. It turned out that the same chemical processes used to find dye-stuffs and colors could be used to make heavy chemicals, pharmaceuticals and photographic film. Those companies, which pioneered original research (Bayer, Hoechst, and BASF) are still around 135 years later.

In many ways, the US set the tone for what corporate industrial research should be. It was companies like DuPont, AT&T and General Electric (GE) which set the trend. The first great lab was General Electric's. The idea came from Charles Steinmetz, their chief engineer and a renowned mathematician. He convinced the corporation to fund the research lab in order to protect its lighting business. The lab went through the same traumas that we saw in the corporations in the 1990s. It was disconnected from the rest of the company, trying to conduct cutting-edge research in a vacuum. It was almost eliminated because the rest of the company noticed that it was not contributing to the bottom line. So the lab instituted programs to get closer to the business divisions and learn more about these businesses. From that springboard, while also proving their worth on relatively small-scale issues, they were able to explode into the future with tremendous advances in radio, medical imaging and other

areas that still form GE businesses today. The lab became so famous that by the 1930s it was known as the "House of Magic". The House of Magic show went on the road all over the country.

World War II started another era in the evolution of industrial research and development. Scientists emerged from the war as national heroes and keepers of the future. As the Cold War heated up, research at universities and in industry received unprecedented federal funding. A lot of this funding was for basic research, enabling labs to grow even faster. Scientists enjoyed a unique freedom to pursue ideas. Over the next two decades, as US firms in autos, steel, consumer electronics and computer memory chips found themselves out-innovated by a host of Japanese and European companies, as well as start-ups like Apple, Cisco and Microsoft, the need to transform research models of big corporate houses became apparent.

A different view of industrial research very slowly took root in the 1980s. New organizational structures and/or changes in organization kept occurring as the crisis accelerated in the first half of the 1990s. There was a blaze of across-the-board cutbacks and layoffs. Funding for basic science was slashed and general turmoil prevailed. Major players were focusing on the 'D' side of R&D, forsaking the more fundamental 'R' work that creates the breakthroughs needed to spawn new industries. One of the big changes, almost across the board, was a change in the way research was funded. Instead of a central funding mechanism, many labs went into contracts with business divisions for big pieces of their budget, if not their whole budget. This meant that they did not get money for research unless the business divisions funded it. And they were going to fund it only if the labs were doing something strategically relevant to the business divisions. This plan came with its own set of risks but did have a lot of pay-offs. It forced researchers to think more about market needs and realities, and understand, to a much better degree, how business and the real world works. Consequently, industrial research came closer to its original aim of applying science and technology for the advancement of industrial goals. Industrial labs have become better at targeting research on areas of corporate strategic interests, both long-term and short-term. They are much more adept at working with customers inside and outside the company and are probably better positioned to be the engines of

tomorrow, which is vital in the ever intensifying global competition for long-term survival.

R&D units in international firms were more portfolios of knowledge islands rather than globally integrated knowledge networks. Integration into the global economy opens up more choices than it closes for R&D. In hi-tech industry, belt-tightening has pushed companies to find cheaper alternatives to conventional research. The National Science Foundation reports that the US accounted for 44% of the total R&D among the Organization for Economic Co-operation and Development (OECD) nations in 2001, more than the rest of the G7 nations combined. A study by Massachusetts Institute of Technology's *Technology Review* magazine found that most leading companies in struggling industries—aerospace, computers, semiconductors and telecommunications—had trimmed R&D outlays. They haven't turned their backs on innovation; they've just farmed it out. R&D models have shifted away from the supply-side approach of big firms funding ambitious projects that create large barriers to entry, towards a demand-driven approach focussed more on speed and need. A more market-oriented approach to R&D started taking root, driving closer collaboration among researchers, partners and customers. Although many companies retain a central R&D unit to take a longer term research perspective, R&D funds now tend to be distributed across a mix of business units and basic programs that resemble stock portfolios in terms of their time scale, risks and expected returns. Competition for talent, new technologies and easier market access has accelerated the process of R&D globalization with countries such as India and China.

Why Innovators Go Off-shore

> *"There is a tide in the affairs of men which, taken at the flood, leads on to fortune."*
>
> —William Shakespeare in *Julius Caesar*

Multiple factors are encouraging the acceleration of R&D and knowledge work in other parts of the world. Increasing R&D dispersion

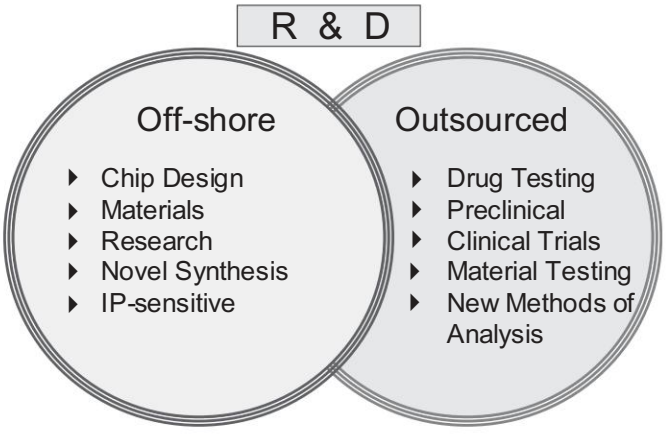


Figure 3.1 India rank's no 1 in both off-shore and outsourced models

arises both from the increasing dispersion of programs within firms to their off-shore locations, and also the increasing level of outsourcing. According to one estimate, in 1996 MNCs from major OECD countries carried out an average of 15–20% of their R&D abroad. Another survey of all new R&D sites established by 32 multinational companies showed that these firms established more new R&D sites abroad during the last 10 years than in the previous 30 years. From Bangalore to Beijing, R&D organizations are splitting research and design work, distributing it around the globe and reassembling the results. Leveraging and mobilizing knowledge across organizational units can create significant economic value. Here's why:

1. **Cost:** Research and other technical talent and facilities cost appreciably less in many areas of the world. Similarly, many foreign nations offer business researchers significant financial incentives to locate R&D units, technical services and manufacturing within their borders. Cost is a driver of globalization too, but its significance can be overplayed as far as R&D goes. Although there are clear economic reasons for locating certain R&D work in lower cost countries, relocating R&D centers solely because of

labor costs is a losing proposition. More important to the globalization trend is the ability to innovate and conduct scientific experiments and collect data round the clock. Speed of development is the most important benefit of the global research economy. "There is no such thing as low-cost intellectual property," declares IBM's Dr. Horn. Aside from travel, co-ordination and communication expenses, the labor rate itself is climbing as recipient countries become more sophisticated economies. The current rule of thumb among India's hi-tech professionals is to expect a 15% pay rise every year. But it is no small task to manage this process. Once infrastructure and co-ordination costs for managing distributed R&D facilities are included, the total savings may not be as huge as popular headlines suggest.

2. **People:** The wide spectrum of skills required to do advanced research in high-technology areas requires a large pool of advanced degree holders from many disciplines in science and engineering. There are many highly talented researchers and technical workers amongst the six billion people on the planet. China and India are graduating more physical science and engineering students than the US every year. US and other Western companies facing global competition want to tap the best and the brightest wherever they may live. The GEs, Microsofts, IBMs and others like them are investing heavily in new research facilities at emerging technology clusters in India, China and elsewhere.

3. **Market Access:** Many business leaders are attracted to the perceived market possibilities in rapidly developing nations such as China and India, with over 2.4 billion people between them. Proximity to customers is often essential to compete for service sector business. Other companies believe they need to globalize their research efforts to overcome foreign governments' impediments for doing business (standards, VAT etc) to ensure that they can gain needed approvals in the future (merger approvals etc.).

4. **Customer Focus:** If constructive interaction with technical experts is vital, collaboration with customers is also being seen as increasingly critical. No matter where they sit in the value chain, differentiation boils down to how firms optimize three types of

knowledge—domain knowledge of a particular technical field, process knowledge for innovating faster, better and cheaper than the competition and customer knowledge of what the end user demands or will demand. Very few can claim world-class expertise in all three areas, hence the drive to collaborate with customers at the concept and prototyping stages.

Henry Ford once quipped that if he had listened to his customers, he would have invented a faster horse. In 1997, Prof. Clayton Christiansen joined numerous boardrooms by arguing, in *The Innovator's Dilemma,* that listening too much to customer input is a recipe for disaster. Somewhere between circumspect views and sugar-coated management treatises about becoming intimate with customers, the voice of the customer and mapping of customer needs is critical for consideration in the selection of off-shore locations, and executives must balance these often contradictory priorities.

5. **Infrastructure:** Several governments are making their own investments is Technology Parks, Knowledge Parks and also in University and laboratory support facilities, transportation, energy and telecommunications to more effectively conduct capital intensive scientific work as efficiently as at the company's headquarters. It is no accident that the new global clusters attracting the most foreign investment and most knowledge work are those with the most advanced infrastructures.

6. **Business Climate:** A great number of top-tier innovation companies explain their moves to Asia by pointing to their less burdensome taxation, regulation and litigation environments. These reflect both bottom-line and speed to market concerns, although many appropriately question whether nations lacking in freedom and robust intellectual property rights can sustain innovation leadership over a longer period of time.

7. **Proximity to Off-shore Manufacturing:** Unlike IT jobs, R&D jobs may be pulled abroad by off-shore manufacturing. Semiconductor industry experts, for example, indicate that chip design work needs to happen close to the manufacturing facilities. Thus, the movement of manufacturing work portends

the movement of more innovative activities. Those activities, which require process development moving from bench scale to pilot and plant scale trials, need to be co-located with the manufacturing unit for effective technology transfer. Likewise, several companies which are sourcing raw materials or intermediates for global operations would require laboratory facilities in host countries to check the quality, safety or regulatory compliance.

Production engineering is an area that lends itself to off-shoring. Given the fact that many mass production facilities are located in developing countries, it makes sense to conduct process R&D (how to produce the same unit more cheaply or more units for the same price) close to the facility where the units are being made.

8. **Strategic Intent:** At innovative firms with geographically diversified operations, evaluation of the strategic and operational effectiveness of divisional or off-shore units depends on the clarity in definition of roles within the larger corporate system. In the domain of international management, research has shown that the decision to enter foreign countries depends on the firm's existing capabilities at the home country base as well as on the firm's absorptive capacity for knowledge in the respective foreign country.

A majority of these off-shore units are intended to *augment* or *exploit* the established capabilities of the off-shore operations.

When the intended role is *capability-augmenting,* the establishing firm hopes to tap into the work of others in the community by capturing some of the spillovers from universities and competitors. If the objective is to create new capabilities within the company, then there is a strong motive to start an off-shore unit, which would cost much lower than one in the home country. To facilitate that, the unit is more likely to be led by someone recruited from the country in which it is situated and whose prior experience took place outside the parent company. In other words, someone with existing ties to other local technological institutions, academic or industrial. Similarly a higher proportion of staff at the unit will hold a Ph.D, a proxy for easier access to the technological community outside the unit. Finally, managers in such a unit will encourage some joint activity with local academic institutions.

For their part, *capability-exploiting* sites are established in close proximity either to factories or markets, or both, and help the local businesses to expand the market through application development work. These units facilitate the transfer of knowledge from the locus of knowledge creation to the locus of production and revenue generation. In other words, capability-exploiting sites help the firm identify opportunities for existing knowledge as well as the need for creating new knowledge. But there are also areas of R&D that concentrate on extending an existing product line's 'functionality', producing it at a lower cost or stripping out certain features to reposition it in another market. These projects tend to be done in a lower cost country rather than in the originating country. If a capability exists in a low-cost country through a service provider in a ready-to-serve form, better management control is the driving force for setting up these competencies.

Some parts of the R&D process are likelier to be done remotely than others. There are times when a company intends to change its basic R&D direction. Fundamental shifts in research direction rarely occur without high level buy-ins from corporate management. Hence, these decisions are less likely to occur far from the home office.

In his paper, "Knowledge Flows Within Multinational Corporations", published in the *Strategic Management Journal* in 2000, Gupta developed a comprehensive framework for understanding the factors that constrain or promote knowledge sharing within multi-unit organizations. He identified three main components of the knowledge sharing process: discovery, motivation and transfer.

1. *Discovery* refers to the process where potential sources and targets of relevant knowledge discover each other, which is often a challenge in large and geographically dispersed corporations.

2. *Motivation* refers to the process where both sides of a potential knowledge sharing dyad have intrinsic or extrinsic incentives to exchange relevant knowledge. It was found that units with superior knowledge that might benefit peer units often have strong incentives to hoard their knowledge so that they can preserve and enjoy the intra-firm monopoly advantages that superior knowledge may bring. On the other hand, many potential

beneficiaries of incoming knowledge often suffer from ego defense mechanisms such as the 'not-invented-here' syndrome. Companies also have to take pains and invest managerial resources to transmit thier culture throughout their global reach, aiming to build common values and ways of thinking to create a corporate culture among their leaders.

3. *Transfer* refers to the process mechanisms through which relevant knowledge actually gets transferred from a source to a target. While codified knowledge—such as numbers, formulae, computer code, and blueprints—is often easily transferred using technology, Gupta found that much of the most valuable know-how is often tacit and can only be transferred through a combination of direct observation and hands-on training under the guidance of those with superior know-how.

The traditional approach to technology transfer is to treat it as a simple problem of transferring information. In the research field, pouring new knowledge into people's head like water from a pitcher to a glass is hardly viable. That kind of knowledge transfer might work for incremental innovations, but when it comes to pioneering research that fundamentally redefines a technology, product, work process or business problem, it is never enough to tell people about some new insight. It requires creating communication techniques that actually get people to experience the implications of an innovation.

Gupta's most recent study looks at the extent to which US multinational companies, when deciding where to locate new R&D facilities in foreign countries, consider the potential to capture 'knowledge spillovers' from competitors with R&D facilities in the same host countries. When firms are deciding where to put a new R&D center, they naturally look at the local workforce and other so-called host country factor endowments. Gupta's study found persuasive evidence that companies are also aware of the possible knowledge spillovers they can capture from competitors, and factor in this possibility when deciding where to locate new R&D facilities. This 'inter-firm' type of knowledge sharing can happen when employees of one firm leave their positions to work for competitors.

The India Experiment

1988

> *"How real are the present trends in India and China?..? Do these changes mean (since most of us who have had the privilege of working with Indians know the tremendous intellectual power of that nation) that India will begin to play the role in the world which many of us have expected and foreseen?"*
>
> —Sir John Harvey-Jones, Past Chairman, ICI Plc, UK in *Making it Happen*

2001

> *"The real benefit of India turned out to be its vast intellectual capability and enthusiasm of its people. We found terrific scientific, engineering, and administrative talent that today serves almost every business at GE."*
>
> —John F. Welch, Past Chairman and CEO, General Electric Co., USA in *Straight from the Gut*

2003

> *"Growth is only just starting, but the country's brainpower is already reshaping Corporate America."*
>
> —The Rise of India, cover story in *Business Week,* Dec 8, 2003

Blue Chip Designs

India has become a critical factor for the international big boys of chip design like Texas Instruments, Motorola, Intel, ST Microsystems and Cadence Design. Companies in the electronic design automation tool

space as well as in the chip design area are continuing to expand their presence off-shore. [Intel, which set up its India design center in Bangalore in 1998, built a new campus and employed over 2000 engineers in 2004.] Intel Inc.'s Bangalore campus is leading worldwide research for the company's 32-bit microprocessors for servers and wireless chips. "These are corporate crown jewels," says Ketan Sampat, Intel India President.

One of the most successful fundamental research establishments has been Texas Instruments, which began its Asia Pacific R&D chip design center at Bangalore in 1985. In 1995-96, it developed a digital signal processor (DSP) that has captured 50% of the world market and more recently released the world's fastest DSP. The 900 engineers at Texas Instruments' Bangalore chip design operation boast of 225 patents.

Cadence Design systems will expand its R&D facility at Noida by adding 300 engineers to its existing 300 plus strong staff. ST Microelectronics' advanced design center at Noida will become the company's largest facility outside the US, employing 1500 engineers. Motorola employs about 250 engineers at its chip design center. Agilent Technologies recently opened a system-on-a-chip design center which will be staffed with approximately 50 engineers. R&D is expected to be in the areas of wireless solution systems and device drivers for electronic products.

Automobile Giants on the Fast Track

General Motors' major research facility is in Warren, Michigan, USA and the company recently established a science lab in Bangalore. One of General Motors' newest research projects is to make a digital version of the human body, which would ride in virtual cars in computerized crash tests. But this crash-test dummy of the future isn't being developed by workers at GM's famed Warren Technical Center, Michigan, where the car maker's research has been conducted for decades. Instead, it is being developed at the new science lab in Bangalore. The lab is eventually expected to employ about 100 Indian researchers with expertise in software, electronics and materials science. The India

Science Lab will focus on projects that complement the research programs ongoing in Warren and will also undertake new exploratory projects of high value to GM.

Several other automobile majors are on a fast track to set up off-shore development centers in low-cost countries. Fiat is the latest international car maker to make India its R&D and production hub for volume cars. As per a Fiat India spokesperson, "There are around 70 engineers on this new research team in India, which will help us transform the Indian unit into an R&D hub for Fiat worldwide." Suzuki and Hyundai announced similar plans for their respective Indian operations. While Hyundai has already shifted production for its small car to India, Suzuki is using Maruti as the research hub for its future small car models.

Pharma Majors Discovering Better Health

Will the CRO route for new drug molecules and clinical trials also extend to MNC off-shore units in the pharmaceutical industry? A host of foreign generic majors are quietly ramping up their presence in India. This includes setting up large-scale manufacturing facilities, hiring scientists by the dozens and, in short, trying to beat India's off-patent drug manufacturers at their own game. The drugs developed and manufactured by the Indian arms of these companies are destined for US and Western European markets for off-patent drugs, where Indian companies have become the lowest cost players.

The Eli Lilly research facility at Gurgaon is its largest in Asia and the third largest in the world after US and Canada. Pfizer's new India facility at Mumbai conducts 5–6 phase II/III clinical trials every year. Astra Zeneca plans to increase its process R&D group in Bangalore with 50 more scientists plus associated support staff. Astra Zeneca will now have discovery phase R&D, process R&D and a manufacturing facility. In 1999, Novartis commissioned its process R&D lab at its Thane plant for scale up technologies. The plant will aid the parent company in developing product dossiers for off-patent generic formulations. The $3.8 billion worth Teva, the world's largest generics company, has hired about 30 scientists at Faridabad to work on the

chemical synthesis of generics and will soon be moving to its own R&D center. Ratiopharm, a leading German generics player, will house a formulations development and stability control laboratory in Goa employing over 100 scientists. Canada's largest generics company, Apotex, is investing about $10 million in a manufacturing facility and research center at Bangalore. Other MNCs are testing the waters. Many of these companies came in quietly some years ago. They began sourcing drugs and stepped up their operations only recently. The reasons are obvious—low manufacturing and product development costs and the ability to hire scientists quickly. The centers they have opened are still small. But slowly, more critical jobs are being entrusted to Indian centers

Tyco, which makes electronic connectors, wire harnesses, cables and radio frequency and wireless systems conducts its high precision tooling at its strategic tool shop at Kochi. Delphi, Hewlett–Packard, Heinz, Daimler Chrysler and Honeywell have set up research facilities in the last five years. For some, like the $12.6 billion Akzo Nobel's car refinishing business, the center came up even before the company began selling its products in India.

Together with the laboratories set up before 1997, the total number of MNC R&D facilities in India today is nudging the 100 mark. The trend is worth noticing as the country aspires to the world's largest R&D destination. The total investment in the 100-odd MNC research labs in India over the last five years has been $800 million–1 billion.

Bringing Good Things to Life

The GE India Technology Center, Bangalore, is General Electric Co's first and largest R&D Center outside the US. The center employs about 1600 scientists and engineers. About 700 of them are attached to GE's corporate R&D and the rest belong to individual businesses such as GE Medical Systems, GE Plastics and GE Transportation Systems. Nearly 25% of them have Ph.D.s, 38% have Masters degrees and one-fifth of the scientists have studied abroad and returned to India. Guillermo Willie, Managing Director of the Center, says, "We

are reversing the brain drain." The focus of the center is to enable the growth of GE businesses through innovation and the use of cutting edge technologies. The teams add value to the GE customer experience worldwide, through research and development in high-impact technology areas like Electromagnetic Analytics, Engineering Analysis, Computational Fluid Dynamics, Composite Material Design, Color Technology, Additive Technology, Non-Destructive Evaluation, Corrosion Technology, MEMS, Molecular Modeling, Power Electronics and Analysis Technologies. "We have a healthy mix of programs where you can quantify the benefits and programs in which GE is taking some risks in the expectation of significant pay backs," Willie says. In transportation, critical parts of GE's next generation hybrid locomotive could well roll out of the hands of the Indian team working on fuel savings technologies for transportation systems. Hybrid locomotive technology involves marrying the use of diesel and electric power to reduce emissions by up to 40%. The center also has a team that will develop engine control systems and electronics.

At least 30% of the GE's global R&D for plastics is being done out of Bangalore, including providing advanced materials characterization support for customer-related issues. GE Plastics supplies advanced plastics materials, which find room as interior and exterior automotive body parts. GE materials are used as body panels in *smart cars*. "A car for two people and a pack of beer." That is how critics describe "smart", the Micro Compact Car (MCC), a joint venture of Daimler-Benz. The smart car departs from conventional automotive design logic. This new product, aimed at frayed nerves and urban congestion, is 40% shorter than most European sub-compact cars, is capable of being parked perpendicular to sidewalks and has an all plastic body. The weathering performance of plastics of all such materials is studied in a $2 million artificial weathering facility at the Welch Technology Center. Two-third of the plastics 300-member team is working on the building blocks or fundamental research on molecules that could result in new kinds of engineering plastics.

GE Motors lab has developed an almost noiseless motor for GE's most sophisticated washing machine lines in the US—Profile and Hot Point. GE Motors India is also the sole sourcing point for a million of these motors a year. Incidentally, "noiseless" is GE's USP while selling

these washing machines in the US. Most motors have a clutch that makes the noise. The challenge here was to develop a motor without a clutch.

Akzo Nobel lab in Bangalore, which employs around 70 paint technologists, is also busy proving its mettle with the parent company. Its mandate: to develop new car paints that are economical to use. Besides improving on existing products, the facility provides the core technology based on which the parent company develops paints for other Asian markets. The center has developed a paint that is being tested in 20 locations. Akzo Noble researchers have made the first batch of paint for the aftermarket which is currently undergoing trials.

Knowledge Process Outsourcing (KPO) in R&D is another area that involves business processes that require scientific expertise and high end talent such as scientists and engineers and other highly skilled professionals. Some examples of services in the KPO domain are IP research, R&D in pharmacy and biotechnology, data mining etc. Writing patent applications in the US is expensive and a typical application costs between $10,000 and $15,000 for drafting and filling with USPTO. In an off-shore mode, an IP specialist can produce a preliminary draft of a patent application, which is then reviewed and modified by a registered US patent attorney who ultimately files it with the USPTO. This can result in cost savings of up to 50%. Many of the off-shore R&D units, like GE and Honeywell also have Intellectual Property Divisions attached, which create global hubs for parent companies with minimal additional infrastructure costs.

