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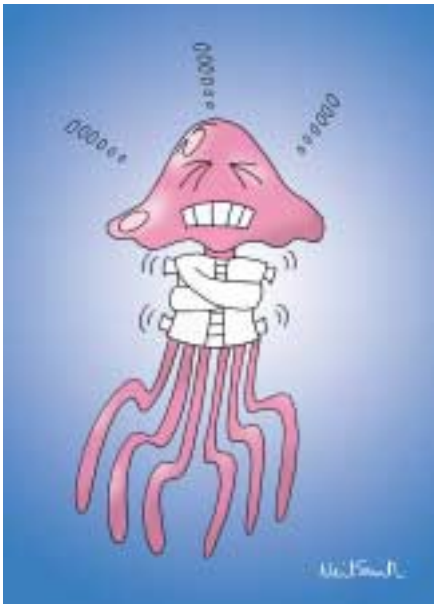
Merging drug companies, submerging creativity? ▼

These days you can barely read something about the pharmaceutical industry without seeing the word 'merger'. Where there used to be hundreds of drug companies, it looks like soon there will be just a few giants left, each with the fiscal power of a small country. I do not want to comment on the economic and business sense of merging although, like most people, I have heard strong arguments for both why only the big will survive and also why only the weak merge. It seems to me that, as in all companies, those that are well managed will thrive and those that are poorly managed will go to the wall, irrespective of size. Then again, what do I know? I am only a scientist. However, it is as a scientist that I would like to throw in my ha'p'orth on the subject of mergers.

We hear a lot about 'critical mass' and the vast resources required to finance a competitive research organisation in this age of genomics, as if all that research management involves nowadays is buying more typewriters and employing enough monkeys. Obviously, whether a drug makes it to the market depends on factors well outside research, but the initial discovery stage is still based on good science. Equally obviously, if the quality of the products emerging at the discovery stage can be maximised, the risk in the development processes can be reduced.



So can drug discovery research be turned into a production line: the bigger it is, the faster you turn the handle, the more candidates will pop out? Call me old-fashioned, but I rather thought that a bit of creativity was needed somewhere along the line (well okay, lets be honest, a slice of luck helps too). Merging will of course increase the physical resources available, but will it increase creativity too?

Creativity

Trying to pin down what makes any scientist 'creative' is like trying to put a straightjacket on a jellyfish. As with any other creative endeavour, the motivation for individuals in science is highly diverse, but I would argue that an essential element is independence and the freedom to follow your nose. Trying to channel research down to tightly defined paths will kill the goose that lays the golden egg. Clearly, if research is to fully bear fruit it must be well managed, but I fear that the nature of the merger is to over-manage.

For a start, priority number one is often to introduce a new, uniform culture throughout the newly merged organisation, ushering in a period of disorientation if not paralysis. In general, scientists are not a passive workforce. By this I do not mean a tendency to rush to the barricades over a poor pay rise, but instead a resistance to change without adequate explanation. Introduction of a new culture from above, accompanied with fanfare and glitz, might work well in some sectors but is counter-productive in the scientific community who are usually quite good at spotting a name change when they see one. All progress is dependent on change, but if the desired change cannot be justified with reason, its validity must be called into question.

Furthermore, if the 'why?' question is neither answered nor tolerated, it will not be well received by scientists. Nor should it be expected to be: after all, why ask a group of people whose merit to the organisation is based on their investigative skills and curiosity to unquestioningly accept anything? Faith is hardly a good maxim for scientific research. In such an environment, the nature of the scientist will inevitably adapt and independence will be subsumed to conform to the 'one-size fits all' culture. If scientists are afraid to stick their heads above the parapet, as well as the potential loss of new ideas,

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there will also be less critical appraisal of those with official approval, with equally detrimental effects. (How many millions have been wasted by big pharma on poorly evaluated collaborations embarked on out of a fear of being left behind, rather than positive strategic intent?) Furthermore, if incentives that motivate salespeople are imposed on scientists, pretty soon you will find they will turn into salespeople too. In all the excitement that accompanies the merger, the need to manage different types of employees according to their different natures should not be forgotten.

Segregation

With the increase in size resulting from a merger, some organisations seek to more distinctly segregate the various disciplines in drug discovery research. This can mean that instead of walking down the corridor or to another floor, a chemist might have to go to another building, another site or even another country to talk to the biologist testing the compound s/he has made. Thus, the main point of contact between interdisciplinary scientists is by formal meetings, and time pressures will inevitably restrict the exchanges to the project in hand.

