



Life Sciences Consulting and Outsourcing

Kinapse White Paper

Big Pharma R&D—thinking big, acting small

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Big Pharma R&D – thinking big, acting small

Kinapse Ltd.



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In order to mitigate the considerable risks in developing drugs, the pharmaceutical industry is going through an extended phase of consolidation to try to realise economies of scale (the latest of which is the Pfizer-Wyeth deal announced on January 26 2009). However, our analysis suggests that Big Pharma might now be too big. We found that productivity (as indexed by cost per NDA approval) falls the more one spends on R&D. The cost a company appears to incur per approval falls with decreasing scale to around 10% for companies ranked between 51-157 as compared with Top 20 'Big Pharma' companies (indexed by their 2006 R&D spend).

We believe that the main reason for the apparent fall in productivity with increasing scale is the concomitant increase in organisational complexity. It is our premise that breaking Big Pharma into entities of more manageable scale will assist them in increasing R&D productivity. Horizontal disintegration (where end-to-end processes in the value chain are kept together, but the scopes of these activities are limited) and vertical disintegration (where end to end processes in the value chain are broken down and carried out by separate companies) should be actively considered as methods of dividing Big Pharma into more manageable units. Disintegration is illustrated with two case studies.

This paper outlines critical success factors for making disintegration work. This includes having talent management with a clear focus on leadership development, structuring operating units around clear areas of competence and performance, having clear divisions of accountabilities and transparent cost accounting between operating units.

In order to thrive, we believe that Big Pharma needs to start thinking 'big' and acting 'small'. Simply tweaking the old business model is no longer a viable strategy. Given the mooted wave of Big Pharma merger & acquisitions this year, disintegration needs to be at the forefront of every senior pharmaceutical executive's thinking.

Introduction

Developing new drugs is a risky business. Taking a drug through development and onto the market may take 10-15 years and cost on average, according to a recent estimate, around 1.2 billion US \$.¹ There is less than a 5% chance of a compound progressing from first in human administration through to becoming a licensed therapeutic.² Over the past 10 years or so, the pharmaceutical industry has mitigated these risks by extensive consolidation, the most recent examples being Bayer Schering Pharma, Merck Serono and now the Pfizer-Wyeth deal which was announced in January 2009.

Consolidation is a way for companies to exploit economies of scale and scope.³ Scale gives an investment tolerance to deal with risks and the opportunity to utilise new technologies. Scope allows access to diverse technologies and intellectual capacity. The two work hand-in-hand, scale enables a company to survive a degree of project failure whilst scope allows the sharing of knowledge and skills, mitigating further risks in the future.³

Whilst the benefits of sharing knowledge and skills

across a company are obvious, it has resulted in greater organisational complexity. Pharmaceutical companies have swelled to a size where matrix working appears unwieldy. We believe, this has contributed to a corresponding decline in R&D productivity.

Data Analysis

The pharmaceutical industry is finding fewer and fewer drugs, whilst at the same time, investing more and more money. In the period between 2002 and 2006, the industry brought to market 43% fewer new chemical-based drugs than in the last five years of the 1990s, despite more than doubling R&D spending.⁴

We looked at the distribution of New Drug Applications (NDA) and the New Molecular Entity (NME) approvals issued by the Food and Drug Administration (FDA) between 2004 and 2007 across the pharmaceutical sector and paired this information with R&D spend to look at productivity. We first divided the sector into tranches, which are defined in Table 1. The Top 50 companies by 2006 R&D spend were divided into cohorts of 10, with the remainder of the sector being divided into the Top 51-157 companies and the rest.