Underwriters Laboratories Inc.: Setting Safety Standards

In a world filled with uncertainty, it is assuring to know that we can rely on standardization to provide some sense of safety and security. While Underwriters Laboratories Inc. is respected as an independent, non-profit organization based in the US that provides global testing and certification services, it is also a leader in standards development. Through more than a century of involvement in standards and conformity assessment, UL's safety standards are used throughout the

world to evaluate and certify products and systems for the US market. As UL's standards continue to be used as the basis of harmonization with other international standards, they will increasingly be used for markets around the world.

UL Inc. announced its plans to tap the opportunity presented by India's emergence as a global manufacturing and outsourcing hub to increase its business in the country. With conformity to global safety and quality norms being a necessity for companies aspiring to compete internationally, a UL certification will almost be a prerequisite. The auto components, medical and electrical equipment and the IT hardware sector are targeted key drivers of UL's growth in the Asia Pacific region. In India, the company plans to double its target business categories to 500 and double its headcount as well over the next two years. The company tests 18,000 product categories worldwide.

While companies setting up captive units in India and those entering the export market are immediate target customers for UL, India's growth as an outsourcing destination for large international retail and manufacturing companies will in turn drive companies in India to seek a UL certification. UL has introduced product-testing programs in India that allow companies to seek certification to market in countries such as the US and Europe. Earlier, products had to be evaluated in labs outside India to ascertain their conformity to global norms. The availability of these tests in India will considerably reduce the cost and time to market.

"The Indian market is currently growing at an average annual rate of 7%, part of which is spurred by the revival in the manufacturing sector. Indian manufacturing has so far been recognized for its excellent design capability. The industry has now acquired confidence in production capabilities and is ready to foray into the global market with cost competitiveness and quality. UL is uniquely poised to test and certify products as per international standards, in order to propel their companies into the global marketplace," said Sanjeev Jesudas, President and Managing Director, UL Asia Pacific.

The increase in the range and volume of exports from India is another captive growth segment for UL. Large US and European companies have specified UL certification as a prerequisite for entering into outsourcing agreements with their Indian counterparts.

UL has made significant investments in establishing its product-testing network and building a team of technical engineers across the country to facilitate delivery of a truly global product.

UL set up its India office in 1997 and over the years, has acquired a large client base across industries. UL's global clients include APC, 3M, Siemens, IBM, Samsung, General Motors, DuPont and Dow Chemicals among others. The India office has recently been assigned to oversee and support markets including Singapore, Malaysia, Australia, New Zealand and South Africa.

Why R&D Is a Big Deal

MNC participation in India is crucial for one reason—India currently spends only 0.8% of its Gross Domestic Product (GDP) on R&D. The new Science and Technology policy announced in January 2003 commits raising investments to 2% of the GDP by 2007. This target will most certainly be missed without private sector participation, particularly from foreign majors. This is because while the private sector incurs 60–80% of the total R&D expenditure of most developed nations, in India, it is the government that makes over 80% of India's total R&D expenditure ($3.15 billion). So, there is a huge gap to be bridged because, by 2007, India will require $7.78 billion in investments in R&D to hit the 2% mark.

Clearly India is nowhere near the big league yet. But it is certainly emerging as a serious contender as a base for new off-shore R&D centers. However, unlike manufacturing, R&D does not have a major impact on the national income. For instance, the 100 new labs in India are investing anything between $200 million–$300 million every year. That is only about one-tenth of India's $3.15 billion (Rs.15,000 crore) annual spending. Moreover, R&D, by its very nature, does not create as huge a number of jobs as manufacturing does. If MNCs continue to base their research activity in India, it may foster a movement that could put us in the league of some of these nations.

Unless the research investment made by foreign companies deliver results, the India experiments may end with a whimper. But so far,

there has been a mixed bag of commercial successes, promising prototypes, as well as outright failures. It would be a big mistake to believe that all the research labs in India are at the cutting edge of technology. A majority of them are doing just development research, i.e. developing or improving on existing products.

Emerson Electric's President believes mechanical engineering is also India's key strength. Emerson has 110 engineers in Pune catering to its global process control requirements.

For more research labs to come up, India will have to offer an irresistible reason for multinationals to base their research here. CSIR's Mashelkar believes that India has the greatest opportunity in areas like Infotech (both hardware and software), chemicals, pharmaceuticals (including customs synthesis, contract and clinical research), biotech and genome-based research. We can strategically promote economic growth if products of knowledge are centered in India. Mindware and chemistry are our greatest strengths, and India's bio and genetic diversity can be huge draws. "That is what we must capitalize on," he says. But talent alone won't be enough to attract fundamental research unless India can offer the advantage of clusters for benefits of collaborative research. When you have centers like these, they become so powerful in their sector that they could make or mar a company's future product development strategy.

> *"Now, here. You see, it takes all the running you can do, to keep in the same place, if you want to get somewhere else, you must run at least twice as fast as that."*
>
> —LEWIS CARROLL
>
> *THROUGH THE LOOKING GLASS*

Despite the advantages, however, there are looming threats. Reports suggest that countries such as China, Russia and Malaysia, which have at least one or both of India strategic advantages of a cheaper workforce and talent pool, are already making pre-emptive bids to grab a slice of the MNC's global R&D investments. And India's advantage of an abundant supply of English-speaking people may be momentary.

China has already made English mandatory in primary education, which means that in a few years China too will start churning out English-speaking talent. Besides, other countries such as Canada and Singapore, through their government-initiated active programs to invite investments into R&D, are also emerging as serious competitors to India. However, as of now, the balance continues to tilt towards India as investment continues to pour in and the list gets longer.

Enter the Dragon: The Chinese Challenge

China is fast becoming a competitor to India as a destination for off-shore R&D units of multinational companies. After two decades of pursuing hi-tech investment, China is now home to dozens of multinationals R&D centers. Almost all the global giants in automobiles, telecommunications technology, computers, software, machinery, electronics, biotechnology, pharmaceuticals and other major industries have made hi-tech investments here. These companies include General Electric (GE), General Motors, P&G, Unilever, Microsoft, Intel, IBM, Motorola, Siemens, Ericsson, Nortel, AT&T, Lucent Bell and Samsung.

Even Japanese firms, which have been conservative in investing in China, have increased their R&D spending substantially. Since 2001, at least six major Japanese firms—NEC, Oki Electric, Sony, Toshiba, Hitachi, Fujitsu and Matsushita Electric—have either set up new R&D centers or concluded R&D joint ventures with Chinese partners. These projects involve work in integrated circuit design, system software, cellular phones and other digital products.

Such intense R&D activity, low- and hi-tech, has propelled China to the world's number three spot in terms of R&D spending, according to a report published by the OECD in October 2003. In 2001, OECD said China's R&D expenditure reached $60 billion, after the US ($282 billion) and Japan ($104 billion). About 60% of such spending came from domestic and foreign firms and the rest from the government.

Bayer built its R&D center to support the group's $500 million-a-year business in China. Bayer is building a $3.1 billion polycarbonate plant at the Shanghai Chemical Industrial Park and a $10 million

Material Sciences Polymer Research and Development Center in Shanghai's Zhangjiang hi-tech zone. The lab is built using the chemical giant's well-known material *Makrolon*, a high-tech plastic used in many everyday items such as cellular phones, pipes, sports gear, engines and eye glasses. The center, opened by German Chancellor Gerhard Schroeder and Chinese Prime Minister Zhu Rongji in November 2001, is a showcase for the Bayer group in China. It has four labs testing and developing technologies for polyurethane raw materials, plastic coating, rubber and other new materials. It has sophisticated equipment and researchers with doctoral degrees, just like Bayer's labs in Germany, the US and Japan. Bayer's center is the new face of foreign investment in China, hi-tech and knowledge-intensive—a far cry from the image of China as a sweatshop of low-skilled labor and cut-price services.

General Electric's China Technology Center in Shanghai is another example of market-driven, off-shore R&D investment. Last November, the conglomerate consolidated its various R&D units to form the center to help the group reach its sales target of $5 billion in China by 2005, up from $3 billion in 2003. The $64 million, 28-lab facility is expected to double the number of researchers to 1200 by 2005. Its job is to develop technologies in advanced manufacturing, electronic and photonic systems, medical imaging and new materials—sectors in which GE has a booming business.

"This new center is at the heart of the strategy to meet our revenue target of 2005 because it brings advanced R&D, broad-based technology sourcing and a means to attract and develop the best talent," says Steve Schneider, Chairman and CEO of GE China. General Electric's China Technology Center in Shanghai is one of the group's three off-shore global R&D centers—the other two being in Bangalore and Munich.

Multinationals are beefing up their off-shore facilities because of the demand of the fast-growing mainland market. Two decades ago, technical centers and outsourcing of R&D work to local researchers were sufficient to solve problems that emerged in the still small Chinese market. Now, it has grown too big and too important. Once production reaches a certain volume, manufacturers will face R&D

problems that need to be resolved promptly and locally. They will also need to come up with new product features to meet the fast-changing tastes of Chinese consumers. BASF has two application centers in Shanghai, one to develop leather and textile chemicals and another for organic pigments. Rohm and Has recently announced that it will build a major research and technical center in Shanghai. When the center is fully occupied, it will employ about 225 scientists.

Many of these centers may not handle cutting-edge technologies. Local labs usually work on adaptations to suit the critical-to-quality (CTQ) specifications of local customers. The trend is for R&D centers in China to move up the technology ladder. More and more multinationals are involving their China labs in advanced product innovation and even basic research. Multinationals are putting up R&D facilities in China because of country's big pool of low-cost researchers and engineers. The OECD study estimates that China has 743,000 people involved in R&D, compared to 1.3 million in the US and 648,000 in Japan. One issue that is holding back some companies from relocating more R&D work to China is the country's weak enforcement of intellectual property rights. Piracy is rampant in China, especially with software and industrial designs.

Vertical Limits

Drug companies, many of which were founded in the nineteenth century, are still vertically integrated. This means that they usually have dominion over all aspects of the drug development process, from research in drug target discovery and medicinal chemistry to preclinical experiments, toxicological testing and clinical trials. Gary Zweiger, in his book *Transducing the Genome,* makes some interesting analogies between the computer industry and pharmaceutical companies. Computer companies were also vertically integrated at one time

In the early days Unisys, Amdahl, IBM, Digital, Commodore and Apple practically built their computer systems from scratch or sourced various parts from an exclusive vendor but that industry underwent a transformation in the 1990s. Intel made most of the central

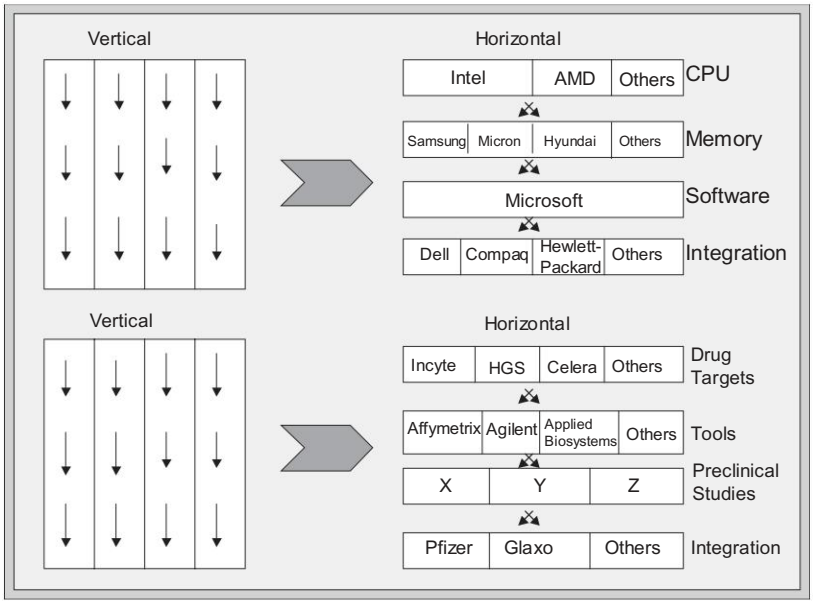


Figure 3.2 Shift of workflow in computer industry from vertical to horizontal integration. Pharma industry may undergo similar transformation (From *Transducing the Genome*, Gary Zweiger)

processing units, Microsoft made most of the software and a variety of different companies produced the disk drivers, memory chips, monitors and other components. Finally, an end-manufacturer bundled them all together and marketed the computers as Dell, IBM, Compaq, Hewlett-Packard and so forth. The horizontal stratification probably helped the computer industry achieve greater efficiency, lower prices and more rapid advances. Perhaps, the pharmaceutical industry may also undergo such a transformation and makeover.

Open Innovation

Downsizing by industrial giants makes headlines. But, at the same time, another open outsourcing R&D model is emerging dubbed as *open innovation*. Companies of all sizes are rounding up more partners, big and small, than ever before, and they're casting wide

research nets, snapping up work at diverse corporate, government and academic labs. So despite the gloomy dollar-spending numbers, R&D may be heading for a healthy makeover. While big companies have been a source of major breakthroughs, small and midsize companies have always been the main front of new products. Globalization and increasing speed to market are causing more and more companies to review all aspects of their business efficiency, including their R&D organization and spending. Even core competencies do not give firms a sustained competitive advantage because they can be copied, replaced or made irrelevant. Corporate researchers are becoming 'hunters and gatherers' of technology rather than originators. At the same time, large firms are entering into an increasing number of alliances with universities and small firms for discovery and development purposes. This trend-setting phenomenon is salient in drug and electronics industries.

InnoCentive is the first on-line forum that brings together leading global corporations and scientists from across the globe to solve tough R&D challenges. Global companies, including BASF, Dow Chemicals, Eli Lilly and P&G, which collectively spend billions of dollars on R&D post scientific problems confidentially on the InnoCentive website where leading scientists and scientific organizations, located in more than 150 countries can solve them. Scientists who deliver results that best meet the InnoCentive Challenge requirements receive a financial award for their work, ranging up to $100,000. Here's how the model works: Drug companies, called "seekers," go to the site and put up a kind of 'wanted' poster that describes the target they're trying to nail. Bounty-hunter scientists, called "solvers," sign a confidentiality agreement and then go to a secure "project room," which contains data and product specifications related to the problem. Like the bounty hunters of old, solvers take on much of the risk in the hope that they will be able to earn a reward.

By harnessing the Web, InnoCentive has built a virtual community of scientists that puts the organization "within one or two degrees of separation from every single organic chemist in the world." So far, 7,000 scientists have registered at InnoCentive and there are 2,400 project rooms in use, organized around 33 problems. Other companies are scouting Web-based research services for talent. A year ago, Dow

Chemical's Dow Agro Sciences unit turned to Lilly's InnoCentive web site to solve a dozen research riddles. Recently, InnoCentive signed a partnership agreement with the National Chemical Laboratory (NCL), Pune. The agreement will enable NCL's scientists and researchers to work on scientific challenges posted by the world's leading corporations and gain scientific recognition and financial award.

Reinventing Corporate R&D

Now, even companies with big research budgets don't try to invent everything in-house. Fifteen years ago, when the world's major nations agreed to stop producing chlorofluorocarbons (CFCs), chemical dynamo DuPont had serious problems. To help it figure out the best way to produce CFC substitutes, DuPont outsourced research to more than 20 organizations, including academic institutions, think tanks and private companies. The outside initiative was a major success and the company ceased production of CFCs in 1993, three years before the internationally agreed upon deadline, and now sells CFC alternatives in five different areas. DuPont may have outsourced $5 million of the $400 million it spent on CFC research, but the company saved that amount many times over by not doing the research in-house. Many other companies are discovering what DuPont learnt with its CFC experience. Namely, that outsourcing discrete R&D projects can be an excellent way for companies to gain access to the expertise and equipment that they do not have time or money to cultivate in-house.

Every month at Merck & Co., groups of scientists in different areas of disease research gather to evaluate the latest breakthroughs. But the innovations they haggle over don't come from Merck's own laboratories. They're generated someplace, anyplace—journals, conference reports, patent literature and visits to other labs. "We scour the world," says Merv Turner, Merck's Senior Vice-President for External Research. At the end of the meetings, each group typically flags a couple of innovations for a small team of scientists to investigate. Recently, one of the brain trusts tagged Amrad Corp., a tiny Australian biotech company that's working on a promising drug to treat respiratory diseases. By June, Merck had ponied up $5 million to seal an exclusive license and a multi-year research collaboration with

Amrad that one day could be worth $112 million. It's just one payoff from Merck's "very aggressive antenna function to survey what's going on in the outside world," Turner says.

At the same time, big companies are becoming more inventive in tapping researchers employed elsewhere to solve vexing problems. Even Xerox, which set the standard for do-it-yourself research, has turned to outsiders to help develop optical-network technology. "We were definitely not doing that 20 years ago," says Herve Gallaire, Chief Technology Officer Xerox. Xerox has contributed its expertise in imaging technology to a joint project with Intel Corp., that produced Intel's latest microprocessor, announced on September 10, 2004. It's tailored for document imaging applications.

Chalk it up mainly to corporate heavyweights learning that they can't develop all the breakthroughs in-house. "It's very hard for any company, even one that spends as much as we do on R&D, to do everything," says Paul Horn, Senior Vice-President and Director of Research at IBM which, in 2003, spent $4.8 billion on research.

Procter & Gamble Co. thrived for years, relying on the 7,500 employees in its R&D group to develop new products. But as the pace of innovation elsewhere increased, P&G faltered. Today, P&G has 53 "technology scouts" who search beyond company walls for promising innovations. P&G has a mandate that 50% of its R&D that will be commercialized will be developed from outside, and that's where off-shore bases like Brazil, Russia, China and India become important.

Clustering Breeds Wealth

R&D clusters are springing up all over world due to the migration of sector-specific processes to different locations—IT clusters around Bangalore, pharma and biotech clusters around Hyderabad and automobile clusters around Delhi and Chennai etc. In a cycle of reinforcement, clusters can become such magnets for R&D that it becomes almost impossible for a firm to choose a location outside of it. A big cluster in the US that had always attracted foreign-owned R&D is New Jersey, which has a concentration of drugs and pharma labs. Clustering enables firms to find sources of their competitive

advantage in their interactions with the local system of sub-suppliers, customers, competitors and incumbents they operate with. The concept of a cluster may also be different from an agglomeration of firms in the same industry and may have to do with a geographic concentration of interconnected companies, specialized suppliers, a given policy environment and infrastructure facilities like export promotion zones. Interconnections between firms and the 'spillover effects', a vibrant business climate and the dynamics of co-operation and competition have a positive impact on clusters.

Government labs, which in many countries were once established to be "strategic national repositories" of expertise in particular sectors of technology, have also of late entered the R&D market, in some cases as a consequence of privatization and related policies. Many of them are perceived to be highly competent providers of state-of-the-art knowledge. Those that are still subject to public sector models of management are not always considered responsive and flexible but could very well be clustering agents for many companies.

The Indian off-shore R&D story is really in its infancy right now. It is poised for greatness but the risk of failure is equally great. There are the real challenges of achieving operational excellence and managing expectations from parent companies. Running laboratories with all the physical assets—instruments, equipment, engineering services, and material logistics—is definitely more than just managing band-width and connectivity and requires a lot more operational robustness besides intellectual capital. The second issue is more of a management and leadership issue on how to manage the expectations of parent companies. Based on the benchmarks set for the IT service companies, it is only logical to expect that parent companies would look for technical breakthroughs and discoveries at a faster rate from Indian sister labs than what they themselves could not achieve over much longer periods with significantly higher dollar investments. They will expect real *Houses of Magic*.

Chapter 4

Testing for Quality? Outsourcing Is In

"Nature has so made us that we do not see our backs; it is reserved for others to see them. Hence it is wise to profit by what they say."

—MAHATMA GANDHI

International trade, globalization, quality of life and cross-border business development are busy frontiers today. Likewise, science-based marketing has its advantages with consumers. Most segments of any population have a positive attitude toward science and technology and public confidence in consumer products is boosted by claims that they are "scientifically tested" or "scientifically proven". The public opinion is generally in favor of institutions that conduct research, manufacture, test products and provide assurances of their quality and performance. Quality is defined by the International Organization for Standardization (ISO) as *the totality of features and characteristics of a product that bear on its ability to satisfy stated or implied needs*. In other words, good quality exists when the product complies with the requirements specified by the manufacturer and the client. The customer can be anybody varying from the end consumer to a manufacturer or a regulatory body. Fostering an environment in laboratories which promotes integrity and confidence in the health and safety of goods is an important part of that accountability. Independent laboratories provide their services in many fields such as chemistry, microbiology, nutrition, food science, pharmaceuticals, agriculture,

environmental science and materials testing. In all of these areas it is necessary for the laboratory to generate repeatable data that meet the client's needs and satisfy the required or implied quality standards. The product of analytical laboratories is the data generated and reported in a test report. This data is often critical in making financial decisions on expenditure of large amounts of money.

The marketplace basically consists of the producer offering his product or service to the customer. The quality of the product is defined by consumer, buyer, grader or any other client based on a number of subjective and objective measurements. Many manufacturers make claims about the performance of their products. On many occasions the governmental authorities, domestic and foreign, may put specific demands on products for reasons of safety, health and environment and these requirements may differ from country to country. All these requirements are laid down in product standards and regulations. If any product wants to compete and survive in global markets, the requirements must be fulfilled in the most economical way.

There are three types of certification:

1. Self-certification is the system where the manufacturer or producer takes responsibility themselves to certify the conformity of the product with applicable criteria i.e. by affixing the Standard/Specification number on the product.
2. Second party certification by the purchaser is normally a contractual arrangement.
3. Independent third-party certification is undertaken by an organization, which is independent of the manufacturer to provide assurance to purchasers in general seeking to identify suppliers of quality products or services.

An example of independent third-party certification is the independent laboratories. A *testing laboratory* is a test facility which performs testing (and or sampling) by using either standard test methods developed by the national, foreign or international standardization organizations (such as ASTM, ISO, USP, BP etc.), non-standard test methods published in technical journals or in-house test methods developed by the laboratory itself. Testing may form a part of inspection or product

certification. Most often independent labs have no legal or financial connection with the supplier or user of the product undergoing the test, although it is not mandatory. The manufacturers or the purchasers may use independent laboratories if they do not have some of the required facilities. For example, whenever a mineral or metal product is bought and sold, there is a requirement for independent assays to determine the precise elemental content in order to ascertain payments and penalties for the transaction. In addition both buyer and seller would like an independent test report on the precise chemical composition besides their in-house reports.

The Developing World of Standards

A key trend of globalization is the growing importance of global standards. A need arises for these standards to promote economic efficiency and international trade. As a result of globalization, consumers experience many new brands and a variety of products produced by firms located in distant markets. An increase in awareness of environmental and social concerns has enforced the need for process standards. These standards have been developed to assure the consumer of the quality, safety, environmental and social characteristics of the production processes in distant locations. With the globalization and openness of the world economy, and as a result of changes in the geopolitical environment, voluntary technical standards of member nations have taken a prominent role in the international exchange of products and services. These standards are used today as the basis for the technical regulations imposed by each country to protect the health and safety of its population. For suppliers from developing countries, compliance to these international process standards can mean the difference between participating and not participating in the world market. A network of quality testing laboratories is a crucial factor for any country trying to meet international standards to boost exports of its products or for one that is aiming to attract foreign investments.

The importance of national/international standards has risen greatly over the past twenty years, driven by business needs, economic factors and government policies. The technical experts drawn from

the industry, government, standard bodies etc., are knowledgeable on the subject of the standard and, for the most part, voluntarily devote long hours for the benefit of the wider community by contributing their experience to the development of the standard. When consumers purchase in an environment in which compliance to standards is the norm, their confidence in product quality and safety rises. Standards are fundamental contributors to this kind of consumer confidence. Without standardization, consumers must rely on hearsay and even at times to unscrupulous marketing practices. True confidence is replaced by mere hope that a given product is safe to use. But adherence to standards, as well as marketing based on certification, empowers buyers with a very specific set of expectations.

