A little too much? Expense versus return in HTS miniaturization

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It's all a numbers game – this is the mantra of high-throughput screening (HTS): testing ever more compounds will give more 'hits', resulting in more 'leads' and drug candidates, which will ultimately lead to more therapeutic agents for market and greater profits for the companies involved in their discovery. According to this mind-set, drug discovery is a matter of ever more efficiently mining the cornucopia of chemical compounds to ferret-out those waiting to be tapped for therapeutic use. But there are practical limits in evaluating the chemical cornucopia that can be mined for drug discovery.

'Miniaturization is the way to go to achieve greater numbers', says one group of screening professionals, as the manufacturers of HTS equipment and specialty reagents stand on the side lines cheering them on. On the other hand, some investigators are beginning to ask if the expense of further miniaturizing screening operations will lead to a sufficient level of increased productivity in drug discovery to offset the costs. Says one wag: 'Once screening operations get to the point where 100,000 to 500,000 compounds, or even more, can be tested in a single day, what will we do with those screening facilities the next day?'

At the last *International Symposium on Laboratory Automation* (*ISLAR*; October 1997, Boston, MA, USA), a panel was convened to consider the question: how does technology impact success in drug discovery? During the ensuing discussion Rich Harrison of Rhône-Poulenc Rorer (Collegeville, PA, USA) noted that a company with the goal of producing 1.5 new drugs a year through HTS needs 40 HTS assays operating, each with the capacity of evaluating 500,000 chemical compounds. To do this with 96-well plate technology is a long tedious process, and considering the potential profitability of a new blockbuster drug, a lot of resources can be justified if it shortens the initial discovery stage and gets a new drug on the market months or years sooner.

But it's more complex than just pumping out ever greater numbers of assays, noted Simon Jones of the Genetics Institute (Cambridge, MA, USA) during the same ISLAR discussion session: 'As the number of assays increase linearly the needs for data handling increase exponentially', said Jones. And what about the secondary assays? As more hits are obtained through higher rates of HTS, higher-throughput secondary assays will be needed to select lead compounds. Pursuing this line of thinking, it soon becomes clear that the move from HTS with 96-well plates to the ultra-high-throughput level (UHTS) by way of miniaturization is a very complex decision.

There is little indication that many screening professionals have fully thought through the cost-benefit aspects of HTS, much less the increased costs of UHTS. During the discussion at *ISLAR*, Carol Homon of Boehringer Ingelheim Pharmaceuticals (Ridgefield, CT, USA) rose from the audience to challenge the panel with some provocative questions: 'Are we getting to the point where we feel we must go to ever higher numbers of assays, but in doing so are pricing ourselves out of the market? In other words, is HTS, not to mention the more costly UHTS, cost effective? Can it be shown that more drugs are actually being produced?' There was no answer to Homon's questions, either from the panel of screening experts or from the audience. Even more telling, when the audience was asked for a show of hands as to the number that had already made the rather easy transition from 96-well assays to a 384 format there was almost no response from a jam-packed room of screening professionals.

So, what's going on? Is the drive to further miniaturization purely the hype of the sales staff of the major HTS-equipment and specialty reagent companies? Are laboratories waiting for others to go first to see if further assay miniaturization is worth the investment? Is there a deep-seated skepticism of smaller and smaller assay technology? Does the available technology need to evolve further to allow an order-of-magnitude leap forward to justify the high cost of the new technology? There are certainly no easy answers to these questions, but in this issue of *Drug Discovery Today* you will find some of the pros and cons explored in detail by experienced practitioners.

Now, if I could just find those test-tubes I washed yesterday and my old Eppendorf, I could get on with those assays…

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  1359-6446/98/$19.00. PII: S1359-6446(98)01205-7