Table 1: Cohort Classification Information

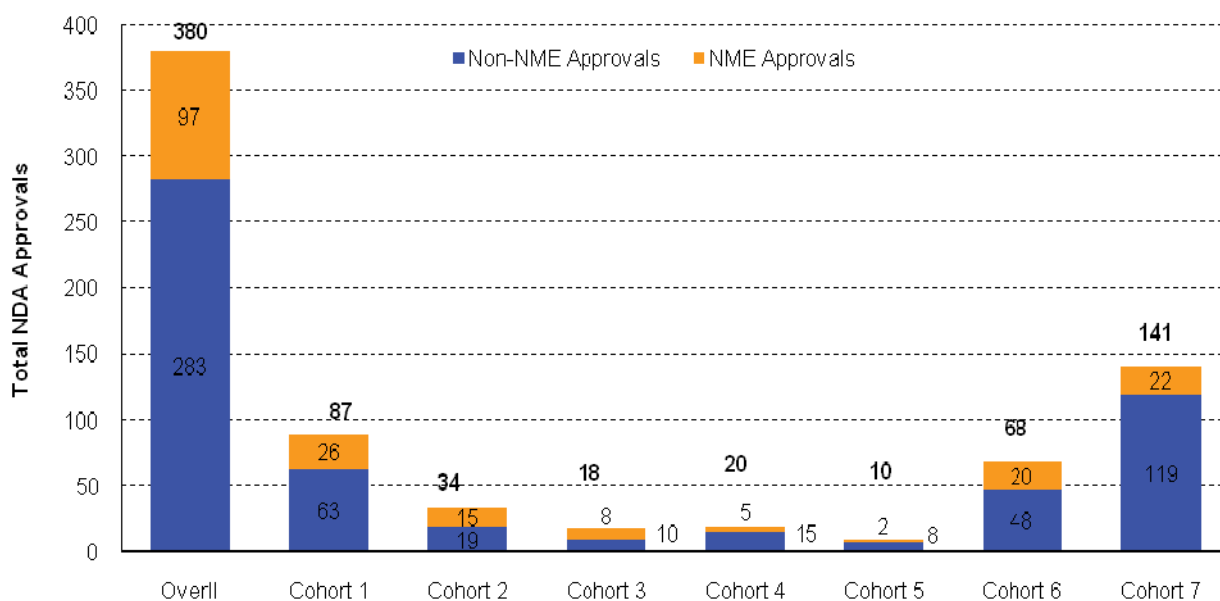
Cohort Type	Definition	Total R&D Spend in 2004 (US \$ million)	Total R&D Spend in 2005 (US \$ million)	Total R&D Spend in 2006 (US \$ million)
Cohort 1	Top 10 companies by 2006 R&D Spend	43,952	44,427	49,166
Cohort 2	Top 11-20 companies by 2006 R&D Spend	19,606	17,075	21,542
Cohort 3	Top 21-30 companies by 2006 R&D Spend	5,615	6,642	7,643
Cohort 4	Top 31-40 companies by 2006 R&D Spend	3,721	3,881	4,539
Cohort 5	Top 41-50 companies by 2006 R&D Spend	2,021	1,667	1,539
Cohort 6	Top 51-157 companies by 2006 R&D Spend	1,761	2,984	5,631
Cohort 7	Outside Top 157 companies by 2006 R&D Spend	N/A	N/A	N/A

Sources: PharmaExec Top 50 Companies Report 2007, 2006, 2005

R&D spends Calculated based on department of Innovation's G1250 pharmaceutical and biotechnology sector R&D spend analysis. In 2006, the 157 companies in the sector spend 47388 GBP £ million on R&D. In 2005 the figure was 40356 GBP £ million. Cohort 6's spend was calculated based on the total spend on the top 50 companies.

We next looked at the distribution of NDA and NME approvals from 2004-2007, across these different cohorts (see Figure 1). There appears to be a positive correlation in terms of greater investment results in greater output (as measured by total NDA approvals). In terms of NME approvals, there is again a positive correlation where greater investment results in greater output. The NME to non-NME approval ratio is highest in Cohorts 2 and 3. As NME approvals are generally taken as a surrogate for innovation, could we infer that the greatest innovation is taking place in these cohorts?