Voluntary technical standards were usually written in developing countries by their National Standards Bodies (NSBs) which are recognized by their governments and are usually part of it. Developing countries, in creating their own standards, generally use international standards as their basis to avoid creating barriers to trade and help their own industries compete in the world arena. But what is an international standard and how it is defined is still a question of debate and an area that the WTO has not been able to fully address. Today it appears that the US and EU are lobbying to impose their standards model. The US voluntary standards system such as the ASTM, FDA etc. is different from the approach taken by the EU, which has for the most embraced the ISO/IEC system. In this system, participation is based on representation from NSBs and a one country-one vote process. In the US, the standards system is based on individual participation, mainly experts worldwide who can offer their expertise in writing standards.

Seen through a laboratory's eyes, each standard or set of standards has a history of necessity, co-operation and relevance—the need expressed by an industry for the document, co-operation on its development and widespread use in the marketplace. Unlike an industrial product, where the CTQ technical specifications and other commercial terms are agreed upon specifically, consumer products are more of the one-size-fits-all type. Consumers need to be assured of the baseline product quality, be it low-carbohydrate foods or organically grown vegetables and implied needs. The independent test services industry

has evolved accordingly These tests and services are very broad in scope, literally the A to Z of all man-made materials and naturally occurring materials, including product groups like GMO crops, drugs, electrical appliances, metals and minerals, textiles, tea, steels and chemicals. Many of the testing requirements between nations relate to legal metrology (i.e. measurements made in the course of consumer trade) such as quantities supplied and purity of the gold, type of crude oil etc. or statutory codes (e.g. safety) for certain sectors of industry.

Independent Test Laboratories: Thriving Amid Imperfections

The laboratory industry has never been a more exciting place because of the role it plays in modern technology trade. The independent laboratory market in the US alone is reported to be US $15 billion (American Council of Independent Laboratories, ACIL, 2003) and is expected to increase in value over the next few years as more companies outsource their laboratory needs due to cost efficiency issues. Thousands of testing laboratories exist worldwide in different scientific disciplines. Contract research and testing laboratories perform an increasing proportion of many companies' R&D and analytical work. The US Bureau of Labor Statistics predicts that the employment of chemists at R&D and testing laboratories will increase by 60% to more than 28,000 between 1996 and 2006 in the country. By comparison, the Bureau, for example, predicts that chemists' employment in the Chemicals and Allied Products (C&AP) industry will grow only 6.7% to 30,298 in the same period, which suggests that the outsourcing trend will affect the employment opportunities of many chemists.

Testing Times: The Traditional Role

For the last three decades, private laboratories in India have been facilitating trade in traditional core sector industries such as pharmaceuticals, fertilizers, steel, cement, building materials, paints etc., helping small- and medium-scale industries with their quality control procedures and product compliances as third party labs. During the 1980s and early

1990s, many pharmaceutical companies involved in generic drugs did not have the facilities required to conduct the testing as per USP, BP and IP protocols and depended heavily on private laboratories. The unbiased and professional services have resulted in building confidence and developing trust among the contracting parties and they have started treating private testing laboratories as valuable partners.

Historically, testing laboratories in India have developed in three distinct and successive phases. In the 1950s, the test labs purely performed the role of helping small-scale industries deal with their lack of in-house testing capabilities and handled some of the test requirements from governmental labs as a back up for clearing the backlog of testing. Standards/regulatory bodies have used private labs for product surveillance testing and for product certification schemes through various recognition schemes and are also outsourcing some of the in-house workloads.

In the 1970s and 1980s, independent labs started expanding the scope of their activities and performed third party certifications and upgraded the quality of their services. Focus also shifted on the accreditation of labs as per the prevailing ISO standards and focus was on quality system implementation and process improvements. Adoption of GATT agreements, aimed at the reduction of technical barriers to trade, stimulated the development of laboratory accreditations as a means to gain international acceptance of test data. From then on, lab accreditation has developed as a specific mechanism for laboratories to obtain third party recognition of their competence and ability to provide calibration and testing services.

It is estimated that there are more than 50,000 laboratories currently offering analytical/pharmaceutical outsourcing with more options being added every year. It is a daunting task to find one with the right capabilities. The internet provides some unique options geared specifically to outsourcing of laboratory-based testing requirements. One example is LabSeek, a Web-based company created in 1999 specifically to help people find laboratories for analytical outsourcing. A visitor to the LabSeek website can use a tool called “Quick-Seek” to search for laboratories and submit Requests For Proposals (RFP) based on techniques, methods, instrumentation, certifications and specialty

areas. "Quick-Seek" immediately confirms if LabSeek has a laboratory that can meet the requirements and allows the visitor to submit information to request a proposal online. The information is then distributed to the LabSeek Member Laboratories that have the necessary capabilities and they can choose to provide a proposal. LabSeek continues to spark interest because of the company's ability to provide virtually any type of scientific service, based on its proprietary database of member laboratory capabilities.

In India, at the end of 2003, there were 202 testing laboratories, 125 calibration laboratories and 32 clinical laboratories that had been accredited by the National Board for Accreditation of Laboratories (NABL) India. The laboratories provide testing services in chemical, mechanical, electrical, thermal, biological, fluid flow, photometry, electronics, radiological, electro-technical and non-destructive testing areas. The details of the distribution of areas of testing among the laboratories is shown in Table 4.1.

Various departmental recognition schemes are converging and accreditation by NABL is being viewed as uniform criteria. For example, the Bureau of Indian Standards (BIS) has been operating a Lab Recognition Scheme for several years under which the number of recognized laboratories has grown to 280. The criteria for recognition has now been aligned with NABL criteria, ISO/IEC Guide 17025, and all recognized labs have been asked to implement quality systems as per the revised criteria to align these quality systems with international standards.

In the world of Indian CROs, Vimta Labs is an emblem of success. This-20-year old firm is proof that large and growing multidisciplinary contract laboratories (Table 4.2) can be built by hard-working and market-savvy scientists-turned-technocrats who successfully help customers with quality and speed of service. Although numerous companies have sprouted in the testing services domain, none has come close to Vimta in size, breadth and profitability. The image of a test laboratory may invoke images of poorly paid technicians performing tedious and repetitive tasks in substandard facilities. But Vimta Labs raises the benchmark on what constitutes a world-class independent laboratory.

Table 4.1 ISO 17025 accredited laboratories as on Dec 31, 2003

	Chemical	Mechanical	Thermal	Electrical	Biological
Testing	158	111	0	32	23
Calibration	NA	91	38	0	0
	Clinical	**NDT**	**Electro-technical**	**Fluid flow**	**Electronics**
Testing	32	15	0	3	11
Calibration	0	0	56	7	0

Source : National Accreditation Board for Laboratories, New Delhi

Standard test labs are designed to operate the business, get the work done, control performance and costs, spot the problems with instrumental downtime etc and bring in the year's results. Extensive accreditations, certificates, compliances and QA policies can be costly to develop and maintain. By choosing to outsource specific analyses, a laboratory can benefit from the contract laboratory's accreditations, quality control and quality assurance processes and protocols. Another benefit to outsourcing can be the separation of the QC analyses from the in-house lab. Using an independent QC lab can help by providing an objective opinion about current procedures and analytical techniques. Generally speaking, projects with strong regulatory or legal issues also tend to be outsourced frequently.

Technical Expertise: Jump-start Solutions

Many types of analyses require a high degree of technical expertise or expensive instrumentation, which would require employing an expert in the field or buying capital-intensive instrumentation for what would be limited use in a company. Outsourcing of analytical tests on projects in the very first stages can give labs an advantage by allowing for pre-testing or trial runs before an investment of time or money is made. Test laboratories have a distinct advantage in hiring and retaining skilled technicians because they can offer fresh recruits a laboratory ecosystem with a broad spectrum of projects and training. Since contract researchers come with expertise in the area to be tested, it gives the project a jump-start. Using a contract laboratory can also help companies to manage their resources among special, extremely large, low priority and new projects.

Table 4.2 Multi-disciplinary private laboratories with specialized testing-facilities

S.No	Name of the Lab	Areas of Testing
1	Shriram Institute for Industrial Research, Delhi and Bangalore	Mechanical Testing, Electrical Testing, Chemical Testing, Microbiological Testing, Environmental monitoring, Toxicology, Calibrations, Radiation Sterilization studies
2	Vimta Labs Ltd Hyderabad, Chennai	Mechanical Testing, Chemical Testing, Microbiological Testing, Environmental monitoring, Toxicology, Clinical studies and Pathology, GM food Testing
3	SGS India, Mumbai (HO) 31 laboratories	Mechanical, Chemical, Energy Audits, Vehicle Inspection services, Food export Inspections, Marine services, Non-destructive testing
4	Shiva Analyticals Pvt. Ltd, Bangalore	Chemical, Geochemical analysis, Environmental Monitoring, Non-destructive testing

Most analytical labs focus on a particular area of expertise. Different industries use labs in different ways. The cosmetic industry has traditionally sent a majority of its work to outside laboratories, where a myriad of claims, many of them unique and not found in standards, can be addressed. Pharmaceutical manufacturers, on the other hand, have most of their work governed by very specific guidelines and the choice is often based upon what is logistically and financially viable.The primary criteria for a partner laboratory is for it to be strong in their specific area of need, with qualified scientists, experienced managers, current equipment and a track record of success. A lab that is competent to perform calibrations in the high voltage field is not necessarily competent to operate in the high frequency field. A certification body that issues ISO 9002 certificates for oil drilling platforms is not necessarily competent to do the same for a baby food producer. The companies verify the laboratory's experience and technical capabilities in quality testing, integrity of data and the required level of sophistication in instrumental capabilities.

Test laboratories have commonly evolved into two distinct models, namely the Edison-model and the Ford-model. Those laboratories falling into Edison-style pattern are more innovative and employ scientists with research backgrounds. They are broad-based in the range of instrumentation available and are more inclined to project-oriented testing services which involve developing new methods of testing etc.,

often with considerable inputs from in-house experts. However, the majority of test laboratories try to emulate the Ford-model, focussing on execution of known test methods with speed and faster turnaround times. They usually employ more technicians and have tailor-made equipment to test only specific parameters in a given area and focus on automation and standardization when volumes are attractive.

A broadly skilled lab allows a wide range of projects to be run in one location, which helps simplify communication and data transfer. As with any outsourced function, if no single vendor can provide the breadth of capabilities to meet all of the company's analytical needs they will need to look for a few labs that are good at what they do, rather than having several vendors for any given test regimen. There is a cost associated with managing multiple vendors, so finding labs that have a broad scope can help decrease the total expenditure.

There is a distinction between a contract lab operating as a profit center and an in-house analytical lab serving a support function in a company. In-house labs usually have considerably more experience with their own particular product types and are aware of specific errors (such as product-specific variations, etc.) that might arise during testing. Since they often possess years of experience in running a particular sample type, in-house chemists can spot a bad answer more easily than contract lab chemists. They also know which corrections and modifications to make in test procedures. There may be a learning curve period in such instances which has to be taken into consideration.

INTEGRITY/CONFIDENTIALITY

The primary factor in choosing a lab is the consideration of its level of integrity. The best way to assess a laboratory's qualifications is to perform an on-site audit, before any contract is signed or samples are sent. More than anything else, what customers expect from laboratory is the knowledge that the information given is true and unbiased. Every manufacturer must be prepared for a forthright analysis of work performed and, possibly, the bad news that the product did not pass muster. It is an old axiom that the "result of any testing method can be no better than the sample on which it is performed". Every contract laboratory has tales of

"shooting the messenger" where the lab is blamed for less than satisfactory results. The laboratory has to be aware of how important test results are for the companies of both the supplier and the purchaser. But if it lacks the integrity to provide accurate results based on its perception of the customer's reaction to those results, then it is time to find a new lab.

Most contract labs will not discuss one client's work with the others. Nonetheless, the occasion may arise when a firm has certain sensitive samples it wants tested and the fact is that it simply does not have a 100% guarantee that the type of testing conducted and the analytical data generated won't be discussed with potential competitors. An organization might have developed a particularly tricky analytical test for a critical analyte. If this information is passed along to the contract lab, it might use the test methodology to analyze competitor products requiring the same type of testing but lacking appropriate test methodologies. In other words, any knowledge passed along to a contract laboratory may, in rare cases, end up helping competition.

Quality/Data Integrity: Off-the-Shelf Expertise

A testing laboratory is an extension of the client in the level of quality it provides. It should be prepared to meet and exceed those reasonable procedures set by the client for its product testing. A world-class laboratory will have a separate quality assurance and control function, not responsible to production management. Further, these laboratories are aware of GMP, GCP, GLP standards/ISO certifications, where necessary, and have appropriate SOPs for quality operations and out-of-specification results. They can also make available results of regulatory internal quality audits in the areas of affecting work and be prepared to assist valid requests in developing quality programs for a client's product testing.

To stay in business, contract labs must turn out reasonably accurate results. If they lose their reputation for accuracy, they will not remain up and running. Occasionally, however, pressure to crank out volumes of test results to generate revenues can lead to sloppy work and, worse, falsifying test reports. Such cases are extremely rare. Most contract analytical lab errors are probably caused by lack of experience in testing the client specific type of food product.

Value for Money

> *"Quality is remembered long after the price is forgotten."*
>
> —Gucci family slogan

It is important to consider more than price when evaluating contract labs. A laboratory might not be noted as a low-cost provider of analytical services, but it might excel in ensuring accurate answers. One lab that is not noted for being low-cost for example, will run a control sample with every set of routine samples submitted for analysis. If an inaccurate result is obtained with control samples, test parameters and instrumentation calibration are carefully checked. If an inaccurate result is reported to a client, the lab will re-analyze samples at no charge. One way to check the accuracy of a contract lab is by sending them control samples (samples of known analyte concentration) along with unknown samples. Companies might even tell labs they are being sent a blind control sample in the samples to be tested. Just knowing that they are being monitored might be enough incentive to inspire the lab's most meticulous work effort.

Some analytical labs deliver only test data in report format, while others have the experience and personnel to provide interpretation, method development, material identification, reverse engineering and other services. If all that is needed is to repeat routine testing that has not changed in years, there is no need to pay for additional services. On the other hand, if outside technical interpretation or development assistance is needed, it might be worth the price.

Infrastructure: The One-Stop Shop Choice

The laboratory should have the space, equipment, systems and personnel required to perform the types of work in a given area. For the Laboratory Manager, operating a laboratory in India in clinical, analytical or environmental testing is a difficult business these days. Assuring the availability, reliability of results and economic survivability of the laboratory is the management's goal. The operating environment for the laboratory depends on the management of their

critical utilities—electrical power availability and back-up, water quality, temperature, humidity, air filtration (laboratory weather) and reagents, controls, calibrations, consumables and quality control costs as the variable per reportable result costs. Many third party laboratories work under sub-optimal conditions and can barely stretch beyond the minimum facilities and capabilities of a laboratory. The main bottleneck for the efficient functioning of test laboratories is the power situation and alternate arrangements in breakdown situations. Those contract labs which operate instrumentation day in and day out have efficiencies of scale going for them that any manufacturer might not have.

High volume and throughput laboratories have turned to the increased use of automation and total integration of resources that the enterprise Laboratory Information Management Systems (LIMS) brings. Investing in optimizing automation, instrumentation and software is one of the ways the laboratory can become more competitive and contribute to the bottom line. Improving processes and personnel interaction with these new, sophisticated laboratory assets is the best way for Indian laboratories to provide significant value added services. For those laboratories that are regulated by FDA, OSHA and other governmental bodies, assuring quality, reducing incident and CAPA reporting management can be a costly endeavor.

Cost-saving improvements for each key instrumentation in the service laboratory is desirable. The operating savings from increased efficiency, reduced instrumentation downtime and unplanned service calls drop right to the laboratory's bottom line. Capital improvements to the laboratory's operation that yield Benefit to Cost ratios approaching 10:1 with an attractive Return On Investment (ROI) are the attributes of smart laboratory management. The true benefit to the laboratory operation comes when the expected ROI and benefit to cost ratios for the improvement are achieved. Lowest operating cost also means operating with reliable results, effective assets and personnel utilization, a low-risk management profile and regulatory compliance. When this critical utility fails, the direct and indirect costs of the instrumentation failures, retesting and outsourcing to complete critical tests due to lost time must be factored into operating costs.

Customer Communication: Communicate, Collaborate and Capitalize

A testing laboratory should be like a scientific wing of the contracting company. The client company should be able to retrieve information as easily as walking down the hall to the lab in their building. Communication should extend to ensuring technical personnel are available to discuss issues, track samples and provide timely response in a user-friendly format to the client—knowledgeable customer service representatives is key. Good customer service begins with good communication. Data regarding capabilities of required granularity is important in determining whether a certain lab can meet the required needs and demands.

Time management for outsourcing translates into turnaround time. No matter what the quality of the data produced is, if it takes too long, it is of little use. When looking at outsourcing labs, it is important to find out how long it will take to receive data on the particular testing of interest. For example, some companies have a standard turnaround time of ten business days, excluding long-term projects and special projects. Data presentation is also an important factor. Communication on how the data will be presented, how long samples are retained post analysis, how long data is kept on file and how data is handled when it is out of expected range are important parameters of operational efficiency. Another factor in data management concerns documentation of contracts, confidentiality and financial documents.

Service Is the Product: Moments of Truth

> *"We have 50,000 moments of truth out there everyday."*
>
> —Jan Carlzon, Ex-President, Scandinavian Airlines

Independent laboratories today provide vital and important services to a wide range of industries and sectors, ranging from governmental agencies and manufacturers to farmers and homeowners. Almost daily, million-dollar decisions are made based on the data independent

laboratories produce. They provide technical know how that the manufacturer does not need to internally develop. They provide objective reviews during the design stage so that the product is designed with zero defects. Most importantly, they provide the data acceptance that will, in turn, provide market access for products and services.

Think about our daily morning routine. In the shower we use soap, shampoo and hair conditioner. After drying off, we may use deodorant. We brush our teeth with toothpaste. As the day progresses, we may use paints or glue for an art or model project. We take pain medication for a headache or an insect spray to clear out a hornet's nest, add bleach to the laundry, or wash a mirror with glass cleaner. Using these types of consumer products is part of modern life. They make our lives easier and more pleasant. The companies do product safety testing so that we can comfortably and safely use these kinds of consumer products. Studies are also conducted to make sure that accidents with these products (such as accidentally swallowing something or getting something in the eye) will cause as little harm as possible. Product safety testing helps stop unsafe products from ever being sold. If you go through the headlines, rarely does a day pass without an announcement of yet another controversy regarding the need for a more stringent control of standards of products—food, healthcare, fire safety, water quality or air pollution and the need to enforce newer and stricter standards for compliance and greener and safer products

However, testing of product quality remains a respected but invisible activity. Even scientists like to spend their time on the newest, fastest and most powerful technologies and consider testing activities as 'after market'. Testing laboratories seem a dull and peripheral topic in comparison but they are central to the laboratory-enabled technology trade. In addition, a testing laboratory has scores of 'moments of truth' everyday. A *moment of truth*, by Carlzon's definition, is an episode in which a customer comes into contact with any aspect of the company, however remote, and thereby has an opportunity to form an impression. The marketplace is increasingly opting to do business with those who *serve*, rather than those who merely *supply.*

A random glance through various newspaper/trade magazine headlines clearly shows the key role of independent laboratories in ensuring

resolution to various regulatory and trade-linked issues and the extra layer of third-party testing that leads to better, safer and more borderless human enterprises.

TIMELINES

> *"I love deadlines. I like the whooshing sound they make as they fly by."*
>
> —DOUGLAS ADAMS

A contract laboratory must be responsive to the needs of the client and provide the service agreed upon. The laboratory should have a sense of when a particular piece of work can be done and advise the client of this upon receiving the sample. Just as in other areas of business, a laboratory should be judged by its ability to meet its commitments. In the CRO business, there is a principle called EWEY or 'everyone wants everything yesterday'. Contract labs work on time schedules and manpower and materials availability but on occasions can schedule rush assignments.

When a firm submits samples to a contract lab, it perceives a certain level of loss of control over when the sample gets done, who performs the work and how testing is performed. Contract labs schedule samples into their workloads. In effect, the contract lab assigns a priority to the work it receives. Even though when, who and how might be important to the firm submitting samples, those issues might not be the lab's priority. Most contract labs also offer 'rush' services so samples are returned quicker than normal, but hefty surcharges are assessed for the privilege, typically twice the normal cost of testing.

Some manufacturers may fear that turnaround time will suffer when samples need to be shipped across the country instead of taking them to the building next door, but a physical separation between customer and lab should not significantly increase turnaround time. In fact, because a successful lab is staffed to be very responsive to customer needs, the turnaround can actually be faster than in internal laboratories. International borders can cause delays, however, and shippers need to determine the carriers and tactics which best serve to expedite their progress.

Despite the finest efforts of all parties involved, outsourcing does sometimes complicate the analytical process. No amount of communication or good intentions can compensate for the fact that adding people and additional steps makes the process more complicated. The most difficult issue to deal with is the conflict between in-house analysts and the outsourced laboratory. Since testing and services are being outsourced, analysts may feel their job security is being threatened. Also, many analysts would rather see new technologies purchased and perform the outsourced analyses in-house instead of having analyses they feel they are capable of performing sent elsewhere. Even with these considerations, the financial and analytical advantages often supercede the obstacles that may need to be overcome in calibration and maintenance of instrumentation.

Testing in Troubled Waters

In 2003, the Center for Science and Environment (CSE), a non-governmental organization, said in its study that 12 brands of soft drinks belonging to the two global cola companies contained pesticide residues above permitted levels. These pesticides—which include Lindane, DDT, Chlopyrifos and Malathion—have apparently contaminated groundwater sources. Cola companies sought to reassure consumers, claiming their products were safe by putting out print advertisements and questioning the credibility of CSE's laboratory where the soft drink samples were tested. They even published independent results from selected laboratories in the Netherlands and India to show that their products, whose combined sales are six million bottles annually—are safe. The controversy again underscores the different standards followed by multinational companies in different countries and the ambiguity arising from outdated national standards in India. It is also a pointer to the role of independent and impartial testing laboratories whose capability and competence will be required to resolve controversies regarding public safety.

Going for the Gold Standard

India is a major producer of gold jewelry and melts about 700 tons of gold per annum. The world market is about $65 billion and, inspite of

the quality the jewelry makers exhibit, our market share is only about 1%. The poor market share of Indian jewelry is attributed to the poor quality of metal being used through under-carating. Considering the loss of consumers due to under-carating, BIS introduced a hallmarking system of purity determination for gold jewelry. To develop India as a leading gold market in the world, commensurate with its status as the topmost consumer, and to protect the consumer, independent laboratories—Assaying and Hallmarking centers—have come up in various cities in India under BIS recognition. The move is expected to provide the much needed impetus for export competitiveness of the gold jewelry industry.

