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Biofinance: what does the future hold?

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The Wall Street Journal Europe's *BioFinance Roundtable 2001* (11 September 2001, London, UK) took the unusual format of four panel sessions, concluding with an interview with Jonathan Knowles, President of Global Pharmaceutical Research at The Roche Group (Basel, Switzerland). Topics ranged from issues surrounding valuation to more scientific topics such as genomics and proteomics, cellomics and nanotechnology. In this overview, each panel will be discussed in turn, concluding with the interview.

Valuation

The first of the four panel discussions focussed on company valuations, factors that affect these valuations and ways to improve your valuation.

How to improve value

Charles Floe (Managing Director, Head of International Healthcare, Lehman Brothers, New York, NY, USA) commented that virtually nothing will drive value at the moment. News flow from companies is currently relatively high but instead of this increasing share prices, people seem to use this as an opportunity to sell their shares. Large products are, therefore, currently the only real area of value, and he commented how important it is to your company's value to have a platform behind your pipeline. Jane Fisken (Managing Director, Head of Global Lifesciences, Dresdner Kleinwort Capital, London, UK) mentioned the current uncertainty relating to the Internet-related healthcare business where she said they have recently rejected many deals and in fact have now stopped looking at plans for this type of company altogether. Dresdner Kleinwort Capital have done one investment in this area but then pulled out, preferring to wait and see if this model really does work. Instead, they are investing much more in later-stage companies where there is less risk.

François Maison-Rouge (Managing Director, Head of European Healthcare, Credit Suisse First Boston, New York, NY, USA) said that valuation of therapeutic companies has decreased more than for technology-enabling companies. If a small venture capital-financed company has some therapeutic products in the pipeline, everyone assumes it will be successful but this is not necessarily true. By contrast, in big pharma, people almost ignore products up to Phase II for valuation and Knowles complained that even though Roche's diagnostic unit is the largest in the world, valuers still seem to ignore it.

Fisken commented that an increasing number of companies are now converting from being a technology company to developing their own products. Maison-Rouge and Floe suggested that many companies (such as Celera) will do this by buying a pipeline to help their positioning in the market. Floe thought that this was generally such a successful approach because investors soon tend to forget that these companies did not get this pipeline by their own means. However, the most valuable commodity is still products that have been developed internally.

M&A and alliances

The discussion then turned to the subject of mergers and acquisitions (M&A) and why there have been so few among the larger pharma companies recently. Jonathan Knowles, questioned as to why Novartis and Roche had not yet merged, pointed out that Roche has a dual share structure and is controlled by majority shareholders and hence, what the shareholders want, goes. He suggested that mergers are not currently happening because of a recent change in accounting rules that make it necessary to capitalize goodwill, putting a big load on profitability. Furthermore, both Knowles and Fisken commented that many biotech companies do not have a clear vision and this is also probably reducing M&A activity. Maison-Rouge said this is compounded by the fact that there are many more good business propositions than good people to manage them. Furthermore, in places like Germany, there are not enough venture capitalists, and this is important because they can provide a company with a good sparring partner and advice to go with the capital. Flow suggested another possible reason for the lack of mergers was that companies that are unable to keep pace with growth need to merge, but because none of the top pharma companies are really outperforming anyone else on growth at the moment (which is at ~9–12%), the pressure is off compared with the beginning of 2001. Furthermore, few of the latest mergers actually created value anyway. Knowles predicted that one of the new waves of mergers that we are already starting to see will be between biotech companies with complementary abilities.

