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.

This approach will add value to a screening campaign because it will have a high likelihood of returning the information that it promises to obtain. Hopefully, it would provide more information about the necessary chemistry of a compound to ensure desirable pharmacokinetic properties. The requirements for throughput rate in this scenario are still open for discussion because this is a 'one-off' type of screen and each assay type differs in the degree of throughput attainable, as well as the quantity of capital required to instigate the technology. Furthermore, we must still weigh the benefits of screening an entire library as England suggests, against the lower costs of testing only the active compounds.

Pharma versus chip industry

Oldenburg suggests that the pharmaceutical industry is similar to the computer chip industry in that 'there is a constant drive to develop new, faster and better products in increasingly shorter timeframes'. This statement might be applied to almost any industry. However, there are notable differences between building a new computer chip manufacturing facility and investing in new technologies for drug discovery, and this is the crux of the issue.

The methods in which chips are produced are highly evolved, and fairly well determined, because engineers have a comprehensive and complete knowledge of the inner workings of a computer, to the degree that one can predict the ultimate effect of changing or improving a component. Unfortunately (or fortunately, depending on one's point of view), there is still much to learn about the inner workings of the human body, such that the ultimate effect of applying a compound is very difficult to predict. Thus, there are many varying and alternative approaches to drug discovery and, unlike the chip industry, we have the choice of using many more methodologies, the outcomes of which are usually unclear until the goal is achieved.

How many compounds to screen?

Clearly, the number of compounds required for screening is a difficult question and the example of testosterone and estrogen presented by England is quite illustrative. However, an alternative outcome of Oldenburg's example for the estrogens might have been the discovery of this pharmacophore through optimization of a weakly active family outside of testosterone. In other words, we must take into account that similar compounds can be arrived at from different synthetic starting points. The question remains, is it more efficient to optimize a hit through single compound synthesis or focused combinatorial synthesis, than to synthesize and screen enough compounds to obtain an optimized lead directly from the screen? The answer probably lies somewhere in-between these two extremes.

Both Oldenburg's and England's comments suggest that we might proceed in the direction of high-information content screening. We might imagine a scenario where there would be enough compounds in the library and information in the screening system to provide details of structure–activity relationships, potency, selectivity, secondary activity and ADME/tox. In this scenario, optimized leads would be produced very rapidly. It is not difficult to choose a destination for HTS; however, the choice of the best technologies to get us there depends on the particular needs of the screening facility and the organization at large. Rather than making large-scale investments on experimental technologies that might force the use of an inflexible format, it is better to make a diversity of smaller-scale investments in a variety of methodologies and, over time, focus on the proven performers.

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Thailand set to become a world-leading supplier of medicinal plants

The Research and Development Institute of the Thailand Government Pharmaceutical Organization (GPO) has signed a collaborative agreement with Oxford Natural Products (Oxford, UK) to use their new analytical technology. The Total Quality Profiling™ (TQP) technology should enable the GPO to chemically and biologically characterize extracts from plants so they can 'fingerprint' the complex mixtures of compounds often present in plant extracts. It is hoped that this new method of validating plant extracts will help overcome some of the current regulatory problems of standardizing efficacy, safety and quality control.

The World Health Organization (WHO) is currently supporting several major phytopharmaceutical projects in Thailand. The GPO now hopes to be able to move some of the 61 medicinal plants it currently uses in primary healthcare into clinical trials.