e-R&D – the net@work

It is difficult to understand how the continuing growth of large monolithic Research & Development organisations can sustain the industry. With the economies of scale providing diminishing returns we examine the promise of e-R&D and explore the potential in networks.

By Dr Alpheus Bingham and Dr Neil Bodick

It has been suggested that critical mass for pharma R&D, the annual spend required to achieve economies of scale and scope, hovers around $2 billion[1]. With the spate of recent mergers (driven more by financial than business fundamentals) many R&D organisations are now operating at or above the $2 billion mark, but economy of scale seems to be failing in the post-merger era. A recent CenterWatch study[2] suggests that the overall (preclinical through Phase III) productivity of R&D organisations in post-merger companies drops precipitously, and data from Strategic Pharmaceutical Consultants suggests that market share also diminishes (**Figure 1**).

The aggregate of these effects is expressed in a comparison of the industry's R&D CAGR (compounded average growth rate), currently in the vicinity of 14% and the Sales CAGR, currently in the vicinity of 10%. Put qualitatively, the curves defining R&D expense and sales growth are diverging – a situation that is unsustainable. After years of dealing with this issue, some of the leaders in the industry are concluding that the traditional approaches to organisational effectiveness are inadequate (**Figure 2**).

In the comments that follow, we will define e-R&D as the vigorous growth of networks in the R&D community. And, we will ponder the potential effects of these new networks on the performance of the large research organisation. In so doing we will borrow a term from the new economy: Network Effect. In the context of this discussion, Network Effect is the benefit that accrues with the meaningful aggregation of data and purposeful formation of communities and markets.

In introducing the notion of a Network Effect, it is also important to understand what it is not – it is not a value proposition. A venture that exploits the Network Effect may or may not constitute a viable business – too often in the discussion of the new economy, macro effects are used to justify micro assertions. Network Effect is an abstraction, an abstraction that exists on the same plane as other heuristic concepts, like, economy of scale. Below, we will propose that 'network' may evolve

Figure 1
Market share drops after merger. Source: Strategic Pharma Consultants

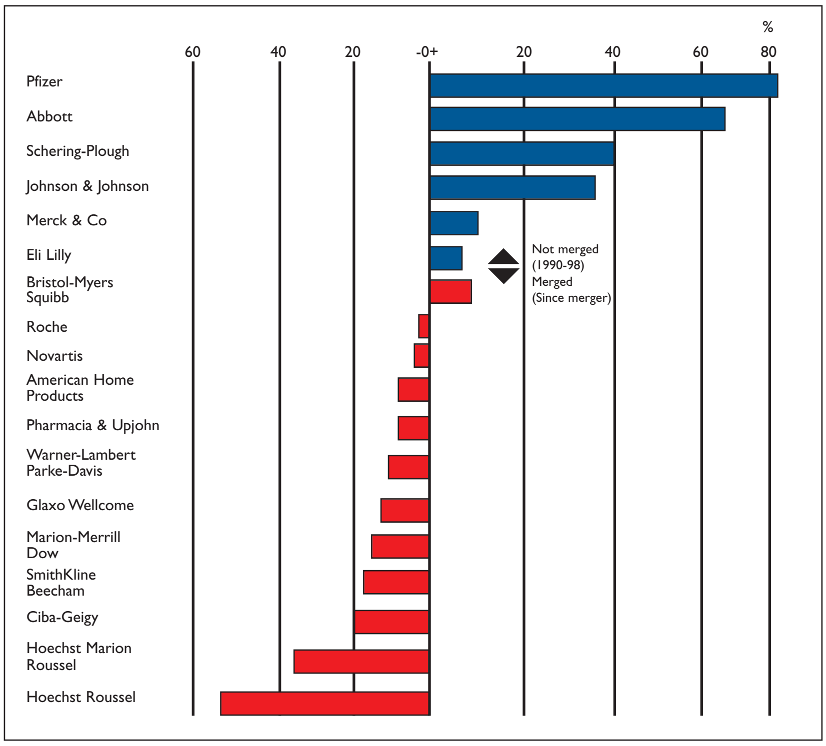
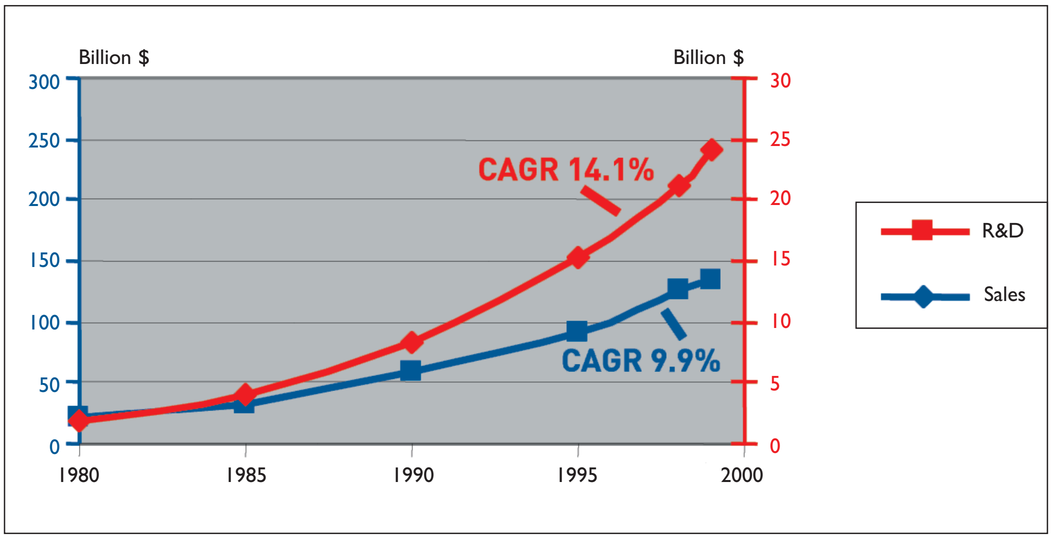


