Architecture of R&D – a conceptual framework for collaboration

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The 1990s have seen a revolution in pharmaceutical industry strategy and structure in response to regulatory and patient pressures and the need for cost containment. The major companies are now leaner, many new small and medium-sized enterprises have emerged along with the advent of the 'virtual' company, and academia has been forced to adopt an industrial focus. The author explores the concept of architectural structure as an analogy in modelling the partnering and collaborative arrangements between such organizations.

The complex nature of drug R&D has been compared with winning the Formula One Grand Prix Trophy – requiring much technical effort, time and expense with substantial risk as to any return. In recent times, both regulatory and medical pressures for safety and efficacy have increased the effort devoted to pharmaceutical R&D in large companies. A measure of these factors can be obtained by looking at the average number of pages in a new drug application (NDA) submission: this grew from 38,044 for the period 1977–1980 to 90,650 for 1989–1992; concomitant increases in the number of clinical trials and in patients per NDA were also observed in this period. It is of course well known that the costs of new products are huge: in 1989, an estimate of $231 million was made for the registration of a new chemical entity (NCE), and in the years since then further increases on this figure have been produced[1–3].

Vertical integration

Throughout the 1980s and early 1990s, the industry response to these pressures produced huge emporia devoted to science, in which the multitudinous activities were usually placed in one site. Glaxo Wellcome's monument to R&D, centralized at Stevenage in the UK, was completed in 1995 at a cost of practically $1 billion, and at the time was the second most expensive construction project in Europe.

One may conceptually draw these efforts as a single Doric column (Figure 1), in which scientific departments align in close proximity. This is the diagrammatic representation of what has become known in business analytical circles as the FIPCO (fully integrated pharmaceutical company). The interplay between disciplines has been enhanced by propinquity, while the effort required to facilitate integration and coordination was minimized by this structure. Of course, multidisciplinary cooperation can founder on interdepartmental rivalry and competition – even schadenfreude; but for the sake of this analogy, we will presume that it does work, as indeed it does in many large companies. The vertical dimension of the column is indicative of the timescale of the efforts that must occur during the course of the discovery and development of a drug, with research at the bottom being ensued by development above.

Adaptation to increasingly difficult and lengthy R&D programmes has required commensurate increases in the height and diameter of the column, representing the demonstrably greater resources required in the process. Substantial infrastructure costs are associated with these in-house R&D efforts: one has only to look at Glaxo's vast site to comprehend this fact. One is even more impressed from the inside, by the marble floors, the solid hardwood doors and the landscaped waterfalls. This is a substantial infrastructure

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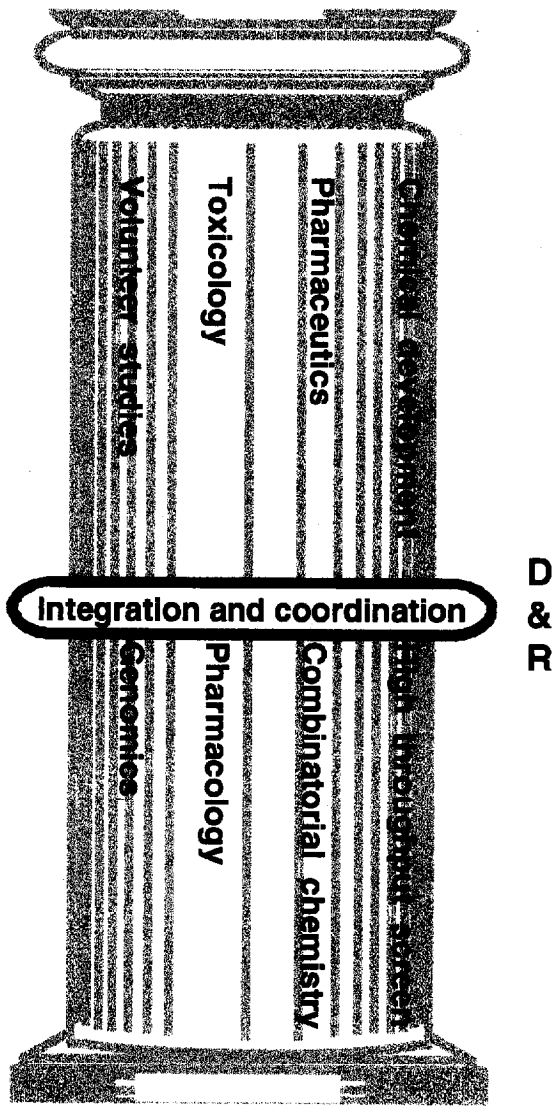

