The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*, e-mail: Rebecca.Lawrence@current-trends.com

The optimal fragmentation principle ▼

This December, I was a speaker in a symposium on Computational Toxicology at the National Library of Medicine (NIH, Bethesda MD, USA), presenting a glowing outlook on new advances with data mining tools for chemists and toxicologists. Ann Richard (EPA) quickly reminded me that, as nice as the tools were, the resulting predictive information 'would never reach the light of day' because they were designed for the pharmaceutical industry where proprietary interests would prevent access to the rest of the scientific community.

Of course, she was right, but rather than sulk on the flight back to San Francisco, I decided to read the *Wall Street Journal*, hoping to find that the rotting carcass of dot.commery was not contaminating the chemoinformatics and toxicology fields. Or better yet, the US Supreme Court had taken a break from deciding elections and ordered the release of all proprietary pharmaceutical information to selected *in silico* toxicology entrepreneurs from California.

But, alas, while reading *The Ideal Form of Organization* by Jared Diamond[1] the cold reality of Richard's comment gave me pause for gastrointestinal discomfort (there might have been a synergistic

effect when I turned over the chicken entrée finding it was not anatomically correct). Diamond was applying the *Optimal Fragmentation Principle* to a discussion of the demise of China's prominence in ocean shipping in the fifteenth century versus Europe's political fragmentation that stimulated 11 European countries to build ships and vie for colonial bounty – and the local monopolies (an example of isolationism) that have always hampered the Japanese food industry versus the openness (trade) of the Japanese steel, metal, automotive and electronics industries. Diamond concluded that a certain fragmentation with competition and open communication is the ideal model for business and government. It struck me that this is what Richard was also saying.

In order for the pharma industry as a whole, as well as the scientific community and healthcare in general, to make real headway in predicting potential toxicity from chemical structure, the industry must be willing to 'share' information. We have technology today that will enable this to happen. A centralized warehouse of information can be created where proprietary information can be encrypted and maintained secure. Large datasets of chemical information could be sorted through fragments without necessarily being able to reconstruct the chemical structures. The entire research community could use this encoded information in several *in silico* systems and it is possible that we could really start to reduce or eliminate major side effects of new drugs before they happen.

Is this possible? It will take innovative and forward thinking – more than just making an entrée look like an entrée.

Reference

1 Diamond, J. (2000) The ideal form of organization. *Wall Street Journal* 12 Dec, A26

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More clinical input required for R&D decision-making? ▼

Tremendous technical advances in drug discovery technologies have taken place during the past few years. However, the number of new drugs is not increasing at the rate desired by the pharmaceutical companies and the drug development costs are still rising. A major contributing factor to the rising cost is the high attrition rate of drugs in development and failure in clinical trials. These factors are recognized by the industry but there is little discussion

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about the contribution of the decision-making process to drug development. I have made several observations while working in both large pharmaceutical companies and as an independent consultant:

- Technical advances, unless backed by a rational decision-making process, are ineffective in making a significant improvement in the current situation.
- Errors of human judgement and lack of an understanding of the real-life healthcare system are responsible for many poor decisions about drug development, resulting in financial loss to the companies. These losses are compensated by higher prices of drugs paid by the consumers.
- The environment within large pharmaceutical corporations, with vested interests of certain groups, are not suitable for frank expression of dissenting opinions in discussions relating to continuation of further work on discovery and development projects.
- Although pharmaceutical companies have high calibre basic scientists, there is a shortage of experienced clinicians with a broad knowledge and mature judgement.
- Drug safety/toxicity is not given as much priority in pharmaceutical companies as it deserves because of allocation of less than the best resources of the company.
- Creating larger corporations by mega-mergers to increase R&D budgets without correcting basic problems cannot be expected to increase the number of new drugs introduced.

Examples to illustrate some of these points are not difficult to find. There is a reluctance by some research groups in the larger companies to discontinue research projects even after it becomes obvious that there will be no useful returns. Some projects are continued and can even enter clinical trials before they are dropped. Even for the projects that are successful, scientists do not have the opportunity of interacting with the clinicians that would be using the product.

Several years ago, I had an argument with a scientist who developed a recombinant protein, which was later approved for human use. He did not feel that there were any risks of adverse effects as the product was pure and is a protein that occurs naturally in the human body. He questioned my proposal for setting up safety monitoring. What he did not realize was that the protein was manufactured in *Escherichia coli* and some people are allergic to this organism (now a well-recognized event, together with a long list of other adverse effects).

I think that the situation can be improved by greater use of expert clinical input at the preclinical stage. Although a great deal of information is available concerning genes and the molecular basis of diseases, target selection and validation would require much more attention. However, the real validation comes with proof-of-efficacy in the human patient. Greater use should be made of independent external medical experts with knowledge of new technologies based on genomics and proteomics. There is a much greater manpower of this category available outside than inside the industry and the main advantage is an unbiased opinion at an early stage of development that should be taken into consideration in the decision-making process within the company. Such an opinion is particularly important before a new chemical entity is moved into clinical trials. Appropriate decision-making with clinical input during the drug discovery stage has also become important with the current trends in healthcare towards personalized medicines and integration of diagnostics with therapeutics.

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Optimizing screening technology: how much to invest? – Reply ▲

Initial letter: Glickman, J.F. (2000) *Drug Discov. Today* 6, 73–74

Response by J. Fraser Glickman

Although Paul England's letter [*Drug Discov. Today* 6, 130] has not convinced me of the necessity for going beyond efficient 1536-well plate automated formats, both England's and Kevin Oldenburg's [*Drug Discov. Today* 6, 128–129] responses suggest some of the many potentially useful directions for HTS. England has suggested that we test compound libraries for solubility, *in vitro* ADME/tox, metabolism/stability and absorption, to provide more information as a starting point for lead optimization. These assays are reasonably good, and are used in the pharmaceutical industry as a cost-efficient alternative to testing leads for potential 'liabilities'. However, it must be remembered that these measurements are not perfect predictors of *in vivo* pharmacology, and there are valuable compounds on the market that would have been eliminated by such tests.

Pharmacokinetic properties

An HTS approach towards measuring *in vitro* ADME, toxicity, solubility, stability and absorption is attractive in that it only needs to be performed once, and then subsequently, only as compounds are added to the library. Unlike some of the ultra-high-density screening formats, this approach would not require a large investment in apparatus development, but rather the application of HTS methodologies to currently available procedures. The analytical steps of some of these assays are still quite slow and might require considerable investment in miniaturized and automated LC/MS protocols, or even faster methodologies.