Figure 1: Total NDA approvals for 2004-2007 by cohort

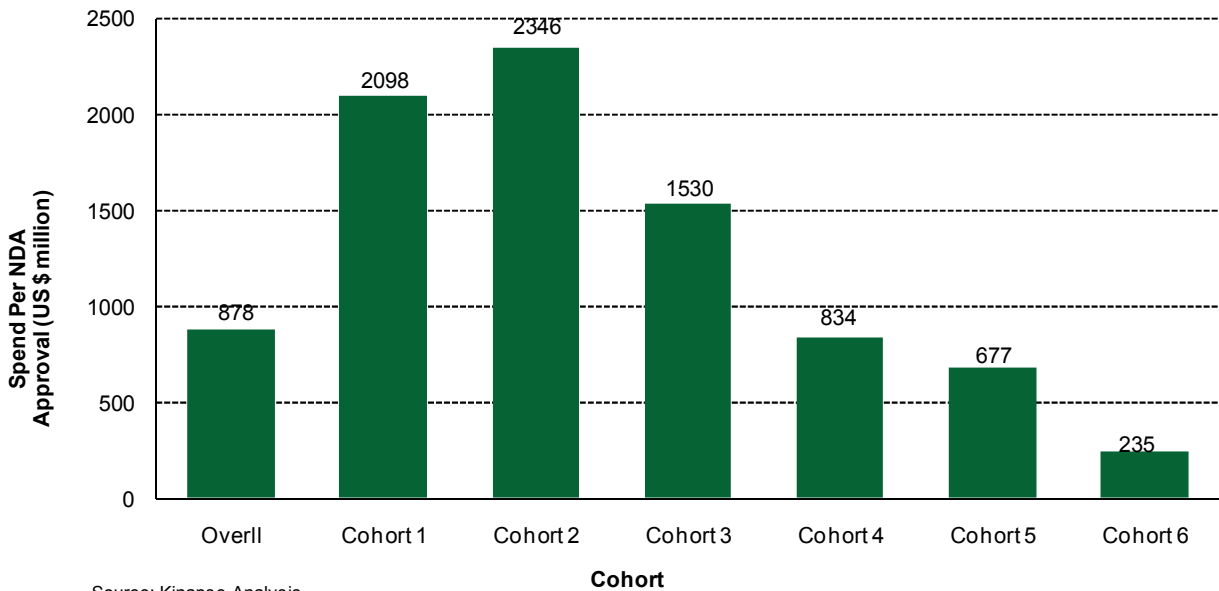


Source: FDA Website, Kinapse Analysis
 Numbers in bold indicate total NDA approvals
 In-licensed compounds not accounted for

Cohort

Finally, we examined the productivity of each cohort by looking at the average spend per NDA approval (see Figure 2). Unlike the number of approvals where there was a positive correlation with R&D spend, here the reverse appears to be true. Productivity, as indexed by spend by NDA approval is negatively correlated with R&D spend. Productivity increases as one spends less on R&D, the cost per approval declining with scale to circa 10% for Cohort 6.

Figure 2: Average cost per NDA approval between 2004 and 2007 by cohort. Figures generated by taking the average across the years, of the mean cost per approval per year by cohort.



It appears from our analysis that Big Pharma's output productivity is relatively low and that the cost per NDA approval declines with decreasing scale. We recognise that this is an imperfect analysis, not least because of the fact that we have not accounted for the time lag in R&D investment versus approvals. Also, this analysis does not take into account the possible confounding effects of in and out-licensing where smaller companies out-license their compounds to Big Pharma (who pick up the Development costs) but remain the applicant on the FDA approval. Nevertheless, from this initial analysis, it appears that although there are benefits to size for a pharmaceutical company, the repeated rounds of consolidation may have left Big Pharma too big to support a highly productive R&D environment.