One emerging new way of doing mergers is the approach taken by Roche when buying Genentech. It slowly bought the company and then re-floated it, generating significant revenue. Other examples of this approach include Merck and Rosetta, and Pharmacia and Sugen. Floe highlighted that the element of independence in this approach is the key to its success, for example, the fact that there are only two people from Roche on

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the Genentech Board. Similarly, Sugen will remain a research organization and, although 100% owned, its independent structure means it is likely to do well. Daniel Cohen (Chief Genomic Officer and Directeur General, Genset, Paris, France) agreed that this is an excellent model that will be increasingly important in the future. Another new important strategy that Roche has taken is to put part of its portfolio outside of the company and retain a small share and then get external financial support for it but retain some opt-in clauses. Further alternative strategies include Knowles' prediction that, in the future, we will start to see compounds being swapped between big pharma companies at Phase I and II stages.

The need, as a biotech company, to approach big pharma at the right time, that is, when they can convince the pharma company that they not only have a pipeline but the potential to increase the pipeline, was put forward by Cohen. Hence, he suggested the best time is once you already have a pipeline of highly validated targets (i.e. at least 2–3 targets in chemistry and 2–3 targets in Phase I or II studies). However, Knowles pointed out that, in fact, the sooner a biotech company approaches pharma companies, the quicker the product will reach the market and, therefore, the more revenue will be generated.

The panel was then questioned on when they thought biotech companies would start to have a positive impact on decreasing the risk of creating products. Both Cohen and Knowles said that, initially, biotech had increased the risk by proposing 'validated' targets with no clinical evidence to support them. However, they are now decreasing the risk, in part, using genetics. Toxicogenomics is also making a significant contribution to reducing the likelihood of failure up to Phase IIb studies, and drug–drug interaction studies are being done much earlier in the drug discovery process.

Genomics and proteomics

Number of human genes

Bernd Seizinger (CEO, GPC Biotech AG, Martinsried, Germany) sparked off the debate in this panel session by discussing the fact that there are fewer genes in the human genome than originally predicted. However, Rosenthal said that the original estimates were just a matter of hype by Celera Genomics, academia and investors because a larger genome is much more interesting to investors. However, those that say there are 100,000–150,000 splice variants are still correct and some targets might be a splice variant. Kari Stefansson (President and CEO, deCODE Genetics, Reykjavik, Iceland) disagreed, suggesting that people genuinely believed that there were 100,000–150,000 genes at the time, and that the figure of 30,000–40,000 genes is highly underestimated because of a lack of sensitivity of the technologies being used.

Furthermore, there was concern over the usefulness of the current state of the human genome sequence. Stefansson pointed out that a significant proportion of the sequence is incorrect in nucleotide identity, placement, or interaction with contigs. When it comes to finding targets and new drugs, a high-density genetic map is needed. Knowles confirmed this, quoting that a comparison of the Celera and public-domain sequences showed that only ~15,000 genes correlated between the different versions, with no correlation at all for a further 15,000 genes.

Should we be using more patient medical record data?

Andre Rosenthal (Chief Scientific Officer, metaGen, Berlin, Germany) raised the point that few companies have integrated technology platforms with broad medical and pathology research. He suggested that we need to obtain high-quality tissues to understand the heterogeneity of these tissues and, therefore, we need to combine patient medical data with disease tissue. We need to copy what Kari Stefansson and his team has done in Iceland and do it in the UK and other countries in a way that is ethically acceptable.

Although Stefansson said that this metaGen approach is good for certain diseases such as cancer, he commented that comparing gene expression between healthy and diseased tissue is dangerous because some genes might be reactive to disease whereas others are participating in the pathogenic process of the disease. However, if you clone the disease gene, then you know it is part of the disease but have the problem of validating it as a drug target, which is where proteomics comes in. Furthermore, Stefansson highlighted that tissue can provide much more information than medical records. Tissue has already been collected in an ethical manner in Germany and there have been no reported incidents of misuse of this tissue so far.