Testing the 'Holy Cow'

In late December 2003, the US Department of Agriculture (USDA) reported the first case of Bovine Spongiform Encephalopathy (BSE), commonly known as mad cow disease in the US. Cattle feed that contains material from BSE infected cattle is considered to be the infectious route through which other cattle can contract BSE. About 40 countries, most prominently Japan and South Korea, very quickly banned the import of US beef. Negotiations between US trade representatives and many of these countries have not resolved the conflict. Japan had already implemented mandatory testing of all cattle slaughtered in Japan. One solution apparently acceptable to Japanese regulators called for the testing of *all* US beef that would be imported for sale in Japan. The USDA controls who can purchase the reagent kit for BSE tests in the US and the tests are conducted in seven USDA approved labs only. The agency denied Japan's request because there is no scientific basis for testing young animals less than 30 months old because the tests are more likely to give false negatives. If the company were to market its beef as 100% BSE-free and if there is a high occurance of false negatives, the public would have a false sense of security. Not surprisingly, those US beef producers who export large volumes of meat are being hurt economically. In a move that has generated much media attention USDA has turned down a beef company's request to test its entire herd for BSE.

BSE test methods include a reliable but complex and time-consuming histochemical procedure used only at the APHIS laboratory in Ames,

Iowa. All presumptive positives obtained would be confirmed using the histochemical test by USDA at the Ames laboratory. USDA decided to do all of this testing on a *targeted group* of cattle that would represent a small fraction of the total cattle slaughtered annually in the US. But, because US producers cannot ship cattle overseas and USDA planned to test only a small fraction of all the US cattle, some producers have looked for alternate solutions to their problem. A few producers have proposed that they take on the testing role themselves or work through capable third party independent laboratories and clear the export backlogs. *USDA does not want to allow private test laboratories at this point of time.*

Antioxidant Controversy: Scientists Seek Standardization

Antioxidant news is increasingly capturing the attention of health-conscious consumers, but there is little scientific data on the actual effect of these compounds on humans. At a recent meeting organized by the American Chemical Society (annual meeting in June 2004),144 scientists and experts from industry, academia and government discussed the latest claims in antioxidant research and agreed for the first time to establish uniform measurement standards for antioxidants. One of the most heated issues at the meeting concerned the identification of the most reliable values for antioxidant measurements. There are currently between 25 and 100 different methods used to measure antioxidants.

The result was widespread agreement that antioxidant measurements need to be standardized but still there is disagreement on the best method to measure the beneficial compounds, which are thought to reduce the risk of cancer and heart disease as well as fight aging, arthritis and Alzheimer's disease. Once official standards are established, the *Journal of Agricultural and Food Chemistry* will become the first peer-reviewed scientific journal to require that contributors adhere to agreed-upon standards only in reporting new antioxidant measurement methods and in measuring antioxidant levels in samples. The decision could ultimately produce more reliable data for consumers, who face misleading claims about the amount and effect of these disease-fighting compounds in their food, health and beauty products.

Likewise, in the absence of guidelines from the Food and Drug Administration, USA, for the labeling of low-carbohydrate foods, consumers in the US have been left to wonder if label claims are accurate. For months the debate has raged within the industry about "net carb" calculations for everything from sugar alcohols to fiber, with no clear answers for consumers.

Mining for Data

In India, mineral survey and prospecting has been one of the main activities of the Central and State Departments of Mines since their inception. Efforts are being made to locate new mineral deposits and evaluate the known deposits for their integrated development. Most of the mineral deposits, which are found on the surface and are easily extractable, have already been explored. New deposits will have to be prospected in difficult terrains and the search has to be conducted at greater depths, with more sophisticated technology. While carrying out detailed reconnaissance surveys of large areas (greater than 25 sq. km and up to 5000 sq. km) it is essential to fly over the area being explored so that airborne geophysical data can be collected to locate the mineral-bearing zones based on anomalies. It is also essential to collect soil samples, stream sediment samples, rock samples and limited bore-hole samples to narrow down the area of exploration. Analysis of the samples collected involves the use of the latest technology and determination of constituents up to 10 parts per billion using such advanced analytical instrumentation. To cover large areas allotted for exploration, thousands of samples have to be collected and analyzed. The technology and resources required to generate laboratory data are considerable. Several international giants like De Beers, Rio Tinto and BHP who received licences for exploring different minerals, precious metals and diamonds are looking for high reliability contract research organizations geared to do this outsourcing work inside the country.

For example, a mining company which received a licence for exploring precious elements in a certain geographical area may be looking for a laboratory which has world-class facilities to estimate the precious metal content at very low levels in the samples rather than having to send the geological samples to their native Australia or

Canada. As the number of samples in mineral exploration are large, a cost-effective, reputed and reliable lab in India makes eminent sense. In financial terms, outsourcing permits a greater degree of freedom in early-stage projects by allowing the analytical costs to be expensed versus the likely need to capitalize the purchase of equipment if analysis were made in-house. Further, outsourcing ensures a higher level of resource flexibility in developmental projects, which can be particularly important.

Shiva Analyticals India Ltd., an affiliate of Shiva Technologies Inc., USA, began its geochemical facility intended to cater to the analytical needs of India's rapidly growing mineral exploration industry. The laboratory has been designed with Australian know-how in order to analyze 500 mineral samples and its promoters claim that the Bangalore facility is "one of its kind between Mongolia and Australia". Trace elemental analysis for gold and other noble metals can be provided primarily to the MNCs and domestic companies involved in exploration of mineral wealth at a much lower cost than in their home countries.

Materials: Strength of New Bonds

The primary goal of pharmaceutical research is the development of a single compound that is effective as a drug, but the primary goal of materials development is the discovery of systems that meet a number of physical, chemical and structural requirements. Materials development requires significantly different techniques from drug research. Unlike focused chemical synthesis for diversity within known metrics, in materials development there are synthesis, mixtures and process variables with an emphasis on broad coverage and synergy. The increasing use of plastics, especially in structural and automotive applications, is generating more demand for testing. From the labs of resin manufacturers to the plants of processors, data gathered from physical and analytical testing of plastics plays a crucial role. Testing is critical and essential, but it is not necessarily the core. Test results become the basis on which decisions are made in product design and development, application validation and engineering data generation for product data sheets etc. Outsourcing is a practical option for many of them.

Dow Chemical Co., like many other companies, started looking outside several years ago after trying to shift lab work among its various sites around the world to handle the overflow. Dow decided to form a joint venture company that would offer analytical testing, and other services to companies that were also beginning to address the need for cost reduction. Called Neolytica, it draws on the strengths of Dow Chemical, Air Products and Chemicals Inc., Intertek Testing Services and Thermo Lab systems. After a six month pilot, the operation was commercialized as a web-enabled, single point of contact for outsourcing and contracting analytical testing services through an extensive global network of independently qualified facilities. In addition to their plastics industrial clients, Neolytica is targeting chemical, petroleum, industrial gases and consumer goods industries.

An important factor in deciding to outsource testing to India is the cost of a given test at an independent lab and the frequency of the test versus the cost of investing in testing equipment and paying labor costs. A Micro-Hardness Test, for example, costs $50 for each sample in the US while the same costs less than $8 in India with the tests performed on identical machines.

A Pollution-free Olympics 2008 in Beijing?

The Chinese Research Academy of Environmental Sciences (CRAES) and the world's leading chemical company, BASF, signed an agreement to initiate strategic co-operation by jointly establishing a Benz M111 engine testing laboratory in Beijing. The laboratory will operate according to internationally standardized testing procedures and will be responsible for setting and supervising product standards related to fuel quality, assessing the quality of Chinese gasoline, improving the quality of fuels for motor vehicles and reducing emission. The ultimate goal is to bring about a cleaner environment in China, given the challenging fact that motor vehicles are increasing rapidly in urban areas such as Beijing. In Beijing alone, the number of motor vehicles has exceeded 2 million since last October. It has created daunting pressure on both traffic and the environment. Beijing is going to host the 2008 Olympics, and the traffic and pollution that will come with it is one of the biggest challenges

ahead. The Chinese government has been trying to come up with the best solutions to cope with the situation.

Agri Exports: Testing "Sour" Grapes

As awareness grows about food safety issues, countries need to provide greater assurance about the safety and quality of food. The increase in world food trade and the advent of the Sanitary and Phytosanitary (SPS) agreement under the WTO have also raised interest in food safety requirements. To ensure a strong presence in global markets, India realizes the need to meet these challenges and keep pace with international developments. The 2003 grape season saw a number of rapid alert notifications from the European Commission on account of the pesticide residues in excess of the maximum residual limits (MRL) prescribed by them. This led Agricultural and Processed Food Products Export Development Authority (APEDA) under the Ministry of Commerce to modify residue monitoring documents in the form of a regulation to control pesticide residues in grapes exported to EU. A number of other steps were also taken, such as the upgradation of several laboratories, setting up of the National Referral Laboratory, training of farmers/exporters/analysts etc.

In India, international standards, guidelines and recommendations are increasingly used to guide domestic as well as international trade and the laboratories are key players. The SPS agreement provides for harmonization of the SPS measures of member countries with the international standards by the *Codex Alimentarius* commission (referred to as Codex). The Directorate General of Health Services in the Ministry of Health and Family Welfare is working to integrate Codex standards into national food laws as much as possible. National standards for both domestic and export trade lay down parameters for pesticide residues, antibiotic residues, heavy metals, aflatoxins, pathogens and other contaminants. Because Codex standards are increasingly used as a benchmark for global trade, India has increased its participation in several Codex committees to ensure that domestic conditions are reflected in the development of international safety standards. The Hazard Analysis Critical Control Point (HACCP) approach has been recognized by Codex as a tool for assessing

hazards and establishing control systems that focus on preventive measures rather than relying primarily on the end product testing. The Codex, HACCP and food hygiene standards have been adopted by the BIS.

Inspection and certification in India has a regulatory basis in the form of the Export Quality Control and Inspection Act of 1963. The Export Inspection Council (EIC) was set up under this act with statutory status to certify the quality of products for export. Under the EIC, there are five Export Inspection Agencies that carry out inspection and certification activities, with 41 sub-offices and laboratories to provide back up. India still needs to upgrade testing facilities to meet international as well as importing country requirements, upgrading human capabilities and empowering personnel in areas of testing, risk analysis, development and auditing of HACCP plans and developing GMP/GHP/HACCP modules for implementation. To meet the requirements for testing, specifically testing for chloramphenicol, nitrofurans and other antibiotics to test at 0.02 parts per billion, several private laboratories have already been recognized.

From quality control monitoring of key chemical components impacting food flavor, texture and functionality to performing analyses to satisfy regulatory requirements, analytical testing performs a crucial function. Independent test laboratories provide a variety of services such as microbiological testing, chemical analysis, nutritional analysis, shelf-life studies, pesticide residue testing, sensory analysis etc. Test labs are used for a variety of outsourced testing purposes. Examples include nutritional testing to satisfy the Nutritional Labeling Act, analytical studies intrinsic to the product development efforts, examination of competitor product formulations (to determine how competitors are undercutting pricing or getting a particular end result), resolution of quality control compliant samples, and residual pesticide testing and heavy metal contaminations etc. An in-house food quality control lab might be analyzing dozens of sour cream samples daily for fat content to ensure maintenance of production specifications. Because the processing techniques are honed to ensure accuracy, chances are a few out-of-spec samples will be discovered. On the other hand, a research analytical lab might crank up its GC/MS system only once a month, run a few samples, and resolve a critical off-flavor problem in a new product line,

leading to changes in product formulation, processing parameters or packaging alterations that prevent future off-problems.

India's First Ever Product Recall

In a crackdown of unexpected proportions, the Central Pollution Control Board (CPCB), Delhi has directed a company to recall all two-stroke generator sets that were manufactured from 2001 onwards. The company faces this stringent punitive measure because, despite making claims to the contrary, it has been shown allegedly selling products that do not comply with Phase II emission norms for petrol and kerosene power generation sets. The company has been told to rectify the defect and ensure that the withdrawn products conform to permissible emission limits before they are returned to the customers. According to CPCB, the company had "managed to a obtain a type of approval certificate for these products from the Indian Institute of Petroleum, Dehradun". In many cases, the problem is that what is supplied to the test laboratories for testing may not be a true representative sample of what is out in the marketplace.

Setting Standards: Classical Style

Certified Reference Materials (CRMs) are physical artifacts carefully characterized for chemical composition or physical property, or for both. CRMs are used in all analytical laboratories to validate measurement results, calibrate instruments and validate new measurement methods. CRMs result from a multistep process that involves planning and performing the analysis, either in-house and more commonly through a 'round robin' method involving several laboratories for the analysis, collecting data and subsequent statistical treatment. Although many CRMs are prepared by standard bodies like the National Institute for Standards and Technology (NIST), a number of private reference standard manufacturers are catering to the growing needs of laboratories. These companies usually decide if a reference standard is required by a significant segment of individual customers, based on assessment workshops, customer inputs and regulatory issues that may require traceability. Several of them are looking for capabilities in developing

countries especially for those skill sets which are not easy to find and, hence, are quite expensive in host countries.

For example, Brammer Standards Inc., USA, produces over 5,500 chemical and spectrochemical analytical reference materials. Brammer, which started operations in 1968, produces Reference Materials using 6–15 co-operating laboratories in an inter-laboratory testing program. The alloy standards prepared are identified by using a variety of instrumental, gravimetric and volumetric techniques to detect the exact percentages of various metallic elements present anywhere from percentage levels to trace (parts per trillion) levels. Many of the classical wet chemical methods are considered absolute while instrumental methods are indirect and relative. But laboratories doing classical inorganic chemistry are almost extinct in western countries since many migrated to manually less intensive instrumental techniques. Classical chemistry also requires high skill levels to analyse complex mixtures and alloys with very high precision and accuracy. In the US, the cost of the analysis could be anywhere from $500–$800 for the estimation of each element in a metal alloy while a similar analysis in India would cost between Rs 500–Rs1000*. Brammer Standards and MBH Analytical Co, UK, outsource some of the inorganic analysis of its metallic and mineral standards to laboratories like Shiva Analyticals in Bangalore, which have sophisticated facilities and can perform elemental analysis from classical chemistry to the most advanced Inductively Coupled Mass Spectroscopy (ICP-MS) techniques.

GM Crops: There Is a Fly Gene in My Soup

Governments around the world are struggling to develop optimal labeling requirements for Genetically-Modified (GM) foods. There is confusion among consumers, because they are unsure as to what exactly GM foods are and whether these foods are harmful. Studies have shown bio-engineered food to be nutritionally equivalent and as safe as conventional food, but the GM labeling issue is not necessarily just about science. Rather, say the politicians and environmental groups in Europe and elsewhere, GM labeling is about consumer choice and consumer rights and is not even a health issue. The US accounts for over two-thirds of bio-engineered crops produced globally. Other

major suppliers include Argentina, Canada and China, growing predominantly biotech soybeans, corn, cotton and canola. In addition, biotech ingredients and biotech processes are used in the production of a wide selection of food and beverage products such as meat, poultry, cheese, milk, wine and beer.

GM foods available today have been put through more testing than any food in history. Around the world, some 25,000 field trials have been conducted on more than 60 crops in 45 countries. Before being approved for use, GM foods are assessed for "substantial equivalence" under guidelines issued by the World Health Organization, the Food and Agriculture Organization and the Organization for Economic Co-operation and Development. This means that scientists have compared them with their traditional counterparts and found them no different in nutritional value and health properties.

Any labeling of GM foods presents major challenges for policy makers. The most fundamental problem relates to DNA detection, or lack thereof, using as laboratory test, because the measurement of DNA becomes difficult or impossible if the GM crop is highly processed. For example, products such as soybean oil or meat produced from GM foodstuffs may not contain any evident GM protein. In addition, biotechnology is used in certain food and beverage manufacturing processes and corresponding fingerprints cannot always be detected in the final product. For instance, most cheese and wine is made with genetically engineered enzymes.

Proponents of mandatory GM food labeling believe that consumers have the right to know whether or not they are eating GM foods. Opponents say that such a label implies a food safety risk that does not exist and trying to label something that is not detectable in a laboratory invites fraud and the fraud cannot even be detected. The US has criticized the EU's mandatory GM labeling as being nothing more than trade protection.

In India, the import of genetically modified seeds for public consumption has not been approved by the Government, although indications are that it's only a matter of time. India's Department of Biotechnology has been created to test and approve GM seeds, and

with an annual budget of $40 million, the government isn't hiding its eagerness to usher in biotechnology. But opposition is mounting on a number of fronts. There are the greens who oppose GM foods in general. Then there are those who are concerned about the religious implications such as vegetarian foods made from 'non-vegetarian sources'.

The need for precise, DNA-based Genetically Modified Organism (GMO) testing has already prompted several private laboratories like Avesthagen Quality Agriculture Services Pvt. Ltd (AQUAS) to join the testing race. Labeling laws now require that customers be informed if 0.9% of a food or food product contains approved GMOs, or if the food contains 0.5% or more of a GMO that has been assessed as safe but has not yet been approved. These are quantitative thresholds, and food producers and consumers want a reliable, accurate and quantitative GMO test to ensure that food products are in compliance with these new laws.

An international market analyst pegged the potential for transgenics in India alone at $400 million. With an opening like that, it is hardly surprising that GMO testing is being pitched as the next sunrise industry to watch out for. A small nation such as Sri Lanka has also begun aligning its quality standards, including traceability tests, to that of the EU. Given the increasing strictures worldwide on GMO imports, India is busy positioning itself as the largest exporter of non-GMO foods, something that definitely would require a key role for GMO testing.

Avestha Gengraine Technologies, a Bangalore-based outfit, with state-of-the-art traceability testing labs for foods, has a cutting edge Polymerase Chain Reaction (PCR) technology, which is capable of tracing a GMO to the 0.1% level. The firm has won accreditation for all of its analytical methods through the United Kingdom Accreditation Service (UKAS), recognised throughout Europe and widely on five continents. AQUAS is now a licence holder of Genetic IDs for Bangladesh and India, following all of its protocols, procedures and instructions. Now the company has also begun providing a Total Plant Certification ID, which is sample-free, besides moving into Seed Purity Testing including guaranteeing genetic purity through DNA fingerprinting.

Being Part per Billion Smiles

Not all threats to our wellbeing come in the form of genetic engineering. Some are the result of "good old-fashioned" chemical mixes. Chemical use is so widespread today that literally no one knows all the possible side effects of ingredients. Antibacterial products remain all the rage, and if you look on the label of many of them, you'll find they share a single increasingly common ingredient like triclosan in several personal hygiene products—even in toothpaste.

Triclosan is an antibacterial/anti-microbial agent approved for use in anti-gum-disease toothpaste and also used in deodorant soaps, deodorants, antiperspirants and body washes, detergents, dish washing liquids, cosmetics and anti-microbial creams, lotions and hand soaps. It is manufactured in the US by Ciba-Geigy, under their trade name Irgasan DP300, and by several other manufacturers outside the US. In the manufacture of triclosan there is the potential for the formation of small amounts of unwanted trace by-products which are of concern. It is possible that several polychlorodibenzo-p-dioxins (dioxins) and polychloro-dibenzofurans (dibenzofurans) can be found in varying low level amounts (parts per million PPM or parts per billion PPB) as impurities in triclosan. Their presence or absence is dependent upon the type and purity of the starting materials used to synthesize triclosan as well as reaction conditions such as temperature, pressure and the like. If present, their relative concentrations as impurities can vary from batch to batch. This raises concerns because of the toxicity of dioxins and dibenzofurans.

As manufacturers develop capabilities to compete in the global market, through variation in the method of manufacture, these materials from low-cost countries, including India, need careful monitoring. Many international companies have actually reduced the tolerance limits for all these dioxins from parts per billion (ppb) to parts per trillion (ppt). The detection of chemicals at those levels requires highly advanced instrumentation like GC-MS-MS and analytical expertise. We need test laboratories with proven capabilities in ultra trace analysis to independently verify the in-house test reports of these materials to keep us smiling even our after daily brush with toothpaste.

Creating Houses of Quality

Another customer base looking for contracting out testing work and which falls in the category of domestic outsourcing is the Indian or MNC company operating out of India but who is increasingly depending on contract laboratories for its testing requirements due to capability gaps or cost advantages. For example, a tea or coffee manufacturer/importer/exporter may be reputed in his area of manufacture/ quality control but may lack the facilities or expertise to test residual pesticides or levels of toxic elements to meet export regulations.

The list of domestic companies that are developing products of everyday use and testing them for performance, quality or compliance and safety is growing day by day. Have we ever stopped to think of how many of our daily activities involve exposure to consumer products? From morning till night, we are in contact with a variety of personal care products and household or workplace chemicals. Brushing our teeth, washing and styling our hair, using sunscreen or lip gloss, washing our hands, doing the laundry, cleaning up the house and routine yard work, all include the use of chemicals. We probably don't think about the potential hazards of using these consumer products, but there is an element of risk involved in all of them. All our cosmetic products, building materials, and food products are undergoing testing in various specialized contract test laboratories as per standard test procedures for their safety and quality compliance.

Informed debate and decisions on important matters such as the depletion of the ozone layer, acid rain and the quality of air in our cities and soil in our agricultural land will depend on the data provided by analytical scientists. National and international trade is critically dependent on results from test laboratories, with chemical composition often being the basis for the definition of the nature of goods and tariff classification. In all of these areas, the quality of analysis or testing cannot be overemphasized.

The cost of the laboratory getting it wrong can be enormous as the following examples indicate.

- In trade, it could lead to the supply of substandard goods and a high cost of replacement with the subsequent loss of customers.

- In the supply of drinking water, it could lead to harmful contaminants being undetected.
- In environmental monitoring, mistakes could lead to hazards being undetected or to the identification of unreal hazards.
- In all areas of application "getting it wrong" leads to loss of confidence in the validity of future test results; at the extreme, loss of confidence puts the future existence of a particular test laboratory at risk. More generally it leads to costly repetition of analyses and, in the area of trade, inhibits the expansion of the world economy.

Cost considerations are certainly important in laboratory management and quality assurance planning. Besides capital and operational costs, adding a quality assurance program will increase the cost of operation and the increased cost must be fairly judged against the benefits derived. Costs are tangible and not too difficult to assess, but some of the benefits are intangible, which makes evaluating their importance based on subjectivity. The public image of the organization, the need for service improvement, the impact of the government laws and regulations and complaints from clients are examples of items which cannot be ignored. A laboratory quality assurance program must consider such matters as part of the overall plan. In a cycle of reinforcement, a busy vibrant laboratory builds credibility and staff morale. Laboratory management staff will have to develop a cost-versus-benefit-analysis in order to achieve an optimum and measurable balance. The objective of this exercise is to minimize the cost of those activities that are deemed sufficient and important to control data quality.

Prevention costs are those required to keep unacceptable data from being generated in the first place. They include the costs associated with performing proper laboratory planning and documentation, preparing sound procurement specifications and criteria for accepting new equipment, materials and services; providing sufficient and suitable training for laboratory personnel; following a rigorous schedule of equipment preventive maintenance; and performing the necessary system calibration to improve and maintain accuracy of the data produced. There are costs to the laboratory that result from the receipt of unacceptable data (by the customer) or the need to recollect

samples following delinquent results. The loss of client confidence and patronage may be the most significant consequence of poor operational practices, which develop in the absence of an acceptable quality assurance program. In some cases, the costs to the client may be passed back to the laboratory which generated the test results.