Figure 2
Compounded Annual Growth Rate for Pharmaceutical R&D and Sales. Source: PhRMA



to be the successor to 'scale' – size without weight, critical mass without massive expense.

As we look at the history of the Pharmaceutical industry, it is apparent that networks have played a steadily increasing role. Twenty years ago, the vast majority of R&D work was done internal to the company by full-time employees. Over the last two decades, we have seen the creation of an entire market of CROs, discovery boutiques, the emergence of biotech firms and exchange of assets between major FIPCOs (fully integrated pharmaceutical companies, an acronym not needed when it went without saying). No longer is the Pharmaceutical firm an island. It is linked to partners who license assets, design trials, conduct studies and author papers. Within Eli Lilly and Company the early 1990s saw the creation of the phrase 'discovery without walls' to articulate this new way of doing business.

So where is this increasingly networked entity headed? How important will the Network Effect be? To answer that question, let's divide the Network Effect into three subcategories – The Network Effect on transaction costs, the Network Effect on insight, innovation and design and the Network Effect on risk allocation.

The Network Effect on transaction costs

In other industries, the reduction of transactions costs is the central feature of what has become e-commerce. The Business to Consumer (B2C) and Business to Business (B2B) companies that have proliferated in recent years include Amazon, e-Bay and numerous online exchanges for everything from energy (Enron) to medical supplies (NeoForma) to intellectual property (yet2.com). Each of these enterprises depends on network structures with global reach and minimal geographical infrastructure. Each of these enterprises radically lowers transaction costs (for at least portions of their value chain).

Within our industry, clinical trials offer the most visible opportunity to use the richness and reach of the internet to reduce the overhead of data aggregation – and that overhead is considerable; some estimates suggest that the industry spends more than $10 billion per year supporting clinical trials.

In the early 1990s Lilly undertook a substantial effort to connect sites electronically, but in that era the costs proved to be prohibitive. There was no pre-existing infrastructure, nor were there platform standards. Consequently extraordinary effort and expense was required to build a network for a single trial. Today, the internet offers bandwidth and ease of connectivity sufficient for exchange of documentation, images and even video between sites and central medical operations. Because the network is in place with agreed upon interface standards (browser tools) and languages (XML, HTML), sites are in effect pre-wired and the cost to put a trial 'online' has gone down by orders of magnitude. Of course there are non-trivial costs associated with systems integration, (the browser interface to connect to multiple in-house applications) but these can be leveraged across many trials.