The previous casual contacts that would occur in the tearoom, or at lunch, or while walking in from the car park are lost. This is a latent resource wasted, as it is these casual personal inter-disciplinary interactions that not only lead to cross-fertilisation and the rapid spread of new ideas, but a general broadening of outlook vital for creativity. By contrast, such multi-disciplinary contact is a fact of life for start-up companies, and no doubt a major contributor to the diversity of innovative research emerging from these companies. Perhaps, as has been suggested, the future of drug discovery research is with the start-ups, whose products are sold on to one of the few mega-companies for development. If this is not to be the case, the challenge for these huge pharmaceutical companies is to foster an environment that brings scientists together with the time and inclination to 'chew the cud'.

Identity

The final factor I would like to mention is that of identity, and its consequences for morale. In a merger, the workforce is plucked from its state of relative equilibrium and plunged into chaos, from which it takes several months if not years to recover. The restructuring (with the concomitant uncertainty for one's personal future) resulting from merging will inevitable weaken any bonds that existed between the company and employee and, rather like childhood innocence, once lost, no amount of assurances and explanation can restore them. In addition to the sense of instability and distrust, the vastness of the new company can lead to the loss of identity and all these factors will cause morale to plummet (I wonder if any merged companies have better morale than in their pre-merged days?).

It might seem a terribly naive notion in the age of personal career plans to consider the organisation you work for as anything other than a convenient means to pay off the mortgage, and doubtless if any company-hopping Vice Presidents read this they will think 'and your point is?' However, I find it hard to believe that morale and having a positive feeling of identity and commitment is not important, as the enthusiasm that results is a vital component of both performance and creativity. To reverse this again requires an approach suited to the nature of the employee, but for scientists, spending a small fortune on a fancy new corporate logo, constant re-organisation and numerous management surveys that conclude 'you are all doing very well' is not the way to go.

The irony is that it takes little to keep the scientist happy as scientists are generally extraordinarily self-motivating, but engendering a feeling of stability and concentrating on the small local things that matter instead of dealing on a corporate-wide level surely must be the priorities. Scientists need a light touch and, if this is the case, morale has a chance of growing in the only way it can: organically from the bottom. It would be nice to think that one is able to perform one's job to the best of one's ability because of, not in spite of, the management environment. These sentiments are of course neither new nor unique to scientists working in merged drug companies, and have been eloquently expressed before:

> 'We trained hard: but it seemed that every time we were beginning to form up in teams, we would be re-organised. I was to learn later in life that we tend to meet any new situation by re-organising, and a wonderful method it can be for creating an illusion of progress whilst producing confusion, inefficiency and demoralisation.'

Does this sound familiar to anyone? I can just imagine Gaius Petronius (who wrote these words in AD 66) raising his eyes heavenwards in a resigned sense of deja vu. Recently, a reunion was held for a research establishment that several years ago failed to survive the merging process: 200 people were expected, 800 turned up. No amount of corporate edicts or mission statements can create an atmosphere like that, they will only serve to destroy it. However, with sensitivity and trust, and resisting the urge to turn everything upside down as an alternative to a genuine strategy, it can be encouraged to germinate.

None of these factors need to be casualties of a merger. It just takes a management that recognises that these are vital factors not optional extras, and that creative science is nurtured, not rolled off a production line. In merging,

the principles used successfully in managing scientists in smaller companies should not be abandoned, because not developing and harnessing the full creative potential of your scientists is an unaffordable extravagance. After all, size isn't everything.

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Optimizing screening technology: how much to invest?

The foundation for long-term growth of a pharmaceutical company lies in the development and implementation of new technologies for drug discovery. Unfortunately, new technologies do not always meet expectations. In the past several years, we have seen vast improvements in the instrumentation associated with the screening of large chemical libraries for drug leads. Yet making rational decisions concerning investments in screening technologies is often very difficult. With finite resources it seems unreasonable and impractical to continually upgrade and instigate new technologies that might not offer what they promise, and that require much testing to determine their true value.

The trends in HTS have been towards testing compounds in cell-based and biochemical assays at increasing rates and in smaller volumes. The proposed advantages are that more leads will be found in less time and with less reagent use and that larger libraries can be screened, thus increasing the information content of the screen and increasing the odds of finding good leads. However, alternative screening paradigms suggest that there are limits to the diversity space of large libraries and that smaller, more carefully designed libraries are adequate, especially in conjunction with the medicinal chemistry effort required for optimizing a lead.

There is a point where screening rates and lead discovery rates no longer present a bottleneck in the drug pipeline and therefore a point at which further investments in screening technologies are no longer worth the benefits they provide. Thus, when planning improvements in core screening facilities, one has to ask whether efforts toward implementing new screening technologies are worth the expenditure and what screening rates are necessary to keep a competitive pipeline.