Research labs and test labs are two sides of the same coin. While R&D labs focus on design and development, test labs focus on robustness of the manufacturing process and compliance with product specifications and regulatory requirements. A successful commercial testing business requires the building and exploration of competencies—the ability to harvest market opportunities from a wide array of choices. No company is smart enough to know what to do with every opportunity it finds, and no lab would be able to pursue all the opportunities. Each laboratory has to really deal with the challenges of growth. However, growth of any kind is inherently disruptive. This occurs because of the tension between the centripetal forces of continuity and centrifugal forces of change. Each laboratory needs to create a core-shell model of competency with a central area of expertise

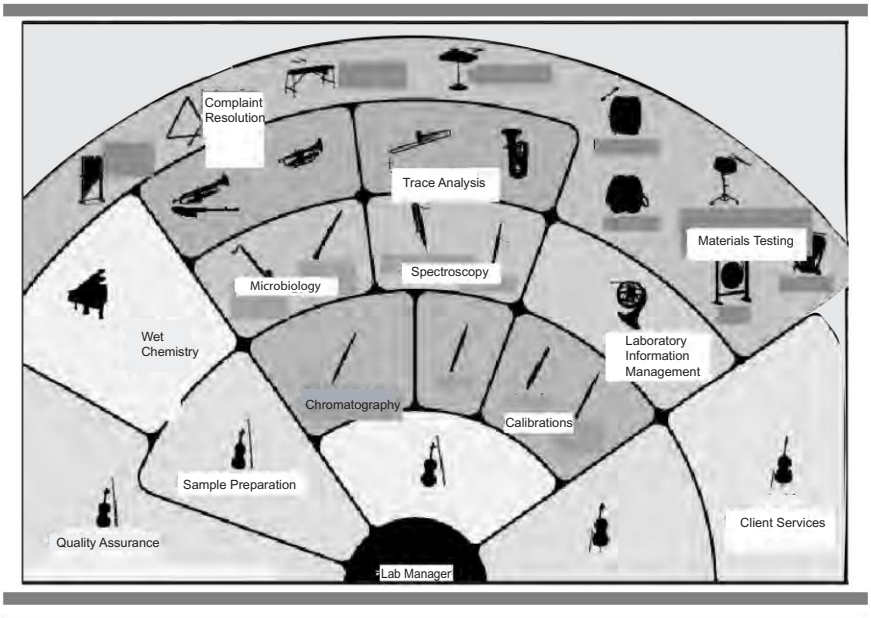


Figure 4.1 Instruments of laboratory orchestra

and an outer shell of areas of expertise which are prone to the high and low tides of market requirements.

Another example, from Peter Drucker, is how a mediocre orchestra like the Chicago Philharmonic became world class in the hands of a new conductor. Drucker went to check the man out. When asked how he managed to raise the standard, he said that the gap between the excellent people in any organization, and those who are average is always constant. So the answer is to raise the level of the top performers and automatically the overall performance level moves up. The trick is to recognize the natural flow of energy and go with it. The market scenario right now is probably the best that ever existed in India for commercial testing laboratories to carve out a niche and perform. In the final analysis, there are no upper specification limits!

Chapter 5

Measured Once, Accepted Everywhere

"Thus every sort of confusion is revealed within us, and the art of measuring, numbering and weighing come into the rescue of human understanding—there is the beauty of them—the apparent greater or less or more or heavier no longer have mystery over us, but give way to measurement and calculation and weight. . . .

Then that part of the soul which has an opinion contrary to measure is not the same with that which has an opinion in accordance with measure. . .

And better part of the soul is likely to be with that which trusts to measure and calculation. . .

And that which is opposed to them is one of the inferior principles of the soul."

—SOCRATES AS QUOTED IN PLATO'S *REPUBLIC*

An almost infinite number of measurements are made everyday in trade, industry and scientific laboratories throughout the world. The results of these measurements are used to make decisions which could be crucial. These decisions affect professionals and consumers alike. In order to have adequate confidence in the correctness of decisions

made, based on measurement results, it is essential that the measurement results are reliable. The history of scientific advancement is closely linked with the human capability to measure and measure accurately. The need for more and more accurate measurements increased with advances in various areas of science and technology. Scientists are constantly inventing newer techniques of measurement to keep pace with these advances. The requirements for measurement capability increased in two ways. On the one hand, there has been an ever increasing demand for the measurement of new parameters and on the other hand the need for more accurate measurements has increased, which was undreamt of in the past.

Measurements are extensively in demand but go unnoticed. These affect human lives in many ways. We are concerned about day-to-day measurements in the areas of trade, healthcare and environmental pollution. As individuals we are faced with measurements taken on a day-to-day basis by market scales—gas, electricity and water meters, gasoline pumps, taxi meters and so on. We are also concerned with the reliability of measurements in healthcare, such as the measurement of body temperature by clinical thermometers, the monitoring of blood pressure and heartbeats and the clinical analysis of body fluids etc., in pathology laboratories. As a society, we are concerned with the reliability of measurement results of environmental parameters such as sulfur dioxide, carbon monoxide and carbon dioxide concentrations in the atmosphere and the density of suspended particles.

Metrology: The Land of Measurement

Metrology, the *science of measurement*, encompasses both the theoretical and practical aspects of measurement. At the international level, mutual acceptability of the measurements and test results of products is a matter of concern for eliminating technical barriers to trade. Measurements are also crucially important for quality professionals working in manufacturing and service organizations. In industrial manufacturing and service organizations, measurements are required to be made at various stages of the life cycle of the product. A number of quality management standards contain specific requirements for the quality of the measurement of results and their evaluation. For

example, the regulatory aspects of weights and measures are part of a metrology system—the international metrology system makes it possible for one kilogram of a substance to be weighed identically in any part of the world—and the dissemination of time by metrology institutions helps us in planning and regulating our daily lives. In research laboratories, measurements are made on various products to test their characteristics. Similarly, measurements are used in calibration laboratories to assess the operational integrity of measuring equipment, whereas in testing laboratories the characteristics of products are measured in order to determine their compliance with specifications. Measurement results also need to be compared among themselves in many situations.

Globalization, international trade and commerce would not be possible in the absence of a globally accepted measurement system. Globalization of R&D is also bringing metrology and the need for reliable measurements and associated issues onto the center stage as never before. David Layden defines the measurement as a kind of language which ensures effective communication. The results of measurements are probabilistic in nature. This implies that another set of measurements of the same parameter could result in values which are not exactly the same but are close to earlier reported values. The measurement systems must be managed with a scientific and robust approach to ascertain parameters which are critical-to-quality (CTQs) and fulfill those CTQs on a consistent basis. The quality system should be considered as the foundation upon which the laboratory is supported. The concept of quality management which involves the three basic principles of client satisfaction, continuous improvement and employee involvement applies to laboratories.

Putting in all the components during the design and development stages of the laboratory system will help to ensure greater accuracy and repeatability of the results. Quality cannot be inspected in the data nor can quality assurance or quality control procedures be initiated after the data is generated. Good laboratory systems have to be built into the front end of the data-generation process. To ensure that all customer needs, technical and regulatory requirements are met, a laboratory needs a well-founded, effective, comprehensive and defensible quality assurance system in place. The need for laboratories to

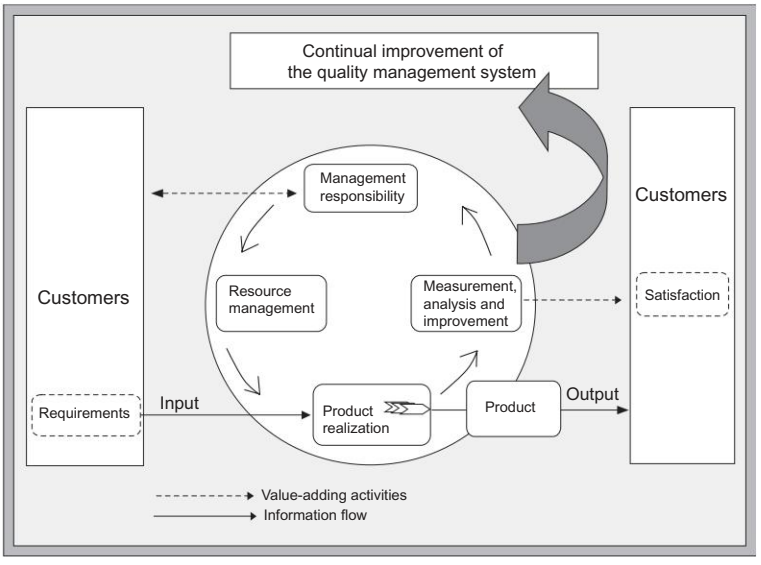


Figure 5.1 ISO 9001:2000 Quality Management system model

demonstrate competence through the adoption of quality systems and recognized accreditation is widely established within the industry as a means of strengthening due diligence regimes. It not only satisfies the client's requirements for assurance of the validity of the test results but also supports other quality management systems. There is no single, generally accepted plan for establishing a laboratory quality management system. Each laboratory, be it an off-shore R&D and testing unit or a CRO, will have its own regulatory objectives and problems that require special consideration and treatment. Once the management decides to pursue a suitable program such as GLP, GMP, GCP, ISO 17025 etc., and is prepared to support it financially and administratively, it must develop a quality plan. First, existing laboratory operations and practices are evaluated with respect to quality assurance needs, including the checks and procedures currently in place. Second, the quality assurance requirements are developed. Third, documents are written that describe the policies and procedures by which those established requirements are met. Finally, the plan is implemented through training and coaching of all members of the staff.

Besides mandatory compliances and accreditations, strategic quality initiatives and management practices like 'Six Sigma' are playing an increasingly important role in global strategy development, planning and deployment. Although Six Sigma sounds like a breakout room in a *Star Trek* convention, it is a corporate quality program, one that emphasizes identifying and avoiding process variation. The Six Sigma approach to quality builds an empirical foundation for decision making to drive people, processes and organizations towards common objectives whether the goal is to articulate a new global vision, define and articulate business opportunities in mature and emerging markets or accelerate integrations of global business operations with off-shore units or with outsourcing partners**.** Depending on whom you ask, Six Sigma was born anywhere from 10 to 20 years ago in corporate engineering communities, which are in the habit of reducing processes to statistically measurable phenomena.

International agreements and decisions concerning global trade, the environment and healthcare, increasingly call for mutual recognition of scientific measurements and standards between nations. Likewise, if global transfer of technical capabilities between off-shore units and parent laboratories and/or outsourcing partners have to progress, it is necessary to have an international quality infrastructure upon which it is possible to make comparable measurements. Such mutual recognition can remove technical barriers to globalization of R&D and international trade. International trade is growing at the rate of 15% per year. It is expected that the exchange of goods will significantly increase with an increased need for sound analytical and quality assurance data. To support this rate of growth, and to overcome the technical barriers that are supplanting tariff-based barriers to trade, the measurements performed by laboratories on one part of the globe to characterize products and enable conformity assessment must be globally recognized. Each nation must therefore ensure the quality and accuracy of its measurement system in order to promote mutual recognition in the world marketplace.

DEFINE

"Quality begins on the inside... and then works its way out."

—BOB MOAWAUD

The proper and complete identification of quality elements is an important consideration in establishing the quality objectives of any laboratory. These elements encompass nearly all activities of a laboratory's operations including administrative and client servicing functions. The emphasis given to each of the identified elements may vary between laboratories depending upon the particular setting, the size of the laboratory, client base, its mission and the quality of the measurements deemed necessary. The most commonly recognized elements which have been identified as integral components of quality assurance programs are discussed here briefly in the evolutionary framework of continuous improvement.

Good Laboratory Practices (GLP)

Good Laboratory Practices (GLP) was originally developed for research-oriented activities such as toxicology and environmental fate studies that were at the pre-market testing phase, to ensure generation of high quality and reliable test data related to the safety of pharmaceuticals, cosmetics, food and feed additives, pesticides and industrial chemicals. GLP defines managerial concepts covering the organization of test facilities and conditions under which preclinical safety studies should be planned, conducted, monitored and reported. These studies, which may involve a wide variety of matrixes or test systems are quite different from most analytical testing which is typically done according to published or validated methods at the post-registration or post-approval regulatory phase. In addition, one of the fundamental principles of laboratory accreditation is the use of proficiency testing samples which is not applicable to GLP studies.

In 1978, the US FDA issued regulations regarding GLP in the conduct of non-clinical laboratory studies. The objective was to ensure that data from such studies would be of high quality and integrity to assure product safety in accordance with the federal Food, Drug and Cosmetic Act and other applicable laws. The FDA also promulgated GLP regulations for Human and Veterinary Drugs that contain requirements for laboratory controls. These regulations call for laboratory procedures that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans

and test procedures designed to assure that components, drugs product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength and purity. The US Environmental Protection Agency (EPA) also issued regulations for good laboratory practice standards for toxic substances including pesticides. These regulations parallel those of the FDA, but are more specific in certain respects. The EPA has looked at the advantage of accreditation, as compared to GLP, in managing the oversight responsibilities of the agency. In 1982, the Organization for Economic Co-operation and Development (OECD) in which about 20 countries and half a dozen international organizations participate, issued the report of an expert group titled Good Laboratory Practices in the testing of chemicals, which was revised in 1997. The OECD document outlines the principles of GLP and provides guidance to test facilities to promote the development of quality control data in the testing of regulated chemicals including industrial chemicals, pharmaceuticals and pesticides. GLP regulations spell out what is expected of an organization that engages in studies to support the safety of regulated products. The GLP regulations provide for inspection of the testing facility by the FDA. In 1987, the FDA issued a rule on these regulations to clarify and reduce the burden on testing facilities. For CROs involved in NCE or clinical trials, GMP and GCP quality elements built around the philosophy of GLP are applicable as well.

ISO-lating Standards

Most commonly, labs seeking accreditations are assessed in accordance with the International Standards Organization's standard of ISO/IEC 17025. ISO/ISO 17025 was developed as a special purpose standard for laboratories to specify the general requirements for their technical competence. It has two major components, namely management requirements and technical requirements. The management requirements are written in language relevant to laboratory operations but were developed to meet the systems requirements of ISO 9001:2001. For accreditation against ISO/IEC 17025, the emphasis is to establish the technical competence of a laboratory for a defined set of tests, measurements and calibrations. In doing so, compliance with the standard's management requirements is also assessed. ISO 9001:2000

is a generic standard for quality management systems applicable to all organizations irrespective of type, size, product, or service provided. Therefore, it is also applicable to laboratories, even though its language is generic. Its purpose is to specify a quality management system that will allow an organization to demonstrate its ability to provide products or services that meet customers' requirements and comply with applicable regulatory requirements. It also aims to enhance customer satisfaction, including processes for continual improvements and assurance of conformity. In applying ISO 9001:2000 to a laboratory's operations, the emphasis for certification bodies will be to establish compliance with quality management system requirements.

A laboratory wishing to be accredited by ISO 17025 must have a Quality Manual satisfying the requirements as described in various clauses of the ISO/IEC 17025 standard. Quality system documentation and its implementation by the labs will have to be verified by the assessors for its compliance in accordance with the standard. The laboratory management will then demonstrate, to the assessment teams, that all requirements, as laid down, specific criteria and other guidelines/requirements are being followed. Typically, a Laboratory Information Management System (LIMS) supports the entire range of processes from order generation and sample processing to analysis and certificate creation. In addition to core functions such as specifications maintenance, results recording, release of samples and reports, even LIMS must meet the requirements of GLP. Globalization and outsourcing necessitate solutions that also work across enterprise boundaries. Instead of stand-alone LIMS, companies are increasingly required to deploy web-based portals in which all classic LIMS functions are integrated.

An increasing number of analytical laboratories are involved in both pre-registration activities covered by GLP and post-registration activities addressed by ISO 17025. These laboratories are thus confronted with the need to meet both GLP and ISO 17025 standards and possibly ISO 9001–2000, which represents a significant burden in terms of dealing with two or three different standards and organizations, each with their own audit requirements. While developing a unified approach to assessing adherence to these standards is one possible

approach, future emphasis is also being placed on integration of these two standards into a single document. EURACHEM has indicated its support for greater harmonization of ISO 17025, ISO 9001 and GLP. Discussions between the OECD panel on GLP and the European Co-operation for Accreditation (ECA) suggests that there is a realistic possibility of combining these laboratory quality standards. Closer integration of these quality standards would be consistent with the international emphasis on facilitating international trade, reducing duplication and promotion of the quality and validity of decision-oriented test data.

Apart from the different emphasis of the two standards, there are some fundamental differences in the processes used by accreditation bodies and certification bodies to establish compliance with ISO 17025:1999 and ISO 9001:2000 respectively. Because laboratory accreditation aims to recognize specific technical competence, the assessment of laboratories are conducted by teams comprising relevant technical experts and assessors, able to evaluate compliance with the management system requirements of ISO/IEC 17025. While management system requirements are important components of a laboratory's assessment for accreditation, the major emphasis is on determining the specific technical competence of personnel and the availability of all technical and material resources needed to produce reliable data and results for specific test methods.

For certification of a laboratory against ISO 9001:2000, the assessment team will consist of auditors with detailed experience in assessment of quality management systems. They may have the technical expertise (or be supported by technical experts) to enable them to apply the generic requirements of the standard to the operations of the laboratory services, but the emphasis is on determining compliance with the quality management system requirements. Some laboratories are not stand-alone facilities but may form part of a larger organization, which may have a need to be certified against ISO 9001:2000 while the laboratory's testing and calibration functions may also need to be accredited against ISO/IEC 17025. The decision to seek accreditation or certification for a laboratory, or both, will depend on the overall needs of each laboratory and the expectations of its customers, regulators or other interested parties.

Besides meeting the regulatory requirements to facilitate trade and the exchange of goods, in today's business environment, a company's ability to develop and 'flight-test' new products in low-cost countries in less time and for less money has become a critical element for remaining competitive. General Electric started using Six Sigma as a corporate initiative in 1996 to fix and design new products. Subsequently, migration of these processes was translated to its off-shore locations, like Bangalore and Shanghai, through a Design for Six Sigma Process (DFSS) for all its new product development programs. Dow Chemical has successfully used Six Sigma principles and methods to significantly reduce the time required to grow transgenic cotton (genetically altered cotton that is resistant to pests and certain herbicides). Shrinking the product development cycle and corporate learning cycle is also a huge issue in the pharmaceuticals industry. As discussed in earlier chapters, outsourcing work from pharmaceutical companies to the CROs would propagate the same pressures to these laboratories. Issues of long product development cycles are also significant in the aviation and aerospace industries and in many other areas of the defense establishment. Major pharmaceutical companies, already burdened with heavy regulatory workloads, are using Six Sigma tools to help them prioritize areas for clinical R&D and to help design, develop and field-test new drugs in less time than in the past. This is extremely valuable information for a company to capture and leverage, as it makes key decisions about the allocation of people, capital and resources. Strategic Six Sigma practices can be of enormous benefit for CROs and testing laboratories and can accomplish the following:

- Accelerate the laboratory's learning cycle
- Help project teams conduct product development research and testing quicker and with more quantification and consistency
- Map customer needs more completely and accurately and
- Ensure more robust laboratory data

Design the flow of work activities in CROs to include the necessary quality assurance and quality control activities. Assessment, correction and improvement are required as part of a quality system.

MEASURE

"Measurement is at the heart of any improvement. If something cannot be measured it cannot be improved."

—HARRINGTON (IBM)

Weights and measures were among the earliest tools invented by man. Man understandably turned first to parts of his body and his natural surroundings for measuring instruments. Early Babylonian and Egyptian records indicate that length was first measured with the forearm, hand or finger and time was measured by the movements of the sun, moon and other heavenly bodies. When it was necessary to compare the capacities of containers such as gourds or clay or metal vessels, they were filled with plant seeds which were then counted to measure the volumes. When the means for weighing were invented, seeds and stones served as standards. As societies evolved, measurement units became more complex. The invention of zero and Indo-Arabic numerals and the science of mathematics made it possible to create whole systems of measurement units suited to trade and commerce, land division, taxation or scientific research. For these more sophisticated uses it was necessary not only to weigh and measure with more complex apparatus—it was also necessary to do it accurately time after time and in different places. However, with limited international exchange of goods and communication of ideas, different systems for the same purpose were developed and became established in different parts of the world, even in different parts of a single geographical area.

Mapping the Land of Measurement

The standardization of various units and their combinations into a loosely related system of measurement occurred in a very fascinating way. For the delight of uninitiated readers here are a few snippets of what scientists consider to be soul-food—measurements of fundamental units like distances, time and weights, etc. Just seven base units allow all the other quantities used in science to be defined, such as density and luminosity. Over the past century, they have been pinned down by

MEASURE UP

Just seven base units allow all the other quantities used in science to be defined, such as density and luminosity. Over the past century, they have been pinned down by reference to one or more fundamental physical properties. Except for one: the kilogram

Current: *ampere*

The current which, if maintained in two straight parallel conductors of infinite length, of negligible circular cross-section, and placed 1 metre apart in a vacuum, would produce between these conductors a force equal to 2×10^{-7} newtons per metre of length

Time: *second*

The time equal to the duration of 9,192,631,770 periods of the radiation corresponding to the transition between the two hyperfine levels of the ground state of the caesium-133 atom

Temperature: *kelvin*

The fraction 1/273.16 of the thermodynamic temperature of the triple point of water

Amount of substance: *mole*

The amount of substance that contains as many elementary entities [molecules] as there are atoms in 0.012 kilograms of carbon-12

Luminous intensity: *candela*

The luminous intensity, in a given direction, of a source that emits monochromatic radiation of frequency 540×10^{12} hertz with a radiant intensity in that direction of 1/683 watts per steradian

Length: *meter*

The length of the path travelled by light in a vacuum during a time interval of 1/299,792,458th of a second

Mass: *kilogram*

The mass of the international prototype kept in Sèvres, France

Figure 5.2

reference to one or more fundamental physical properties, except for one—the kilogram.

One of the primary tasks of all explorers—and scientists are explorers—is to prepare a *road map* of the unknown region. Such a map will serve as a valuable guide to all subsequent travelers. The measurements made by countless researchers have been studied and much of the world of measurement has been mapped. However, even this simplified map may be a bit of puzzle at first.

Tradition holds that King Henry I decreed that the yard should be the distance from the tip of his nose to the end of his thumb! The length of a furlong (or furrow-long) was established by early Tudor rulers as 220 yards. This led Queen Elizabeth I to declare, in the 16th century, that henceforth the traditional Roman mile of 5,000 feet would be replaced by one of 5,280 feet, making the mile exactly 8 furlongs and providing a convenient relationship between two previously ill-related measures. Thus, through royal edicts, England by the 18th century had achieved a greater degree of standardization than Continental Europe. The English units were well suited to commerce and trade because they had been developed and refined to meet commercial needs. Through colonization and dominance of world commerce during the 17th, 18th and 19th centuries, the English system of measurement units had spread and was established in many parts of the world.

In 1790, in the midst of the French Revolution, the National Assembly of France requested the French Academy of Sciences to "deduce an invariable standard for all the measures and all the weights." The commission appointed by the Academy created a system that was, at once, simple and scientific. The unit of length was to be a portion of the earth's circumference. Measures for capacity (volume) and mass were to be derived from the unit of length, thus relating the basic units of the system to each other and to nature. Furthermore, the larger and smaller version of each unit were to be created by multiplying or dividing the basic units by 10 and its powers. This feature provided a great convenience to users of the system by eliminating the need for calculations such as dividing by 16 (to convert ounces to pounds) or by 12 (to convert inches to feet).