Organisational causes of reduced R&D productivity with increased scale

We do not think it surprising that large scale causes problems with R&D productivity. Back in the 1960's, the largest pharmaceutical companies employed in the region of 1000 scientists, grouped together on one or two sites with few management layers and relatively straightforward resource planning.⁵ The reality today can involve in excess of 10,000 staff, working across multiple sites in multiple geographies co-ordinated by multiple manage-

ment layers trying to balance the needs of many more projects and portfolio permutations.

According to JP Garnier, this increased organisational complexity 'may result in a culture of risk aversion, promises with no obligation to deliver and bureaucratic inertia', with an R&D environment where 'there is a loss of personal accountability, transparency and the passion of scientists in the organisation'.⁵

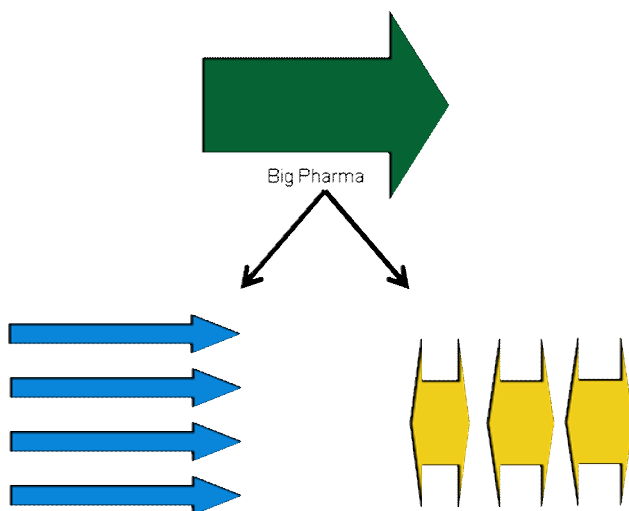
Other factors which may contribute to a sub-optimal working environment as organisations increase in complexity include increased difficulty in effective leadership and communications, increased potential for political conflict and top-heavy management, and reduced ability of an individual to make a difference and positively impact the bottom line.

It is also worth noting that other factors have been postulated for the decline in R&D productivity. These include tougher challenges than in the past (diseases which are easiest to treat/cure have been tackled already), greater regulatory requirements and the increase in cost of R&D activities. Whilst all of these are likely to be contributing factors, we believe that the main reason for the R&D productivity decline is down to increased organisational complexity as a result of increased size.

How can Big Pharma break up?

Big Pharma has utilized its 'fully vertically integrated' R&D operating model since its inception. Vertical integration refers to the degree to which a firm owns its upstream suppliers and downstream buyers. In the pharmaceutical industry, it is typified by one single firm engaged in all the different aspects along the R&D value chain; i.e. from Discovery, Development through to Manufacturing, Distribution and Sales. There are two ways in which Big Pharma could disintegrate – horizontally and vertically.

Figure 3: Breaking up Big Pharma



Horizontal disintegration is an organisational form where end-to-end processes in the value chain are kept together, but the scopes of these activities are limited. For example, it is possible to horizontally disintegrate a company's R&D activities by therapeutic area or by geography.

Vertical disintegration is an organisational approach where the end to end processes in the value chain are broken down and carried out by separate companies, each performing a limited subset of activities needed to create the finished product. Contract Research Organisations (CROs) are an example of companies who typically only provide services in the Development/ Regulatory part of the R&D value chain. Horizontal and vertical disintegration allows a pharmaceutical organisation to:

- Focus on key elements of the value chain where the company has distinct competitive advantage
- Reduce risk while unlocking cash and other value by partnering de-prioritised assets
- Spin out business units into TA/market/tech focused independently traded companies
- Reduce business complexity
- Increase investor transparency
- Have greater strategic and financial flexibility.

Of the two models, vertical disintegration is the more radical. Breaking the explicit linkage between discovery-development-commercial, allows more decision-making freedom to be exercised. It allows the commercial organisation to make more unencumbered portfolio decisions, whilst allowing the R&D organisation to develop deep skills in certain discrete competencies.