Within the current paradigm for the conduct of trials, there are at least three concrete opportunities to reduce transaction costs. First, the emergent use of online CIBs reduces both the risk of reference to outdated documents and the cost of distribution. Second, electronic data entry (replacing the physical assembly and transfer of Clinical Report Forms in global trials) has increased the efficiency of data aggregation. And third the routine work of cleaning and analysis of data has been substantially reduced with the advent of the electronic source document. Documents themselves have built-in error checking, and the rate-limiting step of data cleaning has been, in some cases, completely eliminated. The improvements to process and the concomitant cross-functional integration have the potential to dramatically reduce the time and expense required to deliver data sets of sufficient quality to support internal and external decision making.

Numerous companies have been established to support these activities including Clinsoft (formerly DomainPharma), PhaseForward and CRFBox. In moving to internet-based data management, many pharmaceutical firms have found substantial investments are required to convert the internal IT infrastructure (as noted above). Our analysis suggests that, even with this expense, the implementation of the electronic source document and the attendant process re-engineering have the potential to as much as double productivity for large-scale clinical trials.

Beyond the current paradigm for the conduct of trials, there are economies and benefits of equal or greater potential. The 1747 Group (San Francisco, CA) is conducting the initial test of methodologies supporting direct, sponsor-to-patient studies over the Internet. At the core of a clinical trial is informed consent, the ethical relationship between the physician investigator and the patient. The 1747 Group is exploring the development of an ethical relationship between the sponsor and the patient, without mediation of the physician investigator. We would suggest that this effort represents a fundamental change in dynamics of trials conduct, a change that is made possible by the richness and reach of the Internet. Though the methods are still under development, it is intriguing to contemplate the benefits of direct-to-patient trials. For patients, disease management based upon disciplined analysis of large data sets benefits treatment. For the sponsor, product development is supported by a new and rich dialogue with the patient. In the future, the Internet may be not only the basis for economy of existing transactions in clinical trials, but also the basis for meaningful new transactions.

The Network Effect on insight, innovation and design

The Network Effect on innovation has not been clearly evident in the pharmaceutical industry to date, but its emergence elsewhere may be a harbinger of things to come. Perhaps the most widely publicised instance of the Network Effect on design is the development of the PC operating system Linux. In 1991, a segment of Unix-derived code was placed on a website as the kernel around which an operating system might be built. A well-qualified community self-assembled around the site – these early Internet adopters were united by their technical skill and by a simmering contempt for proprietary systems. Over a period of years the community grew, and million of lines of code coalesced into a fully functional operation system. All of this was accomplished without the benefit of a corporate sponsor, without a project plan and without management review sessions.

Linux is an admirably robust operating system, which has been steadily gaining market share on the basis of its stability. At first, one might marvel that stability emerges as a characteristic in an operating system developed without a master plan, but it may be that stability emerged precisely because there was no master plan. The diversity of thought within the network may have provided a constant selective pressure, a developmental environment intolerant of local solutions at the expense of overall system integrity. Linux may have avoided the systematic weakness implicit in a deterministic project timeline, driven by single-minded portfolio and supported by well-defined process.

SETI@home (the Search for Extraterrestrial Intelligence at home) is a case of equal interest. SETI@home is a network that employs the unused processing cycles of personal computers on the Internet to analyse data collected by the Arecibo Radio Telescope in Puerto Rico. As of February, 2000, SETI@home had grown to encompass 1.6 million participants in 224 countries. The amount of computing time contributed since May 1999 is equal to 165,000 years, averaging 10 Teraflops (about 10 times more than the largest supercomputer on the planet). It is the largest computation ever done, and has attracted the participation of 20,000 groups including schools and private companies[3]. Is this a network accessing 'creative mind' as we would think of it? Is recognition of pattern an element of insight?