Figure 1. *Single site architectural analogy for precilinical drug R&D.*

from a substantial company, one with important economic implications for the UK in particular. The economic significance of companies such as Glaxo helped in past decades in persuading governments of the need for support in the form of realistic prices for their products. But today, such negotiations for new products can be very difficult, and the philosophical commitment of governments to pharmaceutical R&D at any price cannot be taken for granted. Changing the shape of the column is difficult without major efforts; its internal infrastructure is heavy and inflexible, and poorly suited to a rapidly changing scientific environment. When combinatorial chemistry replaces traditional chemical techniques, the parameters for laboratory design are dramatically different. When new drugs are sought from molecular biological investigation, the personnel and the laboratory areas need to be changed.

Buttressing large pharma R&D

Increasingly, therefore, new technology has been sought externally. Large pharmaceutical companies have devoted substantial funds in support of R&D in new biotechnology sector ventures, either in relation to technology or research projects. The partnerships that have formed between these small companies and larger ones are linked in much the same way as the pier buttresses are linked to the main body of a gothic cathedral via the flying buttress (Figure 2). When designed in the Middle Ages, buttresses were constructed to enlarge the cathedral windows, admit more light and generally to magnify the space inside to create a more impressive space in which to worship. In order to achieve these aims, additional force from the outside was applied to prevent collapse.

As much as the original architectural reason for this design was to allow the construction of cathedrals to greater heights where lateral forces due to wind were more evident, one could say that the collaboration of a large company with a technology provider in a research project, or with a contract research organization (CRO) to provide a part of the development work, buttresses the in-house efforts of the large company. If so, the downsizing of the past few years has left a structure within the large company that is not self-sustaining. Equally, the buttress cannot be left without a large company for support – it too will collapse. The need for, and permanence of mutual dependence is suggested too by recent developments in the biotechnology sector. In 1995, the funding of the biotechnology sector reached $3.6 billion through alliances, more than twice that of 1994, and equivalent to around 10% of total pharmaceutical R&D spending.

However, the relative weight of the participation by each partner still has to be optimized. In the Middle Ages, the process of building cathedrals to this design employed a great deal of trial and error to find the correct amount of buttressing that was necessary for structural integrity. There were of course failures, and in the absence of the sophistication of modern day architectural calculations, these led to a rather empirical approach to cathedral design. A recent interpretation[4] is that some of the more flamboyant flying buttresses of the French school were overbuilt with safety in