Similar calculations in the metric system could be performed simply by shifting the decimal point. Thus the metric system started as a "base-10" or "decimal" system. The inevitability of victory of the metric system is something Napoleon himself recognized. "Conquests will come and go," he declared, "but this work will endure." The work he spoke of was the defining of the meter, a task begun in the final days of the French monarchy. In 1792, two French astronomers set out separately on the quest to make an accurate measurement of the globe, a measurement that would enable people to use the constant of the size of the globe as the foundation for rational weights and measures. Their plan was to measure enough of the distance of a north-south meridian through Paris that would then enable them to calculate the distance from the equator to the north pole, and one ten-millionth of that natural distance would be the meter. They aimed for unprecedented precision, and they got it, but not exactly…

It seemed a simple task; a line of longitude from Dunkirk south to Barcelona would be mapped and calculated by triangulating high points, like mountains and steeples, along the line. In practice, it was devilishly, maddeningly and lethally difficult. Weather, disease, the ravages of time, superstition, politics and war all conspired to make the work of a few months stretch into years. The astronomer Jean Baptiste Joseph Delambre, heading north, was mistaken for an aristocrat, detained and suspected of using a church tower as a royalist beacon. His partner Pierre Francois Andre Méchain, who took the southern route, had similar problems, and worse ones, as war with Spain erupted while he was there. He had a fiendish obsession with exactitude, and made measurements of Barcelona's latitude by reckoning with the stars. Unfortunately, they were wrong due to refraction from the atmosphere, and Méchain knew they were wrong, but could not get them right. The knowledge of the error tortured him for the rest of his life. The work could not produce a perfectly precise meter; the world was too irregular for that. Because Delambre later concealed this miscalculation, the meter is 0.02% shorter than it should be. The astronomers work had produced, however, documentation of the more interesting fact of Earthly irregularity!

Although the metric system was not accepted with enthusiasm at first, adoption by other nations occurred steadily after France made its

use compulsory in 1840. The standardized character and decimal features of the metric system made it well suited to scientific and engineering work. Rapid spread of the system coincided with an age of rapid technological development. By the late 1860s, even better metric standards were needed to keep pace with scientific advances. In 1875, an international treaty, the "Treaty of the Meter", set up well-defined metric standards for length and mass and established permanent machinery to recommend and adopt further refinements in the metric system. This treaty, known as the *Meter Convention*, was signed by 17 countries. As a result of this Treaty, metric standards were constructed and distributed to each nation that ratified the convention. Since 1893, the internationally agreed-upon metric standards have served as the fundamental measurement standards. The International Bureau of Weights and Measures located at Sevres, France, serves as a permanent secretariat for the Meter Convention, co-ordinating the exchange of information about the use and refinement of the metric system. In 1960, the General Conference adopted an extensive revision and simplification of the system. The name *Le Système International d'Unités* (International System of Units), with the international abbreviation SI, was adopted for this modernized metric system.

To Err Is to To Discover

> *"The best way to find out about some of the difficulties in making measurements is to make measurements."*
>
> —ANONYMOUS

The detection of small differences with respect to some property is a major problem in science and industry. Two or more companies may submit samples of a material to a prospective purchaser. Naturally, the purchaser would want, first of all, to make sure that the quality of the material he buys meets specified requirements. Secondly, he would want to select the best material, other important factors like quality and cost being equal. When we buy a gold object that is stated to be 14 carats fine, the gold should constitute 14/24 of the weight.

We accept this claim, because we know that various official agencies occasionally take specimens for chemical analysis to verify the gold content. An inaccurate method of analysis may lead to erroneous conclusions. Assuming that the error is in the technique and not some constant error in the scales or chemicals used, the chemical analysis is equally likely to be too high or too low. If all the items were exactly 14 carats, then chemical analysis would show half of them to be below the specified gold content. Thus, an article that is actually 14 carats fine might be unjustly rejected, or an article below the required content may be mistakenly accepted. A little thought will show that if the error in the analysis is large, the manufacturer of the article must make the gold content considerably more than 14/24 if he wishes to insure acceptance of nearly all the items tested.

There are two ways around the dilemma. The manufacturer may purposely increase the gold content above the specified level. This is an expensive solution and the manufacturers must pass on this increased cost. Alternatively, the parties concerned may agree upon a certain permissible tolerance or departure from the specified gold content. In as much as the gold content cannot be determined without some uncertainty, it appears reasonable to make allowance for this uncertainty. How large a tolerance should be set? This will depend primarily on the accuracy of the chemical analysis. The point is that, besides the problem of devising a method for the analysis of gold articles, there is the equally important problem of determining the sources of error and the size of error of the analysis method. This is a recurrent problem of measurement, regardless of the material or phenomenon being measured. There may be those who feel that small differences are not important, because, for example, gold articles will give acceptable service even it is slightly below 14 carats. But small differences are important for a number of reasons. If one variety of rice yields just one per cent more grains than another variety, the difference may be unimportant to the former, but, added up for the whole country, the small differences may mean millions more bushels of wheat to feed the hungry population.

Sometimes, a small difference has tremendous scientific consequences in research and development. Our atmosphere is about 80% nitrogen. In the early days of chemistry, chemists could remove

oxygen, carbon dioxide and moisture from the air. At that time, the residual gas was believed to consist solely of nitrogen. Pure ammonium nitrite, when heated, decomposes to give nitrogen and water. Pure nitrogen, whether obtained from the air or by decomposition, should have identical chemical and physical properties. In 1890, Lord Rayleigh undertook a study in which he compared nitrogen obtained from the air with nitrogen released by heating ammonium nitrite. He wanted to compare the densities of the two gases, i.e. their weights per unit volume. He did this by filling a bulb of carefully determined volume with each gas in turn under standard conditions, at sea level pressure and at 0°C. The weight of the bulb when full minus the weight when the nitrogen was exhausted gave the weight of the nitrogen. One measurement of the weight of atmospheric nitrogen was 2.31001 grams. Another measurement of nitrogen from ammonium nitrite was 2.29849 grams. The difference, 0.01152, is small. Lord Rayleigh was faced with a problem. Was the difference a measurement error or was there a real difference in the densities? On the basis of existing chemical knowledge, there should have been no difference. Several additional measurements were made with each gas and Lord Rayleigh concluded that his data was convincing evidence that the observed small difference in densities was in excess of the experimental errors of measurements and therefore actually existed. There now arose the intriguing scientific problem of finding a reason for the observed difference in density, that the perhaps nitrogen from the air contained some hitherto unknown gas or gases that were heavier than nitrogen, and which had not been removed by the means known to remove the other known gases. Proceeding on this assumption, he soon isolated the gaseous element, Argon. Then followed the discovery of the whole family of inert gases, the existence of which had not been suspected. The small difference in densities, carefully evaluated as not accidental, led to a scientific discovery of major importance.

There are other problems confronting investigators. We cannot measure everything. We cannot put a rain gauge in every square mile of the country. The location of rain gauges in use constitutes a sample of all possible sites. Similarly we cannot test all the steel bars produced by a steel mill. If the test involves loading a test bar with weights until it broke, we would have none left to use in construction. So, a sample of bars must be tested to supply the information on the strength of all

bars in that particular batch. Accordingly, standard sampling techniques have been developed in each particular area of testing. Tremendous efforts are being made to improve our techniques of making measurements, for who knows what other exciting discoveries still lie hidden behind small differences. Only when we know the sources of error in our measurements, can we set proper tolerances, evaluate small differences and estimate the accuracy of our measurements.

The Measure of All Things

Scientists reckon that there are laws of measurement just as fascinating as the laws of science and are beginning to put these laws to work for us. These laws help us understand the errors in measurements and they help us detect and remove sources of these errors. They provide us with means of drawing objective, unbiased conclusions from data. They tell us how much data will probably be needed. Today, many great research establishments have on their staffs several specialists in the theory of measurements. Some measurements require only a simple procedure and little equipment. The apparatus may be no more than a scale marked off in the desired units. It is easy to measure the width of a plastic specimen by using a scale in centimeters and millimeters. The air temperature of a laboratory where all mechanical testing equipment is housed can be easily monitored by reading a thermometer. When proper instruments are available and used carefully, many measurements may require no more than a careful reading of a scale. On the other hand, most scientific measurements involve elaborate equipment and complicated techniques to use.

If a chemist wants to determine the amount of chlorine in water, he may perform a fairly lengthy sequence of operations. First, the chemist must weigh out a sample of the material and record the weight. The sample must be treated with an acid that will dissolve all of the chlorine. Any insoluble residue must be filtered off to obtain a clear solution, and the filter paper must be washed carefully with the excess acid to make sure that none of the chlorine is left behind. It then may be necessary to adjust either the acid concentration or the volume of the solution, or both, before adding a second reagent, usually silver nitrate, to precipitate the chlorine. Enough must be

added to precipitate all the chlorine as insoluble silver chloride. The precipitate of silver chloride is separated from the acid by filtering the suspension through a crucible with a porous bottom. Before doing this, however, it will be necessary to weigh the crucible, making sure that it is dry. The precipitate collected in the crucible should be then washed with distilled water to remove all traces of the reagent and dried. The weight of the empty crucible subtracted from the weight of the crucible and the precipitate gives the weight of the silver chloride. By using the atomic weights of silver and chlorine, the proportion of chlorine in the silver chloride molecule can then be determined. The weight of the silver chloride precipitates multiplied by this proportion gives the weight of chlorine in the precipitate. This, of course, is also the weight of the chlorine in the original sample. The weight of the chlorine divided by the weight of the sample and multiplied gives the percentage of chlorine in the sample, thus completing the determination of chlorine. Each weighing (sample, empty crucible and crucible plus precipitate) is a measurement, and three measurements are necessary to measure the amount of chlorine in the material. This sketch of the analytical procedure reveals that there are several steps, all of which must be taken with great care. If the silver chloride precipitate is not carefully washed, it may be contaminated and appear too heavy. If the precipitate is not transferred completely to the crucible, some may be lost. None of these steps can be carried out so that they are absolutely free of error. For example, since the silver chloride is very slightly soluble, some of the chloride will not be precipitated and may result in error.

Evidently, a measurement is subject to many sources of error, some of which may make the measurement too large while others may make it too small. It is the aim of the experimenter to keep those sources of error as small as possible, although error cannot be reduced to zero. Thus, the task is to find out how large an error there may be. For this reason, information on the sources of errors is indispensable. In order to decide which one of these two materials contains the larger amount of chlorine, we need accurate measurements. If the difference in chlorine content between the materials is small and the measurement is subject to a large error, the wrong material may be selected as the one having the large amount of chlorine. There may also be an alternative procedure for determining chlorine content which could be faster.

How do we know which procedure is more accurate unless these errors in the measurements have been carefully studied? Accordingly, the analyst seeks methods to make errors in his measurements so small that they will not lead him to incorrect answers to scientific questions. The instrument makers continually devise improved instruments and scientists continually undertake problems that require more and more accurate measurements. Today, our requirements for accuracy in measurements often exceed our ability to meet them. One consequence of this obstacle to scientific research has been a growing interest in measurement as a special field of research in itself.

The most critical element of any measurement process is the relationship between a single measurement and the reference base for the unit of measurement. The reference base is the *ultimate authority* for the measurement. Reference bases for fundamental units of measurement (length, mass, temperature, voltage and time) and some derived units (pressure, force, flow rate, etc.) are maintained by national and regional standard laboratories. Consensus values from inter-laboratory tests or instrumentation/standards maintained in specific environments may serve as reference bases for other units of measurement. Most of the scientists who make measurements are almost completely absorbed in the answer they are trying to get. Scientific measurements are often time consuming and require special skills. The work of making measurements is all too often a tiresome and exacting task that stands between the research worker and the verification or disapproving of his thinking on some special problem.

Who Is a Metrologist?

(Or, what does a Metrologist do at work everyday?)

This definition is taken from the *Dictionary of Occupational Titles*, an official guidebook produced by the Employment and Training Administration of the US Department of Labor.

A metrologist—"Develops and evaluates calibration systems that measure characteristics of objects, substances, or phenomena, such as length, mass, time, temperature, electric current, luminous

intensity and derived units of physical or chemical measure. Identifies magnitude of error sources contributing to uncertainty of results to determine reliability of measurement process in quantitative terms. Redesigns or adjusts measurement capability to minimize errors. Develops calibration methods and techniques based on principles of measurement science, technical analysis of measurement problems and accuracy and precision requirements. Directs engineering, quality and laboratory personnel in design, manufacture, evaluation and calibration of measurement standards, instruments and test systems to insure selection of approved instrumentation. Advises others on methods of resolving measurement problems and exchanges information with other metrologist personnel through participation in government and industrial standardization committees and professional societies."

Weigh to go?

In a vault under a courtyard near Paris lies a small, shiny cylinder of precious metal—and a big scientific embarrassment. Once a year three people gather outside the vault, turn their keys simultaneously and open the door. They come to check if that small, shiny cylinder is still there. Once satisfied that it is, they shut the door, say their farewells and depart wondering how much longer science must endure this visible ritual.

It may only be 40 mm tall, but the cylinder kept under lock and key at the International Bureau of Weights and Measures (BIPM) at Sevres in France is beyond price. For, it is utterly and absolutely unique—the one object in *all the Universe* that has a mass of exactly 1 kilogram. Despite years of effort to find out an alternative, the precise definition of the unit of mass, that most basic and familiar property of matter, is still nothing more fundamental than the mass of the chunk of metal created in 1889 from an alloy of 90% platinum and 10% iridium. Anyone who really wants to trace the kilogram to the original has to travel to Sevres and check out the cylinder in the vault. There are copies—primary standards—in various labs around the world, but they are not the real thing. Every few decades, the copies are returned to BIPM for comparison with the real one.

Time is Ticking Away

....You Are Even Older Than You Think!

Co-ordinated Universal Time (UTC), which is the basis of world time distribution, is a combination of the time scales TAI and UT1. The International Atomic Time scale (TAI) is calculated and maintained by the BIPM as a weighted average of data from 230 atomic clocks kept in over 60 national laboratories worldwide. Universal Time (UT1) is a dynamic time scale derived from observations of the rotation of the earth, and is proportional to the angle of rotation of the earth about its axis. UT1 follows the rise and the set of the sun, which TAI does not necessarily do. The problem is that these intervals are actually rather irregular, meaning that there is an inconsistent difference between astronomical time and TAI. Hence, although the relentless TAI is ideal for scientific purposes, its everyday use could eventually result in our having mid-day lunch at night! By definition UTC has the same metrological properties as TAI, which is an atomic time scale. In addition it follows the rotation of the earth within less than one second by the addition or subtraction of so-called leap seconds. The difference between UTC and TAI is, therefore, always a complete number of whole seconds and the difference between TAI and UT1 is always less than 0.9 seconds.

Consequently, a modified time scale known as Co-ordinated Universal Time is generated that is based on TAI but which is periodically adjusted so as to maintain it within 0.9 seconds of the observed astronomical time at the zero longitude meridian by adding or subtracting whole seconds. The International Earth Rotation Service (*yes, there actually is someone responsible for this momentous task!*) decides whether these "leap second" adjustments are necessary to our clocks and watches. Since its introduction in 1972, UTC has been regularly modified through the inclusion of positive "leap seconds". The cumulative effect is that UTC is now about 30 seconds "behind" TAI. So, you *are actually 30 seconds older than you think!*

Reliable measurements depend critically on competent staff, validated and tested methods, comprehensive quality systems and traceability to appropriate measurement references. Recognition of these requirements

is underscored by the increasing adoption of standards and measurement quality systems, such as laboratory accreditation against ISO 17025:1999, or the pharmaceutical industry's GLP and GMP requirements, etc.

Traceability

Traceability is a fundamental aspect of free trade. Traceability is the property of the result of a measurement or the value of a standard whereby it can be related to stated reference, usually national or international standards, through an *unbroken chain* of comparisons all having stated uncertainties. A national traceability system links field measurements to the SI by providing tools such as reference materials, reference data and calibrations. A metrology infrastructure to enable global recognition of measurements and standards must exhibit two major features: vertical traceability, in order to ensure the quality and accuracy of measurements, and comparability with the standards realized and maintained by the National Metrology Institutes (NMIs) of various countries.

NMIs are responsible for national traceability and internal comparability. The function of comparability is becoming more critical in global trade and transfer of scientific data from one laboratory to another. (Figure 5.3)

Besides providing vertical traceability, an NMI also serves to link the national infrastructure to the international measurement system. NMIs have been carrying out and collaborating international comparisons of their national measurement standards for more than a century. But, the ad hoc recognitions resulting from these historical interactions among the NMIs are no longer considered sufficient to promote international trade and ensure equity in trade. In today's global society, comparable results are needed in order to avoid duplicating measurements which cost time and money. A laboratory usually finds itself at the end of a traceability chain. Comparable results can only be achieved by anchoring them to a common base. In other words, we need results traceable to a common base, preferably to one with worldwide recognition. The value of traceability for laboratories and customers are, in many instances,

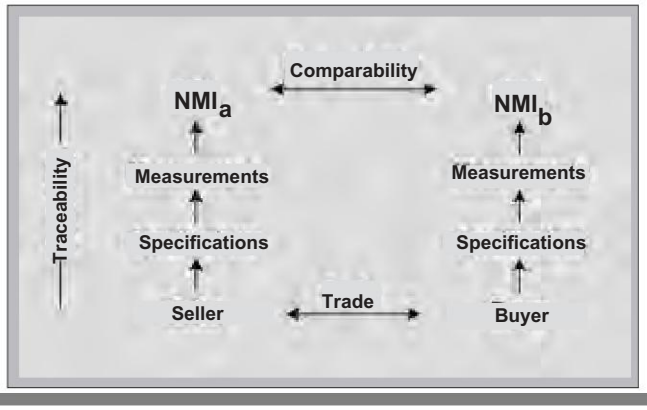


Figure 5.3 Traceability link

closely related to each other. It has to do with the immediate recognition that an accurate value can only be claimed within the limits of the boundaries indicated in the statement on uncertainty. This helps to avoid the over-interpretation of data and provides a clear view on the limits of validity. Measuring devices have to be traceable to the national recognized standards by an unbroken chain of calibrated references with known uncertainty. At the top of the chain the national standard is referred to the international convention. The International Committee of Weights and Measures was a key player in the negotiation and implementation of a Mutual Recognition Agreement (MRA) that has been devised as a mechanism to demonstrate comparability of measurements and standards among NMIs.

Method Selection and Evaluation

The laboratory needs to establish a policy and procedure for the selection and use of analytical methods. Many times laboratories will have multiple methods for the same analysis. The success of the analysis should not be dependent on the arbitrary selection of the method by the analyst. The priority of using standard methods, official methods or in-house methods must be established for all laboratory personnel to follow. Methods used should include a fitness for purpose. Using a method incorrectly can be just as damaging as using an untested, unvalidated method. Specific samples or sources of samples may

require the laboratory personnel to select a method that is not obvious from the use of commonsense. Because methods are so important for the quality of data, it is essential that a procedure for selection of methods is included in the quality program. Many laboratories are engaged in the development and publication of analytical methods. The process used by these laboratories to assess methods becomes an element of their quality program. When a laboratory is going to use a method for the first time, some form of validation is essential for the method in question. After a method is selected and used, it becomes a regular activity to assess the performance of that particular method.

DOCUMENTATION—TRAILING BEHIND

Good judgement must prevail in producing an accurate, reliable and coherent record of experimentation. Proper verification and transparency in research is becoming increasingly important in supporting the validity of results and proving inventorship. Appropriate documentation is one of the key elements of a quality management sytem. A well-maintained and properly documented laboratory notebook establishes a permanent record of research protocols and results which can be referred to in the future, most commonly for the preparation of scientific papers and patents. Additionally, it can be an invaluable source of information for a variety of purposes, including determination of claims of discovery where new inventions are concerned; demonstration of adherence to standards of good practice, and of academic and ethical integrity; and compliance with contractual provisions permitting sponsors to audit work carried out in pursuit of sponsored research.

1. Determination of claims of discoveries

Laboratory notebooks provide important documentary evidence of the *conception,* and *reduction to practice* of an invention. In the US 'invention' comprises both elements: *conception*, the formulation of the complete means to solve a problem in such a way that one of ordinary skill in the art could practice the invention without unduly exercising extensive research or experimentation; and *reduction to practice*, the making and testing of the invention, and determining

that it will work for its intended purpose. Generally a sketch and a brief written description are sufficient to establish *conception*. *Reduction to practice*, however, can be *constructive* (by filing a patent) or *actual* (by the construction and successful testing of a prototype of the invention). In either case it requires convincing and corroborating evidence of diligence (i.e. constant progress from the conception of an invention). Laboratory notebooks supply the necessary background data and evidence for scientific publications and can be used in defense against claims of scientific misconduct. Even if a patent application is not filed on the subject-matter of a research project, it may still be necessary to establish when and where an invention occurred, e.g. in any patent infringement litigation.

2. First to Invent practice in the US

Unlike the practice in the UK and Europe, whereby a patent is awarded based on the 'first to file' a patent application citing the new technology, US patent law requires that inventors satisfy its 'first to invent' criteria. This system relies heavily upon the production of clear, convincing, documentary evidence to support the precise timing of an invention and/or its reduction to practice. Properly maintained laboratory notebooks are critically important to this process. A detailed description of the research undertaken during the course of the project, which can be relied upon and referred to at a later stage to establish the date of an invention, is essential if it is deemed appropriate and desirable to seek patent protection internationally.

3. Verification or reproduction of important procedures

A successful laboratory notebook allows for ready verification of the quality and integrity of research data and enables another investigator to reproduce the procedure which has been documented to get the same result. Entries which are fragmentary, or so difficult to follow that they can be interpreted only by the author, are of little practical use. Laboratory notebooks should permit what step, or steps, in a procedure might introduce discrepancies, and advise on potential solutions.

4. Compliance with sponsored-research audit requirements

If research is being undertaken with the benefit of third-party funding, which is increasingly the scenario in global outsourcing and off-shore R&D units, there are often additional obligations placed on the institution to provide an adequate record of work done during the course of the project. Similarly, research councils, or other government agencies may impose regulatory requirements for certain types of records to be retained by the institution, e.g. research records relating to clinical or public health studies should be retained for twenty years to provide scope for follow-up. Once a laboratory document has been completed, the notebook should ideally be retained for a minimum of six years. This is aimed to ensure that full details of the contracted research in question can be accessed in the future to provide evidence in support of an invention, a publication or adherence to appropriate or regulatory procedures.

In analytical laboratories, the work is performed on samples submitted to the laboratory either by outside clients or in-house product developers working in another on-shore or off-shore location. To ensure that the results generated are attributed to the right sample, it is essential to have a system in place for controlling samples. The system will include receiving, preservation, storage, custody and disposal. The value of analytical results is lost if control of the samples is not maintained. Once the sample has been analyzed and then discarded, the laboratory records become the standing evidence of the work performed. The quality system must have a comprehensive system for document and record control. Protection from tampering, obliteration and destruction must be maintained. Access to records and use of information must also be included in the plans for the quality system. The defensibility of data relies on the ability to produce the data for review in the same condition as it was when generated.

Chain of Custody

Keeping a record of all personnel that handle, analyze and store samples is accomplished through the use of a process and document called a

chain of custody. To be able to retrace all the steps in a process that could have affected a sample's results is important to demonstrate credibility. The quality system needs to have specific instructions for the use and retention of chain of custody.