However, just as we have recognised the limits of Big Pharma's, so we also acknowledge the limits of this more 'disintegrated' approach. The constraints facing biotech companies also illustrate the need for scale in certain areas.³ The costs of late development and launch mean that many biotechnology companies require large pharma support through licensing deals to develop their compounds into medicinal products.³ Indeed, a company needs critical mass to be able to conduct global drug development and to acquire crucial new technologies.⁵ What we are advocating therefore, is an approach which combines scale with agility.

Attempts by Big Pharma to disintegrate

Horizontal disintegration case study: GSK Centres of Excellence for Drug Discovery (CEDDs) and Medicines Development Centres (MDCs)

At the time of the merger between Glaxo Wellcome and SmithKline Beecham in 2001, the industry's interest was piqued by a novel organisation announced by Tachi Yamada and Jean-Pierre Garnier (then the R&D Chairman and CEO respectively) for drug discovery. The six Centres of Excellence for Drug Discovery (CEDDs) were configured along TA lines and charged to take drug candidates generated by GSK's Discovery Research group and bring these as fast as possible to proof of concept (POC). Proof of concept was to be determined based on a contract agreed with the Full Development organisation.

While positioned as autonomous groups, the CEDDs continued to be overseen closely by Dr Yamada, and were required to source routine services from GSK's own infrastructure, and also team with full development staff through a bridging organisation – Clinical Pharmacology & Discovery Medicine – either side of proof of concept. The CEDD Heads were incentivised largely on achieving POCs delivered. After a relatively lean period the CEDD model has apparently delivered increased productivity as judged by the number of POCs achieved, although the commercial viability of these assets has yet to be fully determined. The CEDD model has been reinforced since, and one has been fully virtualised to focus on Discovery through external collaborations.

More recently, as part of further reorganisation under the leadership of Moncef Slaoui and Andrew Witty (new GSK R&D Chairman and CEO) horizontal disintegration has been further pursued through the strengthening of Medicines Development Centres (MDCs), accountable for developing assets transitioned from the CEDDs at POC to successful commercialisation. Different organisational models are being pursued for different MDCs in order to tailor the organisation to the needs of the portfolio in that area. This approach should help GSK in its goal of 'differentiated development' but will doubtless cause many leadership and interface challenges as heterogeneous organisational units interact with their many and various internal and external stakeholders.

Some of the advantages of GSK's R&D structure include:

1. Clarity of incentives for CEDD and MDC leadership with a healthy and focused negotiation on the definition of POC around each asset
2. Increased freedom of decision-making within each group allowing for greater flexibility and focus on the scientific specifics of the respective therapeutic area
3. Reduced scale of operation and span of control within each group allows for increased local leadership and management effectiveness.

However, some of the potential disadvantages are:

1. Both CEDDs and MDCs appear to be challenged by being 'quasi'-businesses. We believe that neither of these organisation units is likely to have full visibility and control over their actual costs which is an impediment to true entrepreneurialism. This means that decisions can be taken in practice without a full appreciation of the business implications particularly in terms of cost management.
2. Operations groups within the GSK organisation need to interface differently with the more entrepreneurial CEDD and MDC groups which may suffer from a lack of operational expertise that cross-TA groups tend to build up. It is also likely that the leadership and management capability required (in terms of numbers of people) will increase as an organisation disintegrates in this way.
3. Resource inefficiencies tend to occur in these types of organisations, in particular where cost accountability is uncertain. This is a risk in both the CEDD/MDC and its services organisations and could become a particular challenge where the tendency is often to consolidate all resources required to get the job done under 'one roof' which risks increased inflexibility and under-utilisation of resources with fluctuating workload.

Vertical disintegration case study: Lilly-Chorus⁷

Lilly set up Chorus between 2002-2003 as an independent division charged with speeding up early-stage development by getting compounds to POC stage faster and cheaper than Lilly's main development engine. Utilising proprietary management software, Chorus aimed to increase the number of late-stage, risk-reduced development candidates, or to 'de-risk' development projects.