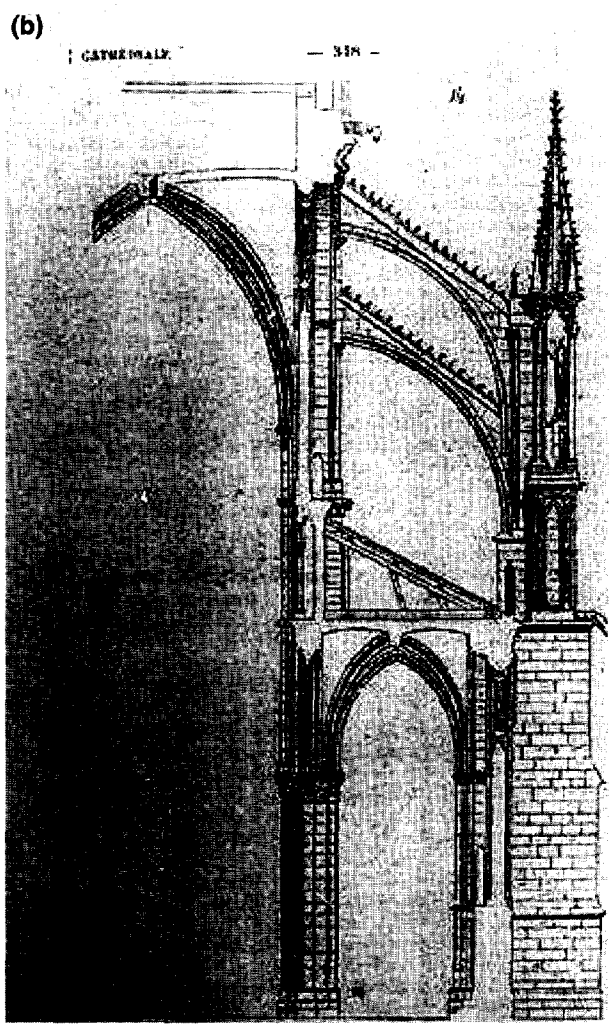

Figure 2. *Flying buttresses of Rheims Cathedral (a) and the drawings of Viollet-le Duc (b) showing the cross section and the structural action of the buttress; from* Dictionnaire Raisonné de l'Architecture Française *Vol. II, Paris.*

mind, and in fact were larger than was strictly necessary for the structural assistance needed to keep the cathedral from falling down. Does this suggest that as partnerships in the industry are becoming a more common approach, we still need to struggle to find the most efficient relative weighting between intra- and extramural resources, and the ways in which they best work together? Moreover, does it suggest that we can only learn the limits of what can be achieved from failed projects? Finally, is the stability of a large pharmaceutical company required for such partnerships to work properly, or can their coordinating role be supplanted by yet another small company?

Partnerships between small companies

There is an increasing number of examples of partnerships between small companies that avoid the multinationals entirely. For example, Aurora has formed a number of alliances that are based upon the use of its automated screening technology. This is in itself an interesting development; historically, the screening of molecules has been one of the areas most resistant to external sourcing, partly because results from initial screens are of crucial importance in terms of the ability of a company to generate new leads. What Aurora offers is state-of-the-art automated screening technology with capability to test up to 100,000 samples per day using miniaturized assay systems employing minimal amounts of drug, usually with fluorescent measurements rather than less sensitive radiochemical ones. Examples of Aurora's alliances include those with small companies, such as Alanex and ArQule, to screen products from combinatorial chemistry programmes, as well as large ones such as Bristol-Myers Squibb. Meanwhile, ArQule has bulwarked its

chemical expertise with technology from the academic arena; it has acquired rights to methods of synthesis from Yale University, and is collaborating with Brandeis on a project to discover novel antifungals and anticoagulants. On the other hand, Aurora has formed an alliance with Sequana that makes use of the latter's expertise in genomic science to discover disease genes.

A pattern is emerging, in which the three technologies of combinatorial chemistry, high throughput screening and genomics are being used as core elements in drug discovery programmes, and they are being provided by a number of small companies, or technology providers. Also, the historical division between industrial and academic research is becoming blurred by the increasing commercialization of the latter and the thirst of the former for new technology, which is becoming ever more rapidly integrated into the drug discovery process.

Consortia

In some cases, large companies have taken the opportunity to build consortia of small companies, with their finances and powers of coordination driving the programme. Rhône-Poulenc Rorer (RPR) and Pfizer are key examples of this phenomenon[5]. RPR's group is called Gencell, and currently includes 14 companies from the US and France, with the expectation that it will enlarge to incorporate other European and Japanese components too. RPR have committed 200 employees and $100 million per year to the venture, which represents nearly 20% of their R&D budget. The group is interested in cancer therapy, cardiovascular disease and central nervous system disorders, and is heavily biased towards gene therapy approaches employing novel drug delivery technology.

Pfizer's effort to build a network of biotechnology providers is known as PfizerGen, and is said to provide a long-term vision to position Pfizer for the next millennium. Substantial allocations of about $200 million per year have been made to maintain such alliances, although the company stresses that the aim is to complement rather than to replace the current in-house activities. This growth in research is a reflection of the optimism of Pfizer's prospects for the future, based on its promising R&D pipeline. Again, genomics features prominently, with screening automation, combinatorial chemistry, drug delivery and new therapeutic approaches external to Pfizer's existing portfolio.