Analyze

In order to guarantee the quality of any product, every laboratory must be able to quantify the variations in their internal workflow process that produces test results. Any process is made up of several components: machine, material, method, manpower, measurement and environment. In the course of variation in the process, each component contributes to the total. Unfortunately, these components are not strictly independent. Measurement methods affect the measurement of all other factors. Just as we often blindly accept results generated by a computer or calculator, many regard measurements as absolutely representative of the characteristic being examined. But, measurement techniques are subject to variation just as anything else in the real world. Consequently, whenever some process variable is under study, the reality of measurement must be considered before the making of an evaluation of the process itself. In addition to determining whether or not the gauge or measurement device is accurate (to avoid systematic variation or bias), the repeatability and reproducibility of the device must be taken into account. These refer to the interaction between the gauge and the people using it. *Repeatability* refers to the variation present when one person measures the same part several times with the same gauge. *Reproducibility* is the variation resulting from different operators measuring the same parts with the same gauge. Repeatability can be referred to equipment variation, whereas reproducibility is due to operators. Since, laboratories gather data for important purposes, such as determining conformance, analyzing non-conformances and controlling processes, we are going to make decisions based on the data which is collected. The decisions will result in actions that will be taken on products or processes.

Hitting the Mark

The first step is to define measurement as a process and identify the sources of variation.

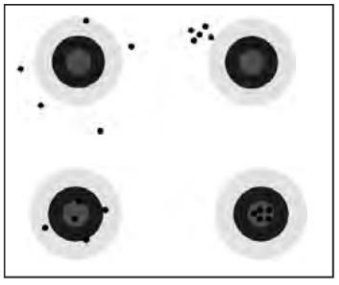


Figure 5.4 Accuracy and precision

Thumb through any instrument specification and you are presented with a whole host of technical terms describing the product's capability. There are some basic ones—*accuracy, precision, resolution* and *bias.* What *is* the difference between accuracy, precision, bias etc.? Four marksmen were aiming for the 'bulls-eye'. This is analogous to making a perfect measurement with the 'bull' being the conventional, "true value". So, take aim and fire five rounds... as in Figure 5.4.

Looking at the first target (*above left*), the shots are widely distributed and mostly off-target—both inaccurate and unrepeatable. However, is the second marksman (*above right*) much better? These shots are closely grouped but they've all missed the target completely! The effort is precise but inaccurate. On to the third (*below left*) case, the shooter has reliably hit the target but the shots are dispersed, so we have accuracy (two in the "bull") but imprecision. Of course, the final target shows the way it should be done—an Olympic champion's performance perhaps—little deviation from the "true" every time, showing both accuracy and precision. Measurements which are *precise* may not be accurate for their correctness (relationship to national standards). The degree of accuracy and precision results from the combined effect of measuring equipment, technique, environmental conditions and the characteristics of the item being tested. If a series of repeated measurements were made and the data plotted as a histogram (Figure 5.5), the shape described by the bar-heights represents the *distribution*.

The plots show the performance of our marksmen when given machine guns (lots of data), where their aiming-point (bulls-eye) is

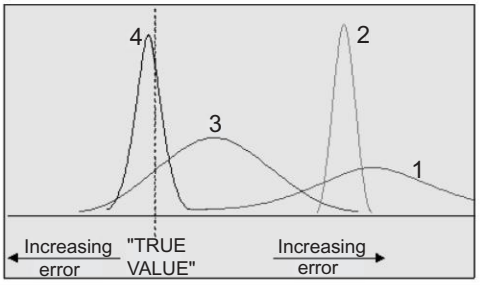


Figure 5.5 Distribution of data

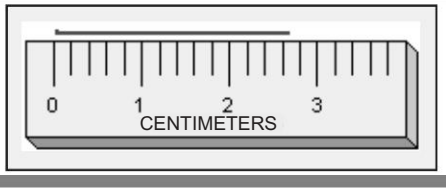


Figure 5.6 Resolution

the "true value". The distance of each peak from the "true" is their average error and the width of the curve shows the dispersion. Whose performance is represented by each plot?

1. The "beginner" is inaccurate/imprecise.
2. The second effort is repeatable but has poor accuracy.
3. The third case is with accuracy but not good precision.
4. The best case is accurate and precise.

Sometimes *resolution* is mistaken to be the same as accuracy. This misconception often relates to instruments with digital read-outs where a similar assumption is that, for example, a frequency counter with 11 digits must be 100 times more accurate than one with 9-digit resolution. Resolution is just the discrimination that the instrument can show.

Look at the metric ruler in Figure 5.6. Its resolution is 2 millimeters (one-fifth of a centimeter) even though it can readily be used to measure the length of the line drawn over the ruler with better

estimated resolution (certainly to 1 mm and possibly 0.1 mm with magnification). However, our ability to visually subdivide between the marked graduations contributes to the uncertainty of the measurement. From inspection, the evidence is that the line is between 2.6 and 2.8 cm and, considering only the resolution, it would be reported as 2.6±0.2 cm. If some form of magnification were available, the measured value might be stated as 2.65±0.05 cm.

CALIBRATION

The uncertainty associated with the measurement is likely to increase with the use of Testing and Measuring Instruments (TMI). In order to ensure that the measurements made by the TMI are accurate and reliable, they are required to be checked periodically for their performance during their useful life. The process of checking the performance of the TMI by comparison with a standard is termed as calibration. In order to rely on the measurements through TMI systematic and periodic verification is important. Further, the unbroken chain of calibration of standards and TMI, termed as traceability, ensures that the measurements are traceable to a common reference, an important consideration for the exchange of technical data. At present, there seems to be no single best practice of establishing and adjusting the calibration interval that applies to all TMI. The reason being that we encounter many varieties of instruments in various fields such as electrical, electronic, thermal, optical, mechanical, biological, medical etc. The simple concept behind calibration is that measuring equipment should be tested against a standard of higher accuracy. For any parameter/range we should be able to illustrate this type of hierarchical relationship:

National Standard..... Accurate to 0.002 %
Calibration Laboratory..... 0.01 %
Company "Master" Item..... 0.07 %
Company Production Equipment..... 1.0 %
Produced Product..... 10.0 %

These calibrations need to be made on a planned and periodic basis with evidence of the comparison results maintained. These records

must include identification of the specific standards used (which must be within their assigned calibration interval) and some means of knowing the method used and other test conditions. By examining these records, it should be possible to demonstrate an unbroken chain of comparisons that ends at the agency responsible for maintaining and developing a country's measurement standards. This demonstrable linkage to national standards, with known accuracy represents 'traceability'.

Certified Reference Materials

Determination of the amount of substance often requires measurements of different properties. For example, sample mass, on a balance compared to a mass reference, analyte identity by comparison to a reference, perhaps using a spectrometer and a database of known compound and analyte quantification by comparison to a different

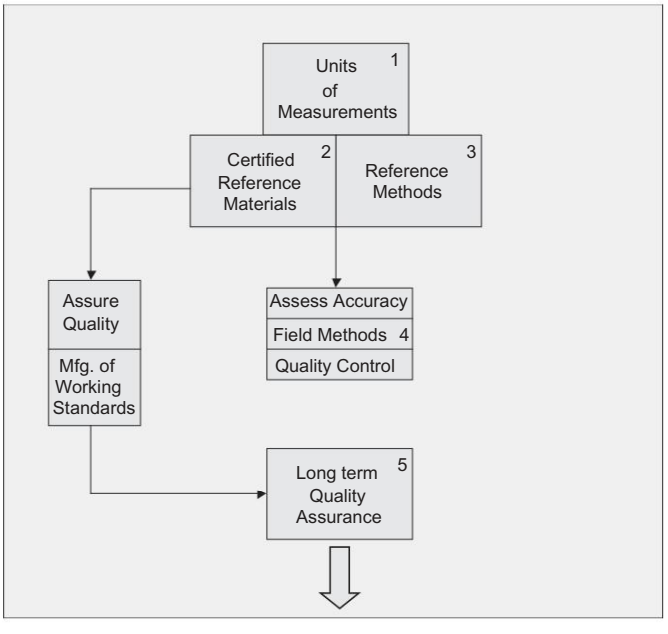


Figure 5.7 Systems Approach to the use of Certified Reference Materials

reference, perhaps a reference material. One key to traceability that must be supplied by laboratories is the traceability of values carried out by references, especially by Certified Reference Materials (CRMs). Because analysis of unknown materials depends on comparisons of response from a standard with that of the analyte, it is critical to know that the standard used contains the concentration of analyte that the user believes is present. To establish and document the accuracy of the standards used on a daily basis in the laboratory, some form of reference standard is needed. The accuracy of the analysis can be tracked over time by having and using a reference standard that is analyzed repeatedly. In 1906 the National Bureau of Standards (since renamed the National Institute for Standards and Technology, NIST) started to issue samples of materials for standardizing analytical techniques and methods. Today, the NIST inventory of standard samples, which are issued under a NIST registered trademark, SRM ®, consist of over 230,000 units of more than 1300 different products. These SRM are usually the result of collaboration between NIST and representative of industry and science. Thus, SRMs serve as crucial reference points in establishing a comprehensive measurement system for the US. SRMs are available for use in industrial materials production and analysis, environmental analysis, healthcare measurements and basic measurements in science and metrology. For many years, SRMs have helped those countries that were in the process of developing a national measurement system of their own based on reference materials and reference methodology.

UNCERTAINTY

"We think that our reported value is good to 1 part in 10,000.

We are willing to bet our own money at even odds that it is correct to 2 parts in 10,000.

Furthermore, if by any chance our value is shown to be in error by more than 1 part in 1000, we are prepared to eat the apparatus and drink the ammonia."

—DR. C. H. MEYERS, REPORTING ON HIS MEASUREMENTS OF THE HEAT CAPACITY OF AMMONIA

Despite what some suppliers may often claim, no measurement can be guaranteed to be perfect. An uncertainty is a figure of merit associated with the actual measured value; the boundary limits within which the 'true' value lies. Contributors to this 'potential for inaccuracy' include the performance of the equipment used to make the measurement, the test process or technique itself and environmental effects. Additional imprecision may result from behavior of the phenomenon or item being measured. To prove that a product complies with specification or doesn't, the uncertainty must be less than the unknown's specification. A skilled metrologist will assess and combine these various components in an uncertainty budget.

Extreme Measures

Scientists are homing in on the fundamental nature of the universe, using instruments of transcendent elegance. To do this they collect data of stunning accuracy, expressed in terms of a beautifully consistent set of units themselves defined in terms of fundamental constants. Improving measurement accuracy and the technology to deliver it continues to offer fundamental and exciting challenges for physics and materials science. At NIST's Advanced Measurements Laboratory (AML), scientists ensure the standards we live by—that a watt is a watt; that a certain transistor is one ten-thousandth of an inch, not two ten-thousandths of an inch; that a gigabyte is no more or no less. Some of these laboratories will have temperature controls so sensitive, they can be adjusted by one ten-thousandth of a degree. Other rooms, in which the tiniest imaginable piece of lint in the air could destroy an experiment, will have circulators changing the air 300 times every hour. Some hi-tech labs will be suspended on air springs, inside of which computer-controlled bladders of air make real-time adjustments to any vibrations coming in from the outside world!

Improve

> *"If you're not part of the solution, you're part of the precipitate."*
>
> —Steven Wright

Round Robin Testing

Comparison of results within the laboratory and with other laboratories is one way to locate and correct *out of specification* situations. Using proficiency testing samples between laboratories on a regular basis is an excellent way to improve a laboratory's performance. Using quality control samples within a laboratory is an excellent way to assess the competency of the analysts. This key element of the quality program also requires feedback to the analysts and their supervisors of the intra- and inter-laboratory sample results. The laboratory personnel will improve their accuracy and precision when the intra- and inter-laboratory results are provided to the analysts that produced the results.

Reducing Defects: Men in Black in Action

Most people rarely think about statistics, except perhaps in Las Vegas or Atlantic City! Instead, people tend to expect the natural world to work in predictable ways. When they lean on a rock, they expect the rock to hold them up. But science deals with statistical uncertainties all the time (except sometimes, as in the case of falling through the rock, the uncertainties are exceedingly small). A measurement, which most people would think is an absolute fundamental quantity, is really a statistical quantity. Six Sigma (6) is a business-driven, multi-faceted approach to process improvement, reduced costs and increased profits. The term *sigma* (a Greek letter) is used to designate the distribution or spread about the mean (average) of any process or procedure. For a business or manufacturing process, the number of sigmas fitting between the specification limits is a metric that indicates how well that process is performing. The higher this number, the better the process. Sigma measures the capability of the process to perform defect-free-work. A defect is anything that results in customer dissatisfaction. The number of sigmas indicate how often defects are likely to occur. The higher this number, the less likely a process will produce defects. As this number increases, costs go down, cycle time goes down and customer satisfaction goes up.

The companies that invented Six Sigma back in the late 1980s developed special names like *Black Belts* and *Master Black Belts* for each of the

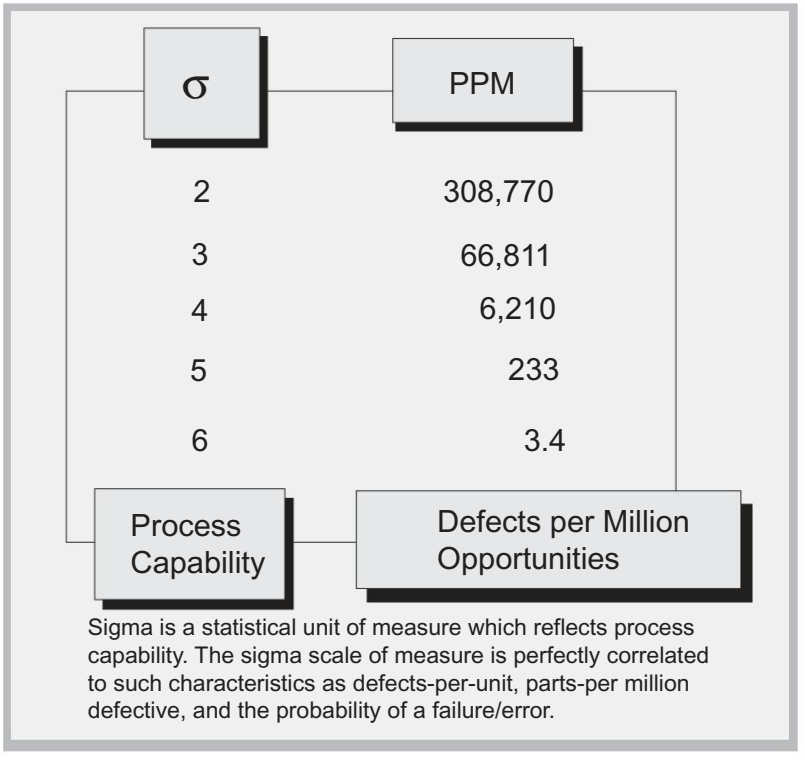


Figure 5.8

leadership roles created in the organizations for these improvement processes (based on the practice in Karate of having colored belts that indicate the levels of mastery) in applying statistical tools. With a fundamental principle to improve customer satisfaction by reducing defects, its ultimate performance target is virtually defect-free processes and products. Six Sigma methodology consisting of the steps "Define-Measure-Analyze-Improve-Control" is the road map to achieving this goal.

Corrective and Preventive Actions

A process for documenting corrective action, the mechanism for compiling and analyzing it, and the use of corrective actions to improve

the quality program are needed. The review and assignment of the responsibility for taking corrective action is determined by management. When re-occurrences of a corrective action take place, it is an indication that preventive action is required.

Internal Audits

A means of assessing the implementation and development of the quality program must also be established. One of the elements of the classical continuous improvement scenario includes an assessment phase. To improve the quality system itself, the laboratory personnel need to develop a way to measure the present state of the system as well as changes that have occurred. Audits can be quantitative or qualitative in their focus.

Management Reviews

For the quality program to continue to function properly, it is necessary for the laboratory management to be made aware of the status of the program. This element is a requirement in ISO 17025. The quality assurance personnel are responsible for determining the condition of the program and bringing it to the attention of the management. These reports are formalized and archived for future reference.

Control: The Defining Moment

Conformity Assessment

Certification, registration, approval, accreditation, assessment, compliance—they all mean the same thing, right? *Wrong!* There are some particular words that should be used in relation to conformity assessment. The terms certification, registration and accreditation are often used interchangeably in relation to independent assessment of a quality system, product compliance with a standard, or servicing competence. The process of determining whether products, processes, systems or people meet specified requirements has been given the name, *conformity*

assessment. ISO's Committee on Conformity Assessment (CASCO) provides several ISO guides on the subject. The tools of *conformity assessment* are listed in the order of their emergence in Table 5.1 with an asterisk to indicate usage by first parties (suppliers), second parties (customers, regulators or others who demand compliance with requirements) and third parties (laboratories independent from both suppliers and their customers).

Table 5.1 The "tools" of conformity

	First Party	Second Party	Third Party
Manufacturer's declaration	*		
Inspection	*	*	*
Testing	*	*	*
Auditing	*	*	*
Certification			*

Declaration of Conformity

Commonly called self-certification, it is what a supplier (first party) does by giving written assurance that their product meets specified requirements (e.g. a standard specification for the product). It is the earliest and most common form of conformity assessment and may be supplemented by the other forms of conformity assessment: typically inspection and/or testing (including calibration) of the product, auditing of related product production systems and processes and, more recently, certification (or registration) of the supplier's quality system.

Certification

This is defined as a procedure by which a third party gives written assurance that a product, process or service conforms to specified requirements and is applicable to all CROs and independent testing.

With the growing use of these conformity assessment tools has come the need to assure the competence of the conformity assessment bodies in order to enhance confidence in the results of conformity assessment processes. The following are a few additional representative certifications in specific fields of testing. Each country has certification bodies like the FDA and EPA in the US and the BIS in India that are responsible for implementing quality standards in their region and regulatory field. In India, the Bureau has a chain of labs for conformity testing of certified products and samples offered by applicants for the grant of a license, which is an essential feature of the BIS Certification System. BIS also approves a number of testing labs in different product categories for testing as per specific protocols.

Accreditation

In theory, the task of third parties is to provide the consumer and the regulatory authority with enough evidence that the products are in conformity with the requirements—in theory, that is. How do we know that these independent laboratories do their job correctly? Because they are independent of the producer? Maybe. But is that enough? On this level of supervision, there is also fierce competition amongst the certification bodies, the laboratories or among the inspection bodies. Thus, to equalize supervision at level one, an additional layer of supervision is required. This layer is called accreditation. Its function is to establish that certifiers, inspection bodies and labs conduct their work in the correct way, have a quality system and that they are competent to do their job. Accreditation is an important factor in facilitating trade at the national and international level. To perform accreditation in such a way that it can have this facilitating action involves several aspects including traceability, metrology and fully independent and non-commercial operation. Accreditation has been defined as a formal recognition that a testing laboratory is competent to carry out specific tests or specific types of tests. The objective of laboratory accreditation is to improve the consistency of analytical data, to improve comparability of data generated in different laboratories and finally to reduce the number of analyses. For example, if a food product is traded between two countries, analysis should be performed only in the exporting country and only a few

checks should be necessary in the importing country. The results of analysis performed in different laboratories in different countries should be the same as within previously specified limits. During the accreditation process, the accreditation body is required to approve and issue a "scope of accreditation". This is a supplementary certificate document that outlines the lab's technical capabilities. Labs are required to document each calibration or testing parameter, parameter range, the best measurement uncertainty for each parameter and the calibration/testing equipment or standard(s) used for each parameter.

Important elements of added value that labs may expect from accreditations are:

- An opportunity and motivation to improve and formalize their quality systems, as well as the evaluation and maintenance of their technical competence.
- An assurance for the management that the system is documented and assessed regularly, hence facilitating the continuity of the desired level of the quality of lab services.
- The recognition of the value of accreditation by the market, and where relevant by public authorities which prescribe measurements and testing in the context of regulations.

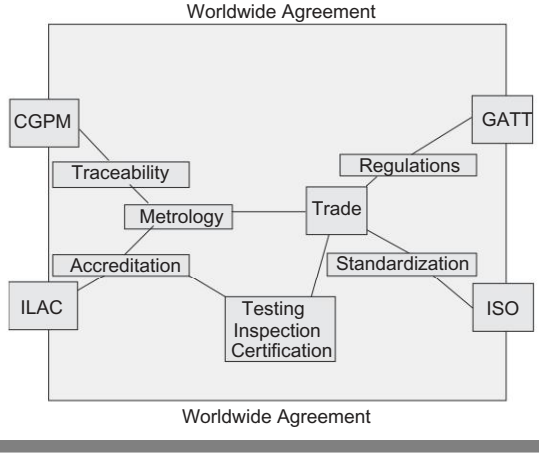


Figure 5.9 Free trade construction and role of metrology and laboratory quality systems

We now have the building blocks for free trade and providing guarantees to customers and regulators. These building blocks are :

- Product standards or regulations
- Independent supervision on a competitive basis
- Supervision of the independent supervisors on a non-competitive basis

These are, however, only the building blocks. To actually accomplish free trade we need a little more. We need a solid foundation, traceability and international standardization.

Mutual Recognition Agreements: Construction of Free Trade

An international arrangement signed in Washington DC on Nov 2, 2000, enhanced the acceptance of technical data accompanying goods and services crossing national borders. The arrangement which involves 37 member bodies from 28 economies represented at the General Assembly of the International Lab Accreditation Co-operation (ILAC), means that other signatories will accept goods tested in one country by a lab that is accredited under a signatory to the arrangement. This is a major step toward reducing or eliminating the need for re-testing of goods by the importing country. The arrangement came into force from Jan 31, 2001. The concept of "one test, one accreditation, accepted the world over" moved a step closer with the signing of MRAs.

Belinda Collins, Chair of ILAC, noted the significance of the signing, "For many years, the re-testing of goods by an importing country has been considered a major technical barrier to trade. The WTO identified such technical barriers as a major concern to world trade since the mid 1970's. Such barriers can not only add significant costs to goods entering a country, but can also delay and, in some cases, prevent the goods being accepted by foreign markets." The agreement will facilitate the acceptance of goods already tested by an accredited lab and they should enjoy easier access to foreign markets participating in the arrangement.

Reconnaissance mutuelle

des étalons nationaux de mesure et des certificats d' étalonnage et de mesurage émis par les nationaux de métrologie

Paris, le 14 octobre 1999

Mutual recognition

of national measurement standards and of calibration and measurement certificates issued by national metrology institutes

Paris, 14 October 1999

Comité international des poids et mesures

Bureau international des poids et measures	Organisation intergovermentale de is convention du métre

Figure 5.10 Mutual Recognition Agreement (MRA)

The key to the arrangement is the developing network of accredited testing and calibration facilities around the globe that are evaluated and recognized as being competent by specific authorities, known as laboratory accreditation bodies, in participating countries. The cornerstone to the new arrangement is the utilization of existing or developing regional arrangements established in America, the Asia-Pacific region, Europe and S. Africa. The bodies participating in these arrangements are

responsible for maintaining the necessary confidence in accreditation bodies from their region that are signatories to the new agreement. There is now a firm foundation in place for manufacturers and exporters, that have their goods tested by accredited labs, to enjoy greater market access and lesser costs associated with re-testing and greater overall competitiveness in global markets.

Chapter 6

Inventing the Future: Citius, Altius, Fortius

"Know ye not that they which run in a race run all, but one receiveth the prize."