Genomics versus proteomics

There were differing views on the relative importance of genomics and proteomics to finding new drugs and drug targets across the panel. N. Leigh Anderson (Chairman and CEO, Large Scale Biology Corp., Rockville, MD, USA) argued that it is generally extremely difficult to work purely from genomics. He said that proteins are the bottom line in the business of biology: almost all drugs either bind to proteins or are proteins. The reason why we are not currently succeeding particularly well with proteomics is because many proteomics technologies are very large scale and not readily available. Stefansson, however, held a conflicting opinion, arguing that because all proteins are made by genes, the point of least complexity is the genome. Hence, the only way to develop understanding of how proteins fail in disease is by understanding the genome and its role in disease. He further suggested that proteomics technology

would not be particularly empowering without basing it on what we know about the underlying genomics.

Cellomics

William Bains (Director and Chief Scientific Officer, Amedis Pharmaceuticals, Royston, Hertfordshire, UK) introduced this session by first defining cellomics as 'the industrial biology of the cell'. It encompasses whole-cell analysis (analysis of targets and extensions into development); computational simulation, analysis and extrapolation; and whole-system approaches to experiments and modelling.

Anderson pointed out that 100 years ago, 30,000–100,000 genes seemed impossibly complex. Now, this large number of genes does not sound so threatening but it is still challenging because we do not have the right data yet and we cannot see any way to build models that work without detailed information such as proteomics. The main question now is: who has the nerve to do this? Many biologists see this as career-limiting, whereas mathematicians see it as a good opportunity to build a new model. However, we still need quantitative identification of the biology to put into these models, which has not been possible so far. The acid test will be to do something we could not do without this knowledge. Many have said that this would be the creation of life from earth, fire and water. Anderson suggested that we will be able to do this within the next 20 years, although Bains thought this would be highly unlikely.

Thomas Lengauer (Director of the Institute for Algorithms and Scientific Computing, GMD – German National Research Centre for Information Technology, Sankt Augustin, Germany) commented that the metabolic data we are still lacking should be available in appreciable volumes within the next five years. Successful integration and curation, as well as quality assurance of these databases is still a big problem and is both a political and an organizational issue. One way to analyze all this data is to use inference engines or machine learning where data is visualized as clouds of points in high-dimensional space, and this will provide added value in the near-term. However, cellomics requires a different paradigm of combining structure, sequence information and everything else. Hence, to analyze this, you need both biological and mathematical theory and this will take at least one human generation, which means it is not good for investing in right now.

Anderson further proposed that there might only be a finite number of drugs and that 30 years might be a reasonable time to find them all. We already have enough information to create a model of the human heart (Physiome Sciences, Princeton, NJ, USA) but Bains put the ease with which this was done down to the organs' homogeneity and limited electrical activity. Similarly, Bains suggested that the brain would also be relatively easy to model, not in terms of cognition, but in terms of, for example, epilepsy. However, we are nowhere near being able to extend this to other organs. The next stage will be to look at metabolites and then at gene induction, but to do this and to integrate all the different levels of information will require an accurate version of the human genome sequence.

Nanotechnology

Scott Mize (Chairman of the Advisory Board, Nanotechnology Opportunity Report) opened this final panel session by defining nanotechnology as 'the science and technology of precisely structuring and controlling matter on the nanometer scale'. He compared the current early state of the field with IT before the integrated circuit (early 1960s) or biotech before recombinant DNA (early 1970s). The US Institute of Nanotechnology (Evanston, IL, USA; http://www.nanotechnology.northwestern.edu) was set up in 2000, and is akin to the 1971 'war on cancer'. There are currently many large companies dominating the activity in this field, especially in Europe, and Europe and the USA are at comparable stages of progress. There are also several research consortia emerging such as nanobionet (Germany; http://www.nanobionet.com) and some good sources of general information on the field (such as http://www.cmp-cientifica.com). Further information will also be available from the upcoming Nano Opportunity Report, a White Paper that is due out in December 2001.