These examples represent a major change in research strategy beyond the simple one-to-one partnerships practised uniquely until very recently. Industrial and academic components find themselves increasingly rubbing shoulders. The role of the modern multinational pharmaceutical company is quite different from the traditional one, focusing increasingly on coordination and integration rather than operating with in-house technical expertise in parallel with the technology provider. How can we see this shift in functional terms, and what is the logical end point for drug R&D?

Box-girder architecture for R&D

Returning to the architectural analogy, we can see that since the gothic cathedral, alternative designs have been found to be even more effective for the construction of tall buildings. In the last century, the skyscrapers of Chicago were built with the benefits of new materials with an improved strength-to-weight ratio, and were the first to use the box-girder steel framework based on horizontal and vertical steel components, which could then be faced with brick. Under this analogy, the process of preclinical pharmaceutical R&D can be represented by the structure shown in Figure 3. The horizontal elements of integration and coordination connect the technology providers, represented by the vertical elements, and are an important component of this structure. In the industry, these are known as the virtual companies. In architectural terms, they are essential for structural integrity. The structure shown has a number of advantages over the monolithic single-site structure of the traditional pharmaceutical industry, and may represent a means by which a network of entirely small companies can effectively perform drug R&D. Although the structure is suggestive of permanency, one needs to realize that as a project proceeds, the components of the framework will change. Alliances are often designed to operate for only a portion of the drug development process. Some partners will fall away from the project, and others will need to be brought in at a later stage.

This structure is light for its height; the thin columns of the frame represent specific technologies essential for the project to succeed, provided by single discipline providers. Many of the peripheral elements that are embedded in the single-column, large-company format, and equate to the substantial overheads of that format, are either not represented, or are brought in as needed. It is flexible; the pillars of specific disciplines of research and development are but examples of what may be needed to compose a total project. These may be increased or curtailed depending on the nature of the project at hand, and on the temporal stage of development of the project.