—I Corianthians 9:24

Peter Drucker remarked that knowledge, like electricity, is a form of energy that exists only when it is being used. The same is true of talent. Economic success accrues increasingly to those societies and companies that are most capable in identifying, educating, developing and exploiting the talents of their people. Economists tell us that advanced economies are supposed to "leverage their comparative advantage" to develop higher wage jobs, as the lower skilled work becomes commoditized and migrates to lower cost production facilities. One of the reasons for the sound and fury around off-shore outsourcing today is that it seems to have entered a new era. Advances in communications technology like broadband internet and satellite communications have made once-distant hi-tech workers in advanced economies compete in real time with service providers from emerging countries, while these service providers continue to improve their quality, processes and expertise at a much lower cost. Going forward, the quality and intensity of global competition will only increase. All countries will continue to make their business climate attractive to global innovation leaders, and many will retain a labor-cost advantage

in the near future over wealthy nations. The challenge for low-cost countries, and for multinational corporations who are using them, is to achieve clear benefits of the global free markets, while seeking to offset their inherent imperfections. Outsourcing of laboratory processes can become a success story if it provides cost-effective, innovative and value-added scientific advancements. Innovative technology firms have the capacity to invent, create and/or acquire new ideas, but can also command resources to put them to demonstrated good use. The dynamics of a global knowledge economy has presented a complexity of variables that cannot be left to serendipity. Technology leaders need to be in constant surveillance of good ideas and practices which might increase time-to-market and/or market differentiation. This demands a new culture of sharing, interdependence and interaction which is not reflected in traditional hierarchical managements.

For multinational companies, the long-term deliverables of off-shore R&D units are innovations and inventions, but that is not the only goal. The ancillary goal is to also create a climate of innovation that attracts people to the laboratory and to gain a deep understanding of the technological processes involved. If a company is making chips and something goes wrong with the chip, it may be that someone with fundamental knowledge in surface state chemistry can help solve the problem. Another goal is to create a bridge to the rest of the world. Core teams inside the company can understand, relate and adapt discoveries from outside the company and apply them to business needs. In August 2004, Procter & Gamble, the $51 billion multinational that uses cutting-edge technology across its products and services, entered into a tie-up with India's Council for Scientific and Industrial Research, New Delhi. The collaborative research tie-up will use the varied expertise of both organizations for mutual benefit. The thrust of P&G's 'connect and develop strategy', not only develops in-house core competencies, but also goes out and complements work with capable suppliers and institutions where they have the ability to help the company bring better, faster and superior innovations. There are other spin-offs of globalization of R&D in host countries as well. Off-shore R&D units of multinational companies will also be keen on establishing links with local scientific institutions and sometimes may subcontract part of their research to universities and laboratories.

Other benefits include enhanced technical learning by local scientific talent and gains for local industry from the technology spillover effects, such as custom or toll manufacturing.

The success of any organization is increasingly linked to its ability to manage its intangible, and often invisible, assets such as knowledge and competence of employees. In today's fast-changing business environment, companies tend to lose competitiveness if their employees cannot keep pace with advancing knowledge in their disciplines. People, teams and companies are feeling the heat to come up with new products, services and business models. The time-span between the discovery of knowledge and its use has shortened considerably in recent years. The new knowledge industries have created a shift toward accelerating the process of technology development. The organization of the future is about three things—*stretch* (stonger), *innovation* (higher) and *speed* (faster). Business models and work cultures are changing and their impacts are manifesting in areas such as wealth creation, nature of work and corporate structure. The experience of work itself is changing as people are becoming more mobile and reluctant to stay long-term with any single firm. To make knowledge work productive is a challenge to both individuals and organizations. Employers are looking to a new mix of skills and improving the capability of their staff by innovatively applying an existing body of skills across the enterprise.

There are some troubling caveats that surround a lab's existence because it is harder to expropriate research ideas for company profits. Even though research is recognized as the starting point of ideas and products and pays the bills in the long run, it is the last thing which gets cheered and funded heartily in a big company. It comes after sales and marketing, development, manufacturing and all the rest. Coupled with the fact that the *farm-to-fork* cycle is long, expensive and uncertain, low-cost off-shore R&D will fit with the "uncertainty budgets" that these firms can absorb with a smile. Most work is conducted on a fee for service or full time equivalent basis in which customers are billed for the number of scientists devoted to a particular project. Fees can be $225,000–250,000 per Ph.D. scientist per year in the US while the Indian or Chinese labs are paid anywhere from $40,000 to $60,000 per head inclusive of all expenses.

Heads…We Win

The Indian government says in its official plan for 2020: "Our vision of India in 2020 is of a nation bustling with energy, entrepreneurship and innovation." The Ministry of Education, Government of India, claims, according to the 2001 census, that 65.4% of adults are literate and the aim is to have universal literacy by 2020. Because traditional social hierarchy gave the upper layer of society leisure for study and contemplation, India has long had a high reputation for learning. It is also one of the three biggest book markets in the world by volume, according to the Federation of Publishers' and Booksellers' Association in India. The market in 2002 is reported to be worth around INR 70 billion, about $1 billion. The books purchased are mostly education oriented (about 70%) with the rest bought by the educated professional classes. The number of universities in India is growing at around 5%. The quality of education ranges from the sometimes heartbreaking zero-facility degree colleges to the inspiring IIT-end of the spectrum. Both India and her bigger and powerful neighbor China are educating a rapidly growing number of scientists and technologists, building legions of competent, capable and hungry young innovators eager to compete. *The Economist* usually ranks India as the third-fastest growing economy in the world with a GDP growth of around 5.0% and industrial production growth of 5.7%. In contrast, China, the fastest-growing economy, has a GDP growth of 6.7% and 16.5% growth in industrial production. The disparity in industrial production growth is because India has had a far higher growth in services than China. The US Census Bureau's projection on the demographic map of 2020 of labor supply (Figure 1) and shortages around the world shows a huge surplus of population in the working age group in India, enough to cover much of the deficiencies of skilled labor in most parts of the world. It is estimated that by 2015, close to 55% of India's population will be less than 20 years old. This age group will decide the future of India in the 21st century. An enlightened policy environment should help realize the potential of the underlying competitive strength of India by enabling the younger generation to cater to the requirements of knowledge-based industries. The future for Indian knowledge workers is bright and perhaps the future is closer than we think!

IT has had a head start. There is a sense of déjà vu. Reams of news and commentary rehash the discussion on off-shoring of knowledge-based

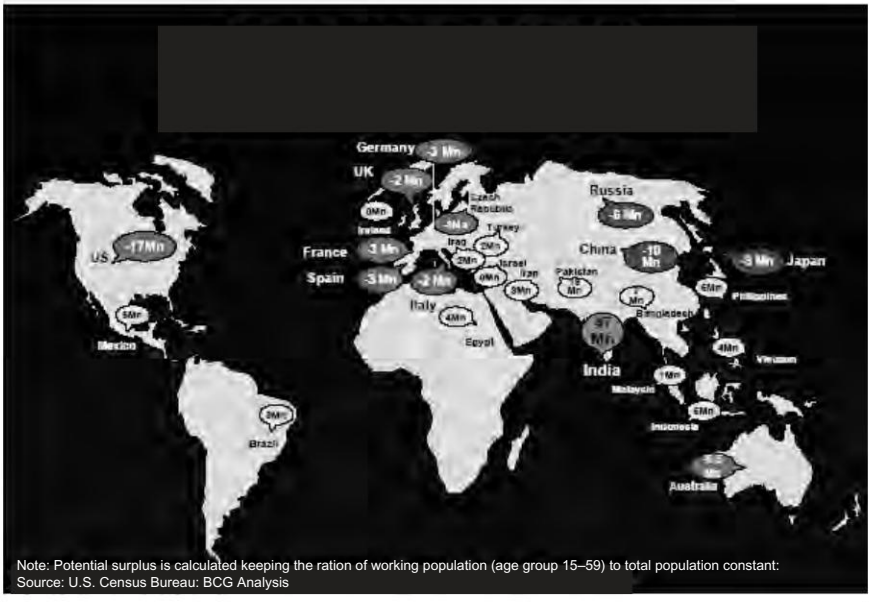


Figure 6.1 Future demographic map—potential surplus population in working age group (2020)

work to India and China that has become so painfully familiar in recent times. Twenty years ago, when the first IT industry survey was carried out by technology magazine *Dataquest*, it revealed a Rs 100 crore industry with small, unlisted companies and hardly any published data. Today, information technology is a Rs 75,000 crore industry that gives India a modern identity. The world now has what was considered unimaginable even 30 years ago—the blueprint of life, the human genome sequence. The potential is obvious. It is estimated that by 2025, biopharmaceuticals will replace 70% of conventional therapies. As one scientist puts it, "If we can live for the next 25 years, we will be able to live for another 75 years. In the next 25 years, we will be able to design new organs, correct bad genes and fix the problems that eventually lead to aging and death."

Mind the Gap

The Indian vision of a knowledge-based economy will be realized only when it is based on the foundation of a vibrant industrial economy and science and technology infrastructure. The 'leapfrogging' argument,

whereby India skips heavy infrastructure building and transforms directly into a knowledge economy, is still suspect. There is no dearth of fascinating stories about IT-enabled changes. But there is little discussion about whether such changes are sustainable and effective when other areas of the economy continue to lag. Proponents of leapfrogging describe how isolated villages without conventional telephones have directly adopted cellular phones. However, the underlying principle is not scalable to the level of the national economy where many complex sub-systems work together. The laws of physics do not allow IT to substitute the physical movement of goods by a 'virtual' movement. A broadband information network will not in itself help achieve faster and cheaper road transport.

Even on the human resources front, the available talent to the projected demand in skill matching is debatable. In chip design, industry experts say, there is big shortage of people in the EDA space. It is getting difficult to scale up operations as per plan. The irony is that India has been so successful in this field that every overseas company in the sector wants to rapidly swell its crew. All campus hires need six months of training to become productive and this time can be recovered, experts say, if tool sets are given to universities and students in their last term to get hands-on training at the institute. While universities provide some exposure on the subject to students, this is still not enough. If India wants to become the design hub of the world in every sense of the term, the country will require that all fresh graduates have a good understanding of the very latest trends, platforms, tools etc.

Industry growth may be limited by the lack of some types of researchers because Indian universities are slow to develop interdisciplinary programs. For example, trained chemists know little about other disciplines such as biotechnology. For pharmaceutical research, India is strong in chemistry but weak in some critical areas of biology. Some companies are partly filling the gap by training young Indian organic chemists and partly by luring back successful scientists based abroad. In any field of research, the job requirements depends on the nature of the service undertaken. Scientists in the field of synthetic organic chemistry, molecular biology and bio-informatics are required for biopharmaceutical companies. The synthetic work on new drug

molecules involves screening pharmacologists, chemists and experts in the field of genomics, computational biology and bio-informatics. Clinical investigators, clinical research physicians, analytical chemists, medical writers, statisticians etc. are required for conducting clinical trials. Some companies also have special programs to customize the talent to fit corporate needs. Because of the quality of human resources that the GE + Bangalore duo succeed in attracting is so critical to the quality of research, GE works closely with universities and academic institutes. To help promising new recruits with fresh Master's or Ph.D. degrees makes the transition from the academic world, and to improve their usefulness to GE, the company offers the graduates the opportunity to join the Edison Engineering Development Program. For two years, participants attend GE-designed courses and complete various assignments while on the job. These engineers are more likely to become part of GE's technical management and keep up their research skills in line with the needs of the company.

Traditional human resource management practices which have been in vogue in many of our manufacturing and service industries, may prove ineffective in managing such knowledge workers. Managers in emerging knowledge-intensive organizations may have to recognize that technical expertise is as valuable as management expertise. In India, some of the leading IT companies have developed outstanding human resource management strategies and practices to deal with the above-mentioned issues. These companies have demonstrated their capabilities to attract, retain and utilize the country's best knowledge workers.

When Candles Cost More than the Cake

Unlike the IT industry which requires mainly bandwidth for the inputs and outputs to flow, experiment-based research involves material movements, instrument purchases and maintenance and governments have to play a crucial role. Laboratories are complex, technically sophisticated and mechanically intensive structures that are expensive to build and maintain. Laboratory business development introduces new clients and new samples to be tested. Animal experimentations, customs clearances, regulatory approval delays and

so on have been the bottlenecks so far. Besides the regulatory role, start-up, installation of laboratory equipment, service support, part inventory maintenance, power backup, spare parts procurement and the support structure for a trouble-free laboratory operation is very weak. Power availability and poor quality of power when available are major hurdles in successful operations and, unlike in the IT industry, running them on power backups is not an economically viable option. While researchers in the west bemoan budget cuts and funding constraints, their colleagues outside this wealthy enclave are struggling to pay frequently inflated prices for lab equipment and materials. Scientists in poorer countries like Poland and Brazil have to pay up to 70% more than their wealthier colleagues for identical supplies, a survey by *Nature* has revealed. Suppliers point out that they do not have control over of prices in individual countries, which are set by local distributors. The discrepancies are explained by market conditions. The suppliers note, in particular, the higher costs of doing business in smaller and less established countries. Although detailed surveys on the Indian situation are not available, it is unlikely to be any different from what exists in other developing economies.

"Most scientists will become contract workers; they will work as temporary gangs of 'fungible' researchers, specially brought together to work on a particular problem and, at the conclusion of each project, redeployed or discarded. Researchers will become totally proletarianized as they lose their property, both in the skills of stable paradigm-based research and in the rights to their results."

—J.R. RAVETZ IN *SCIENTIFIC KNOWLEDGE AND ITS SOCIAL PROBLEMS,* OXFORD UNIVERSITY PRESS, 1971

Creating intellectual wealth needs physical wealth to begin with. Scientific research is marked by long gestation periods. For example, biotechnology involves taking a gamble with the processes of life. It requires at least five years of focussed, expensive research, before a viable innovative product emerges. And, with living processes, there

are no guarantees. To stay afloat in the interim, the company would need a long-term commitment to support expensive research and other more short-term sources of revenue. To breed innovations and technological breakthroughs is as important as human talent, physical infrastructure, regulatory agencies, and co-located industries and other support services.

Fuzzy Divide

> *"Do not confuse the moon with the finger that points at it."*
>
> —Zen

The source of funding is perhaps the most obvious way values enter science and research. The old defense-industrial complex is being replaced by the corporation-university-private laboratory linkages. Science is changing in the way it is being funded, the way it is becoming commercially driven and the way its internal borders are constantly getting dissolved and redefined. Funding also influences the choice of problems to be investigated. If the funding is coming from a government source, then it will reflect the priorities of the government. Private-sector funding, mainly from multinational firms, either in-house, off-shore or outsourced, is naturally geared toward research that would eventually bring dividends in terms of hard cash. No private firm has ever supported a major particle accelerator in the last decade, while the mapping of the human genome was eagerly propelled by private interests because sequencing of the genome is an inexhaustible mine of innovative and marketable products. Commercially driven research undertaken by multinational companies has two main attributes. It focuses on certain areas of research, mostly 'celebrity problems', at the expense of other world problems such as malnutrition, infectious diseases etc.

Globalization has transformed modern society, in Buddhist terms, from *every-man's-on-a-raft* thinking to *we're-all-on-a-raft-together* orientation. Consequently, globalization of R&D throws some paradoxical problems for scientists working in developing countries. There

are several examples of profit-driven global industrial research taking a stake at intellectual property claims on traditional forms of knowledge from other cultures. The companies are also involved in patenting non-western genetic resources, indigenous knowledge and ancient learning. Mexican beans, Filipino jasmine rice, Bolivian Quinoa, Amazonian ayahuasca and West Africa's sweet potatoes have all been subjects of predatory intellectual property claims. Botanically termed as *Azadirachta indica*, the neem tree is a hardy, fast-growing evergreen tree that is common in arid regions of the Indian subcontinent. The *Upavanavinod*, an ancient Sanskrit treatise dealing with forestry and agriculture, narrates in standard operating procedures how neem should be used for protecting plants from pests, curing ailing livestock and strengthening the soil. Formulae are also given for making a whole range of medicines for diseases such as leprosy, ulcers, diabetes and constipation. Other texts have identified neem as a potent insecticide against locusts, brown plant-hoppers, nematodes, mosquito larvae and beetles. In the early 1970s, a US timber merchant noticed that the neem-based pesticides used by Indian farmers were far more effective than the imported Western ones. He carried out safety and performance tests on a pesticidal neem extract called Margosan-O and patented the product in 1985. Three years later, he sold the patent to G.R. Grace and Co., the multinational chemical corporation. The floodgates were open. So, what was free and widely available knowledge became the property of a corporation.

Likewise, innovations derived from nanoscience would likely generate intense international competition for patents and a drive to harmonize intellectual property rights across countries. Nanotechnology is emerging into an already evolving global patent landscape where multinational companies are attempting to own downstream access rights to enabling technologies. As governments and industry around the world begin focussing on nanoscience, and especially its anticipated economic benefits, the need to consider links between nanotechnology and globalization grows. One important impact linked to globalization is that nanotechnology may reinforce, and magnify, existing disparities between the rich and poor. Differential rates of diffusion of these technologies may create a nano-divide. Like the digital divide that accompanied the introduction of new information and communication technologies, it is likely that there will be a nano-divide. Some

proponents of nanotechnology argue that scientific advances in this field will bring the end of material scarcity, for example, by making raw materials such as wood and oil obsolete, due to the ability to synthesize new material. But more critical thinkers suggest that nanotechnology will accelerate the trend toward corporate concentration of power and monopoly formation, because research on nanotechnology is too expensive and complex for a small organization to conduct. Countries like India and China have the opportunity to bridge that divide as off-shore partners enabling the birth of these new technologies.

Likewise, the global standards of world trade mainly originated from developed countries with the increasing participation of western businesses, NGOs and consumers alongside their governments. Compliance to these international standards can mean the difference between participating and not participating in the world market for suppliers from developing countries. These suppliers could be CROs involved in clinical trials or laboratories involved with certification agencies. Despite growing research on the potential effect of international standards, little is known about the impact on suppliers from developing countries. How do standards influence production processes or the product quality of suppliers in developing countries, and how do they influence relationships between the suppliers from developing countries and buyers from western countries? Studies point out two opposite effects on linkages which external buyer's compliance to standards can have for suppliers. One view is that when suppliers comply to standards, buyers are assured that their supplier meets a minimum 'capability' threshold. This enables them to enter into collaboration with other areas of the supply chain, such as marketing and distribution. This implies that buyers may develop closer, more collaborative ties with fewer first tier suppliers. In this perspective, standards can have an 'order qualifying' character. The other view is that compliance to standards leads to more 'arm's length' contracts. Due to a certification of some kind, a customer, to a certain degree, is sure of the relevant features of the product. If a majority of the suppliers have this certification, a buyer could easily switch between them without sacrificing on the level of quality. In this perspective, standards start as order winners but, as more competitors comply, they merely end up having just an *order qualifying* character.

Future of the Present

"India has the potential to become the number one knowledge producing centre in the world by 2025, going by the way that things are moving. It is a story of lilies in the pond, where intellectual capital keeps doubling."

—R.A. Mashelkar, Director-General of the Council for Scientific and Industrial Research, India

The rise of the global knowledge industry is so recent that most economists have not begun to fathom the implications. For developing nations, the big beneficiaries will be those offering world-class talent, state-of-the-art laboratory infrastructure and knowledge centers, the speediest and cheapest telecom links and investor-friendly policies. In the West, it's far less clear who will be the big winners and losers. Corporate downsizings, of course, are part of the ebb and flow of business. The general impression was that they were selling their seed corn—i.e., they had sacrificed their long-term future in order to concentrate on short-term improvements to existing products. *The New York Times* said that the resulting shortfall of new ideas could "shackle the economy". Research labs do go through periodic upheaval but stay vibrant and healthy. Any impact of off-shore hiring is hard to measure in the West since, so far, a tiny portion of US white-collar work has jumped overseas. Entrusting R&D to far-flung foreigners sounds risky. For security and practical reasons, many corporations are likely to keep crucial R&D close to home. For companies adept at managing a global workforce, the benefits can be huge. Corporate America has already become comfortable hiring outside companies to handle everything from product design and tech support to employee benefits. Immigrant Asian engineers in the US labs of Texas Instruments, IBM and Intel have for decades played a big, hidden role in American technological advances. The difference now is that Indian and Chinese engineers are managing R&D teams in their home countries.

After the initial euphoria of migrating laboratory work to low-cost countries, research sponsors will start judging quality and performance. CROs and off-shore R&D units must take into account all service features and all modes of customer access that contribute value and

lead to customer acquisition, satisfaction, preference, referral and to business expansion. Operational excellence of laboratories is really the soft underbelly and has both current and future components; understanding today's global technology needs and anticipating future trends and opportunities. It also demands anticipating changes in regulatory practices and awareness of technical advances. Organizations will depend on the measurement and analysis of performance. Performance measurement should include technical outputs such as patents, publications, technical reports and levels of progress toward commercialization, customer and service performance against benchmarks, comparison of employee and cost performance etc. These factors include the organization's relationship with global/parent companies that help build trust, confidence and goodwill. Customer-driven excellence may mean reducing defects and errors, not merely meeting specifications, or executing research projects on time. In addition, a laboratory's success in creating intellectual property, moving from bench-scale to pilot-scale and ensuring the quality and integrity of data is crucial to continue to attract off-shore R&D investments. Communication among the off-shore units/CROs and head offices are critical. There is a trade-off between the flexibility that a multinational company needs to allow its sub-structures to operate (and develop tacit forms of knowledge), to know with whom to pursue new forms of knowledge and the function of 'gate-keeper' that the company needs to embody in order to assure a codified and shared form of knowledge. This becomes the form of communication which assures a fruitful transfer and exploitation of knowledge absorbed from the outside. Investments in formal in-house R&D is only one way through which firms increase their knowledge and experiment with new technologies, but R&D is also important in making the organization absorb and exploit knowledge produced elsewhere

The market orientation of science, with an eye on leveraging global technical resources and its increasing domination by commercial and consumer interests, is also transforming science from within. The conventional production of scientific knowledge, generated within the boundaries of a single discipline in cognitive context, is now being replaced by new systems such as Mode 2 Knowledge Production. In their seminal work, *The New Production of Knowledge* (1994) Michael Gibbons and his colleagues describe several attributes of

knowledge production under Mode 2. Scientific work will no longer be limited to conventional institutions like universities, government research centers and corporate laboratories. There will be an increase in sites where knowledge will be created. Scientific work will also be conducted by independent research centers, industrial laboratories, think tanks and consultancies.

In his book *New Thinking for the New Millennium*, Edward De Bono comments that any design process demands a high degree of *value sensitivity*. Photographic films have an indicator of light sensitivity. A 200 ISO film is not very sensitive, 400 and 1000 ISO films are extremely sensitive to light. The scientists in developing countries feel that local organizations, both private and public, have been unable to see the value in their ideas. The companies, who are mostly competing for their own survival, were looking for only one value and failed to see the others. Since value sensitivity is central to creativity and design, the global opportunities provided by the outsourcing wave would improve value sensitivity of Indian talent as happened with the success rates of Asian immigrants in the West. De Bono comments that the secret is in emulating nature. Nature found out early on that the way to create vast amounts of change is to find a core of constant values and keep spinning around it. For example, nature created animals on the principle of polar symmetry. Physically, we are all symmetric at the poles. Once nature found out about the power of polar symmetry, it kept that as a constant value and created a two legged animal, a four-legged animal and even a centipede around it. Keeping that value as constant, nature has been able to create endless variations of life forms around it.

The path of discovery is zig-zag and random and is full of surprises. It requires plenty of passion and hard work, and success depends on being in the right place at the right time. The process of discovery is 95%–99% hardwork and 1% enlightenment. Such is the nature of discovery and the process of invention—you know it when you see it, but you cannot plan for it. But one must have prepared minds to experience the joy of discovery and stumble on inventions. Jean-Maria Lehn, Noble prize winner in 1987, says, *"Often an experiment wants to tell you more than what you first expected, and often what it tells you is more interesting than what you first expected*." We hope the same holds true for the outsourcing experiment as well!

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