In the past few years significant improvements in two areas of routine screening have been made:

- A switch from 96 to 384-well liquid handling in 20–30 μl volumes.
- A variety of mix-and-read, cell-based and binding assay methodologies, for example, luciferase reporter assays, time-resolved fluorescence resonance energy transfer, fluorescence correlation, fluorescence polarization, scintillation proximity, and luminescent oxygen channeling.

Although it is difficult to quantify the overall contribution of these improvements to drug discovery, one can safely say that, given a choice to run an assay in 96 or 384-well formats, one would always choose 384. Furthermore, given the choice between plate washing or mix-and-read, one would choose mix-and-read. The benefits of 384-well, mix-and-read formats are that one can process twice as many assays per person per dollar with 30–40% of the reagent usage. The technology that is commercially available is easy to use, reliable and cost-effective.

We will probably find the same to be true with 1536-well screening in 5–9 μl volumes. The optical readers, imagers and dispensers that are becoming available are relatively good. Although in many cases, considerable effort must be put into reformatting libraries, by analogy, we would expect to see the same dramatic improvements in screening efficiency as we have observed with 384-well screening.

However, contrary to what some technology advocates would have us believe, many of the novel screening technologies that promise greater levels of miniaturization are of questionable practical value in drug discovery. The production of assay reagents is no longer a limiting factor with the currently available levels of miniaturization. One can test 50,000 targets (every protein in a cell) with a few milligrams of compound. With modern gene-expression technology, producing a few milligrams of protein reagents per screen is not a limitation. Furthermore, novel ways to measure compound-induced biomolecular changes are desirable only to the extent that they can measure formerly intractable 'prize' targets. Such screening-unfriendly targets include enzymes involved in sugar and lipid metabolism, for which we have seen little improvement in screening methods.

Many of the more 'academic' technologies are tested with unrealistic proof-of-principle experiments. Development of these technologies will require a new generation of liquid handling systems, compound handling systems, chemical synthetic procedures, plate materials, optical technologies, automation and bioengineered cell lines, which come at a large expense. In routine screening of compound libraries, the speed and efficiency that 1536-well screening affords with the battery of assays now available is more than adequate to meet lead discovery needs. With appropriate automation and organization, libraries of one million or more compounds can be screened in a week or less. If one wants to increase the screening throughput, one can increase

the level of parallel processing, an approach that is considerably less expensive than investing too early in visionary new technologies.

Although continuing efforts at maximizing the efficiency of HTS are worthwhile, we must keep in mind the law of diminishing returns. If we abide by this law, we will be free to invest our efforts in the more compelling problems of drug discovery, for example, validating targets, improving times for lead optimization, increasing the rate of *in vivo* testing of optimized leads, and developing better experimental predictors of clinical safety and efficacy.

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Whither solid-phase chemistry? – Reply ▲

Initial letter: Terrett, N. (2000) *Drug Discovery Today* 6, 16

Response from Tony Baxter

I agree with much of the detail of Dr Terrett's letter. Certainly, preparing and screening mixtures of compounds is now seen as largely an outmoded concept. Improvements in synthetic methodology and, in particular, analytical techniques have ensured that the quality of single compound libraries has significantly increased and this, coupled with improvements in HTS techniques, has meant that screening mixtures is now largely redundant.

With regard to the use of solid-phase chemistry, I am not totally in agreement with Dr Terrett. Whilst solution-phase techniques have been more widely embraced within the library synthesis community (certainly at Oxford Asymmetry International, >50% of compounds are produced using solely solution-phase methods), it is still true to say that solid-phase chemistry plays a valuable role in the production of larger 'lead discovery' libraries and can have a significant impact on the speed in which certain lead optimization programmes can proceed.

The main issue with solid-phase chemistry is that it takes significant resources, training and time to build up a critical mass of knowledge and skills that can then be applied to various projects. The pharmaceutical industry, typically, does not have the time or resources available to dedicate to producing such a skill base and I suspect that it will be the larger service-based companies that will be the main users and beneficiaries of such technologies in the future. It should also be stated that solid-phase chemistry should not be seen in a competition context with solution-phase methods but more realistically as a complementary methodology in which both techniques have their place in the synthetic armoury of today's medicinal chemist.

We very much support the efforts of the academic community who are further developing new solid-phase methodologies that can be applied to industry-based synthetic problems. There is a view that such new methods and technologies represent new and better tools that can be added to the technical 'toolbox' and applied to an ever-increasing range of given problems.

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