Chorus pursues only what it needs to demonstrate POC, forgoing other activities which are required before starting pivotal clinical trials, but which also increase time and cost to POC. Chorus assumes that most of its compounds will fail, whereas most the Industry assumes 'success-based behaviour'.

Chorus operates as a lean, virtual organisation (24 people oversee all aspects of development for a maximum 10 compounds), utilizes software which allows all the key players instant access to all the key information and outsources 75-80% of the work, relying on external networks of experts and service providers.

As well as ties with Lilly, Chorus also has a partnership with Versant Ventures, testing compounds sourced by the venture group. This arrangement gives Lilly access to compounds it might not have seen, and gives Versant preferential access to Lilly's de-prioritised candidates.

Some of the apparent advantages of Chorus are:

1. Productivity gains: Rapid POC and potential to save money by failing the failures faster and cheaper. Chorus reaches POC in 29 months (compared with Lilly average of 40 months) at a cost of \$3.2 million (Tufts data quotes Phase I only, without reaching POC, costs about \$15 million)
2. Value creation: additional time required post POC is offset by the savings accrued getting to POC because there is a big valuation increase for compounds which demonstrate positive POC. It allows Lilly to unlock value that would be otherwise trapped in its R&D pipeline. Drugs which don't make Lilly's criteria for full Development or even positive POC might be well suited to another company.
3. Benefit of being independent to, yet linked with, the larger parent company. As Chorus works autonomously from Lilly, it is not restricted by the organisational infrastructure of the larger organisation. Chorus is also compound 'agnostic'; no-one at Chorus has a driving loyalty to a molecule which might sway them to select one project over another.

However some of the potential disadvantages are:

1. There is no evidence that the Chorus model works well for successful compounds. A Chorus POC-approved compound cannot immediately be put into registration trials; many of the activities which were skipped over in pursuit of POC need to be completed. It is possible that development may actually take longer in the long run.
2. Chorus has limited capacity and the Chorus approach is not right for all development programmes. For example, it won't work for novel compounds which don't have predictive biomarkers; probably slow down drug programmes pursuing well-validated mechanisms, or where time to submission is crucial and confidence is high. Also, because Chorus works autonomously, in isolation from other groups, it seems less suitable for working on molecules with challenges that require more substantial work, e.g. complex CMC or manufacturing problems.
3. The level of outsourcing which Chorus requires is likely to be troubling to most Big Pharma. It seems unlikely that companies would be willing to adopt such a strategy unless there is significant proof that improves R&D productivity.

How to make disintegration work

It is our premise that breaking organisations into entities of more manageable scale will assist Big Pharma in increasing its R&D productivity. We believe that both horizontal and vertical disintegration should be actively pursued, breaking up Big Pharma into more manageable organisational units.

A good operating model from which to learn in setting up such organisational units is the military's concept of mission command.⁸ The two main aspects of mission command are to establish alignment by setting out the 'what' and the 'why' and granting a high degree of decision making authority to appointed leaders in the organisation who deal with the issue of 'how'. Instead of following detailed orders, the responsibility of subordinates is to understand their commander's intention and to take whatever actions are deemed necessary to complete it.³ When the situation changes, the original intent dictates subsequent decision-making. Much like the concept of 'empowerment', this involves giving decision making power to those that need it and not allowing it to be withheld by those who do not. By aligning everyone on the 'what' and 'why' and pushing down decision-making, it creates organisational units that can adapt rapidly in the face of uncertainty while retaining cohesion.³

With governance provided by a Management Board in the parent company, we propose ten high

-level steps that need to be taken to implement a disintegrated operating model:

- i) Determine areas of distinctive R&D competence and performance, where possible using objective and externally validated process performance measures. Classify processes at which the R&D organisation excels, performs acceptably and under-performs the industry.
- ii) Structure operating units in support of these processes. These units should trade clearly defined inputs and outputs which can be bought from suppliers and sold to customers. Exit processes which significantly underperform through closure or divestment.
- iii) Define clear and separate accountabilities which can be written in a simple list for each operating unit head. These accountabilities will include financial performance of the unit, successful delivery to customer requirements, people and team development and retention of key talent.
- iv) Review leadership talent across the R&D organisation. Identifying the right talent is a must, Leaders should have a track record of implementing new ideas with a willingness to take measured risks. Leaders which bring engagement and passion to get the job done 'whatever it takes' should be at the top of the list.
- v) Appoint existing best leaders to most critical business areas, wherever possible aligning technical and therapeutic skill sets with the organisational unit. Where clear gaps exist, seek external talent from smaller R&D and services organisations where a clear track record for business leadership has been demonstrated.
- vi) For all Unit leaders and potential successors, invest in leadership development, career development and succession planning. In all Units, leaders must spend time with their team members and Units should therefore have no more than three organisational layers below the Leader.
- vii) Increase emphasis on business skills including communication and negotiation skills as well as customer and supplier management. Seek regular career moves for best performers between organisational units to increase 'joined up' thinking between customers and suppliers in the network.
- viii) Invest in an enabling infrastructure which allows transparent cost accounting at the level of each organisational unit, with unit leaders

quality, outsourcing management should also be considered in the network, ideally as financially self-standing operating units which may or may not be owned by the parent organisation.

- ix) Ensure operational decision-making resides within the unit. The Management Board should intervene only when fact-based operational performance issues become apparent through pre-defined performance metrics. Consider exiting under-performing operating units.
- x) Accept that successful units will tend to grow as unsuccessful ones will contract or disappear. This raises the question of the ideal size of organisational units? It is interesting that many organisations, including the military, hunter-gather societies and some businesses favour Dunbar's magic number of 150 (the postulated maximum number of individuals with whom we can have a genuine social relationship).⁹ Over time, the network needs to be managed with incorporation of new units and breaking up of larger units to ensure the benefits of disintegration are maintained in the long-term.

Conclusion

In order to thrive, Big Pharma needs to start thinking 'big' and acting 'small'. The 'industrialised' business model which has served Big Pharma well in the past appears to be faltering. In today's R&D environment, Big Pharma needs to consider the benefits of a more radically disintegrated model – groups need to use different processes, become more nimble and develop a culture which allows individuals to 'try new things'. Individuals need to be empowered and Unit leaders need to lead. Although disintegration is a radical and potentially risky approach, simply tweaking the old business model no longer seems a viable strategy. Given the mooted wave of Big Pharma merger & acquisitions this year (e.g. Roche's hostile bid for Genentech, reports that Sanofi Aventis is lining up funds for an acquisition and news that Merck is considering a major buyout) – disintegration needs to be at the forefront of every senior pharmaceutical executive's thinking.

References

1. Tufts Center for the Study of Drug Development (2006). csdd.tufts.edu Accessed June 2008
2. I Kola & J Landis. Nature Review Drug Discovery, 711-715 (2004)
3. S Bungay, D Roblin & D Slavin. Pharmaceutical Executive Europe (2006)
4. Online.wsj.com Accessed June 2008
5. JP Garnier. Harvard Business Review (2008)
6. Invivoblog.blogspot.com Accessed June 2008
7. R Longman. In Vivo May (2007)
8. S Bungay, British Army Review, 137, 22-29 (2005)
9. M Gladwell. The Tipping Point. Abacus (2000)

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About Kinapse

Kinapse works with its life sciences clients to provide value creation through information processing, business transformation consulting and asset value consulting. We provide synergistic capability to enhance value in these three areas separately or in combination. Our business model blends experienced consultants with a high calibre analytic and delivery team based in India with industry veteran Consulting Partners who bring deep experience and expertise of R&D processes and functions.

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