More down to earth, access to mind through the reach of the Internet is the basis for a number of new businesses, companies that tap into the knowledge resident in large populations to trouble shoot computer problems (www.helponthenet.com), to identify potential prior art for patent applications (including biotechnology intellectual property: www.bountyquest.com), to author customer software packages

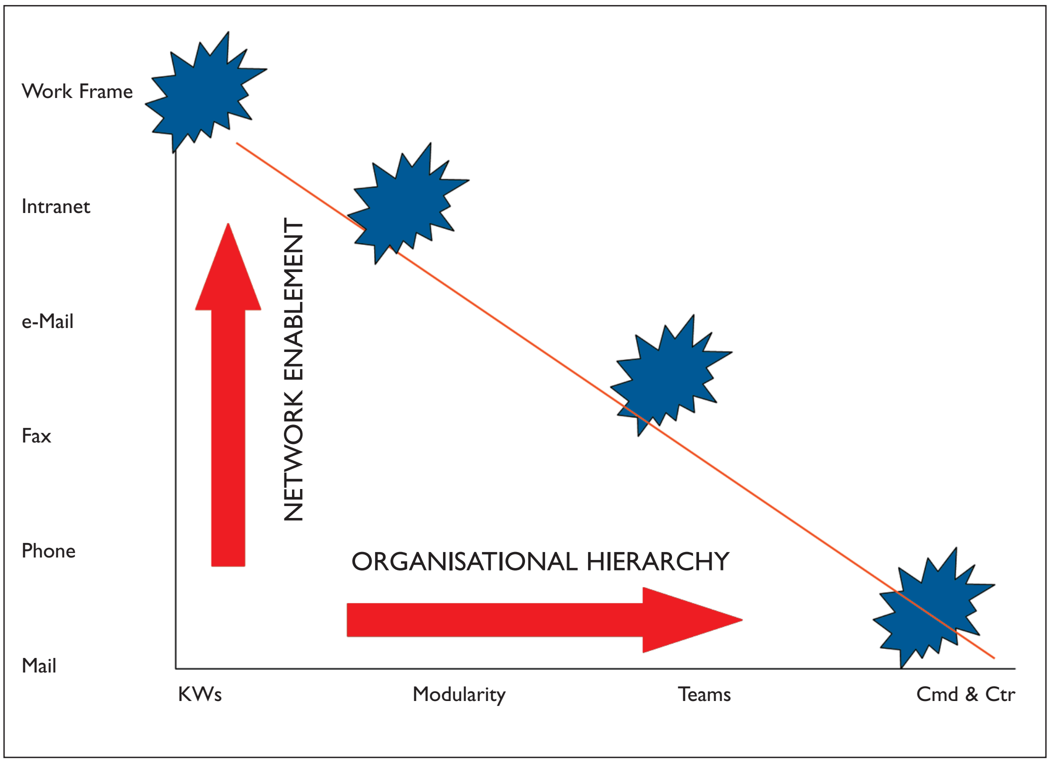


Figure 3
Co-ordination through hierarchy and network

for specific applications (www.forinstance.com), to compose product reviews (www.epinions.com) and even to design specialised electronic circuits (www.hellobrain.com). This is hardly an exhaustive list but illustrates some of the emerging ways that companies are driving innovation, insight and design on the network.

In service of what we consider pharmaceutical innovation, new consortia, new networks, are emerging. Six major Pharmaceutical companies and an arm of the US National Institutes of Health have committed a total of $40 million over five years to an ambitious project to elucidate the mechanisms of cell communication (www.cellularsignaling.org). The project brings together 50 scientists in a national consortium in a sweeping effort to produce an accurate, quantitative computer model of cellular communication. Within the SNP consortium (www.snp.chsl.org), 10 of the leading drug companies have joined with five gene laboratories to catalogue genetic diversity within the human race.

The integration (across companies and institutions) and mining of data sets constitutes an import opportunity, and there has been progress in this domain[4]. Work groups have self-assembled to share clinical data in an effort to improve the available depression rating scales and to understand placebo response[5]. Other opportunities to pool data may be found in collections of SARs, correlation of chemical structure with toxicology, predictive utility of animal and microsomal data for clinical metabolism and pharmacokinetics, relationship between chemical structure and biopharmaceutical properties. But it should be said that real and perceived barriers to sharing data across companies persist.