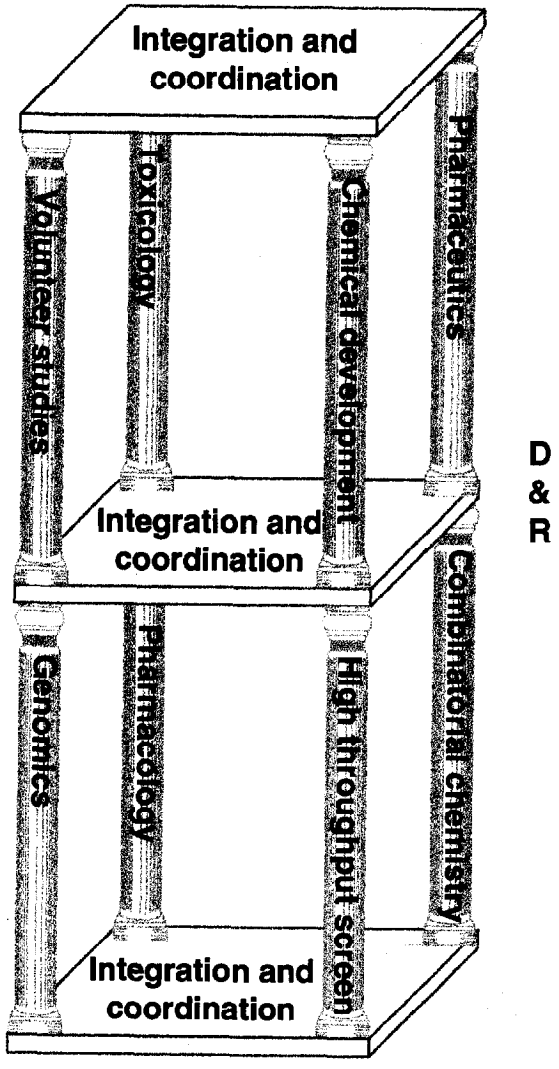

Figure 3. *A lightweight alternative to classical R&D architecture.*

A good example of a group of collaborators involving a combination of providers of technology for combinatorial synthesis, automated screening methodology and biochemistry/pharmacology is that of Tripos, The Automation Partnership and the Cruciform Project in the UK. The alliance between the Cruciform Project and The Automation Partnership has been awarded grant funding from the UK Department of Trade and Industry's Foresight Challenge programme. This combination of biochemical expertise (Cruciform) and engineering capability (Automation Partnership) will work with compounds supplied by combinatorial techniques from the US company Tripos/Panlabs. From these considerations, it should be clear that the conduct of a modern, high-throughput assay for drug discovery based either on libraries generated by combinatorial chemistry or from natural sources should be feasible employing almost entirely out-of-house resources.

The architectural analogy establishes the conceptual difference between the technology provider and the virtual company, whose sole role is to integrate the activities of others. It also clarifies the difference between the technology provider and the multidisciplinary research project partner, which can be considered as providing a complete stage in the vertical development of the total R&D construct. It can be seen that the purposes of the CRO, the academic research group or the small entrepreneur are similar, although the ability of each to fit into the framework depends on the size and shape of the column that is required. The CRO's role may be to conduct an overflow project or to be a key provider of a number of services. Their experience of many different kinds of development projects has given them a breadth that few other companies in the pharmaceutical arena can match. Most virtual companies, particularly those that aim to carry a project through late development, use CROs extensively, if not exclusively, for the work they need to conduct. On the other hand, companies that are involved earlier in the drug discovery process can often also include providers from academia and the biotechnology sector.

The difficulty of organizing this network in a successful manner should not be underestimated. The structure needs to be sufficiently robust to cope with the problems of delay, which can produce consequential slippage through difficulties in rearranging studies at collaborating organizations, or even withdrawal through financial failure. Although represented as thin planes, in reality sufficient resources have to be placed in these horizontal components to facilitate the complex coordination of the project. Furthermore, their positioning at the top and the bottom of the technology columns, is artistic licence. In reality, coordination needs to occur throughout the discovery and development process, in a continuous rather than discrete fashion.

Communication, a key component for success

A key component for the success of the network of providers is communication. Single-site projects operate substantially through decisions made at meetings, where all the disciplines and people involved in the project may be represented. This is not possible with distantly separated groups, where the bulk of communication will be by telephony, and communications are a much more important

element. The improvements in electronic communication over the past 10 years are of dramatic importance to the feasibility of collaborative work in general, although the changes in the next 10 years are likely to be even more dramatic.

Information technology (IT) is a powerful tool with the potential to change fundamentally the way companies carry out research, and has great applicability to devolved projects. The advantages of intranets, which offer the ability to communicate by methods similar to the World Wide Web, are presently being recognized as having provided greater returns on investment to large companies than all other IT investments. Intranets clearly also benefit groups of small companies, providing concerns of security can be assuaged. The term 'collaboratory' is entering our vocabulary[6] to describe this type of activity, in which research findings can be posted to a common notice board and viewed by other parties with granted access rights as soon as they are available. Issues of security are particularly important for the pharmaceutical industry, and there is substantial research in progress towards the establishment of secure links via the Internet. Newer encryption methods have application in other industrial sectors, particularly banking, and it seems certain that technology to address this issue will be available in a short time. Quintiles have invested heavily in computerized acquisition of data, with great benefit to multi-site clinical studies, each contributing data that need to be amalgamated at a central location; clearly, there is great potential for the utility of this type of data manipulation in preclinical as well as clinical investigation.

Adapting by integration

The structure of Figure 3 places much emphasis on the integrative processes, in an effort to achieve more with less. This is not unlike the adaptive changes to structure that accompany the ageing of the human brain. Increasing integration becomes a compensatory mechanism for the decline in numbers of functional nerve cells that affects us all from our 20s onwards. Greater numbers of synapses enable people to maintain their mental faculties by using their remaining resources more effectively. The human race is successful in large measure because of the brain's plasticity in the face of mortality. The pharmaceutical industry is currently demonstrating similar adaptation as it prepares to enter the next millennium.

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