One concern expressed by Mize was the difficulty some had seen in trying to obtain funding for this research as there is a perception that this is a long-term field. Furthermore, the fact that it is mainly large companies that are involved in the field at the moment (e.g. Novartis and IBM recently worked together to develop biosensors), can be problematic because the difference in their approaches often makes it difficult for them to work together. Mize, therefore, suggested that what is really needed is a small cottage industry of young companies that have been brought up to think across these different industries. He said that the California Nanosystems Institute (based at both the University of California, Los Angeles and the University of California, Santa Barbara; http://www.cnsi.ucla.edu) is leading a new generation of people that are already thinking in this new way.

In the near-term, James Gimzewski (Professor, California Nanosystems Institute Department of Chemistry and Biochemistry, University of California, Los Angeles, CA, USA) suggested that fast methods for bioassays and diagnosis will be the first tools to benefit from nanotechnology (e.g. the recent paper in *Nature Biotechnology* on using microchip microcantilever technology to generate a bioassay for prostate-specific antigen)[1]. Andrew de Mello (Senior Lecturer of Analytical Sciences, Department of Chemistry, Imperial College of Science, Technology and

Medicine, London, UK) similarly suggested the first areas to benefit would be medicinal and clinical diagnostics. There are already many microfluidics devices that can do this but they are primarily in the laboratory at the moment. For example, de Mello mentioned that Caliper Technologies is already doing HTS using microfluidics and miniaturization. Gimzewski highlighted other advantages of nanotechnology such as the potential to rapidly screen single cells using, for example, silicon microelectronic structures. Mize suggested that nanotechnologies that use tagging (i.e. where radiation or fluorescence is used to show the presence of a protein or chemical precursor) will get to the market much faster as they will not have to pass through the FDA. Meanwhile, areas such as drug delivery will need to pass through the FDA and, therefore, the first nanotechnology in this field is probably at least seven years away.

Re-engineering the Roche R&D department

In the final session of the day, Knowles was interviewed on the reorganization of the R&D department at Roche over the past few years. This reorganization was done to try to produce a 'seamless approach' to strategy and decision-making. The new structure comprises three committees, each one with 50% representation on the other committees, enabling good understanding across 50 different disciplines within the company such as clinical, drug discovery and drug development.

Over the past three years, Roche has also moved its screening from a centralized location in Japan to the implementation with Carl Zeiss of a third-generation screening system in all sites. Furthermore, multidimensional drug optimization and predictive micro-screens for oral bioavailability, half-life in serum and drug–drug interactions, are all now being carried out early in the drug discovery process. There has also been a significant change in the company's data architecture, which has been redesigned to enable real-time global access to all experiments within the organization. This has, therefore, required standardization of all experiments across all company sites.

Knowles was, however, critical of the new model being used at GlaxoSmithKline (GSK) that allows different groups to compete with each other. He said that Roche had previously used a semi-autonomous site model and this was not particularly successful in terms of clinical candidates selected. It can mean that the key synergies of the chemistry library and informatics are missed (although GSK might have ways around this), as well as missing out on peer-review. He also commented that internal competition is difficult to manage and can kill an organization as people will have differing views about the value of things and, if not careful, this will lead to negative views about other parts of the organization.

Conclusions

This meeting provided interesting discussions on a wide variety of topics. The format of having all panel sessions was good because it enabled discussions between key people approaching the areas from different angles. However, there was not much interaction in these discussions from the delegates and many commented it required much more effort to follow all the discussions.

In summary, it appears that there is still quite a lot of nervousness in the market and concern over the lack of innovation in the pharma industry, but a new wave of more innovative M&As are starting to take place which could help this situation. As always, there is still much debate about the best way to go forward with the new information from the human genome sequence, but key to its usefulness will be the creation of a much more accurate and high-density map. Meanwhile, both cellomics and nanotechnology are still in the early stages and although both fields hold much promise for the future, we still have a long way to go.

Reference

1 Wu, G. *et al.* (2001) Bioassay of prostate-specific antigen (PSA) using microcantilevers. *Nat. Biotechnol.* 19, 856–860