A number of other novel approaches to insight and design are in play at Lilly. One initiative, a collaboration with Pharsight[6] has already provided concrete results. Pharsight has assembled a suite of software tools for modelling PK/PD relationships, simulation of clinical trials, modelling market development and resource planning. The collaboration has materially impacted clinical design and resource deployment for major programmes. One might ask how does large-scale simulation of clinical trials constitute a Network Effect. We have observed that the construction of simulations engenders the integration of internal and external data sets (in fact the simulation becomes the motive for accession of these data sets). Further, the construction of the models engenders a quality of dialogue among the Physicians, Pharmakokineticists, and Statisticians that heretofore has not been achieved – in essence the process of simulation promotes the Network Effect within the team, and clinical design benefits.

Network Effects on allocation of risk

In developing a definition of risk, we start with the borrowed hypothesis that 'business is essentially a mechanism for co-ordination'[7]. In this context, 'co-ordination' may be achieved by a combination of two complementary mechanisms: organisational hierarchy and information flow. In general, the observation is made that simple non-interactive tasks (for example disseminating the co-operate newsletter) have in the past been accomplished with information flow and without need for a strong organisational component, whereas co-ordination of complex, highly interactive tasks (for example clinical development) have required strong organisational influence.

With technological enablement, the development of rich information flows among organisations and individuals, it becomes possible to manage more complex tasks with less dependence on hierarchy.

As depicted in **Figure 3**, the emergence of strong networks facilitates movement of complex tasks from the right to left – from co-ordination of work through hierarchy to co-ordination of work through network. The emergence of networks culminates the formation of what we term Work Frame – sets of tools that facilitate transactions, design, decision making and resource management.

The last two of these activities, decision making and resource management together constitute risk management. In the hierarchy-dominant mode, risk is managed through resource allocation in service of a portfolio. In the network-dominant mode, risk is managed through resource attraction in a market place.

Essential to the reallocation of risk is the emergence of new specialised Work Frames, to be more specific, new specialised marketplaces that efficiently attract resource to projects and which efficiently deploy property to participants. To glean insight into these market places, let's consider markets for work and markets for intellectual property.

Work markets might be defined in the following way: they are networks wherein workers and organisations self select for participation in a project and wherein rewards can be made commensurate with level of contribution. Epinions[8] is an early example of such a work market. It is a website where product reviewers provide opinions to the community and the community responds by assigning a value to the opinion and ultimately to the reviewer. The value to the community ultimately determines the level of reward to the reviewer. Of course, this early entrant is focused on a domain with minimal architectural needs. We all use a product of some type, we all have an opinion and a significant number of people can author a credible product review. As we enter specialised industries, there are new barriers to co-ordination that must be addressed and the complexity of creating work markets sufficiently sophisticated to handle pharmaceutical development is not to be trivialised. But recent start-ups such as CompanyWay[9] are enabling such models.

BioStreet[10] and ActiveCyte[11] are early attempts to provide efficient markets for buying and selling the intellectual property associated with new chemical entities. The heretofore-private markets 'owned' by the portfolio management, business development and research acquisition functions of large corporations have operated with imperfect information and have been strongly influenced by the need to optimise valuation for the corporation. In other words, these functions have been inefficient in valuing/pricing assets internally and externally. In an open market place (that is represented by these new entrants) asset valuation is likely to become transparent, and the selective pressures on assets is likely to increase.

In closing let's once again consider the relation between hierarchy and organisation diagramed in **Figure 3**. The following observation is made: as complex tasks move to the left, the need for the monolithic R&D organisation is reduced and the investment required for the maintenance of the large research plant is also reduced. These observations leads us to hypothesise that successful business models will be those that can effectively redistribute the cost and risk that is currently associated with maintenance of large R&D plants. It is difficult to understand how the continuing growth of large monolithic R&D organisations can sustain the industry, and with economy of scale providing diminishing returns, new business models – models that are likely embedded in specialised networks – may be required to rev the innovation engine. DDW

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