carbon-14 labelled poloxamer is not a trivial exercise. A detailed evaluation of the distribution, metabolism and excretion of the polymer was presented but, interestingly, immunological effects were not addressed.

I agree with Hunter and Moghimi that a paradigm shift (a popular notion) is required but I do not agree with the one that they suggest. Most certainly, pharmaceutical scientists working on parenteral formulations need to be cautious about the use of synthetic polymers. Even well known materials can give unexpected adverse effects. But is a synthetic polymer really needed? Other, better characterized excipients or delivery systems, could well fit the bill. What is the risk to benefit ratio of synthetic polymers? What are the costs associated with the introduction of a new material? What are the time scales?

Hunter and Moghimi are correct in their assertion that much of the past work has been blighted by the use of poorly defined polymeric materials and/or the presence of contaminants and even endotoxins. The availability of better synthetic polymers (in terms of defined structures, purity and toxicological assessment) could lead to their greater use in parenteral products that reach the market place. However, it is difficult to imagine such quality materials being provided by suppliers until a clear unmet medical need is demonstrated. As is often the case in drug delivery, 'market pull' and not 'technology push' will be required. We might not like the limited range of materials we have at present but who is going to provide (and pay for) the synthetic polymers of the future? In my view, it will not be the Research Councils and other public funding agencies.

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Stanley S. Davis
Institute of Pharmaceutical Sciences
The Boots Science Building
University of Nottingham
Science Road, University Park
Nottingham, NG7 2RD UK

Diagnostics meets therapeutics: the impact of pharmacogenetics ▼

A recent review by Ross and Ginsburg in *Drug Discovery Today* [1] discussed the emerging trend of integrating molecular diagnostics and therapeutics in modern drug discovery and patient care. The authors highlighted the recent advancement in the areas of pharmacogenomics and toxicogenomics toward the development of personalized medicine, one of the most promising products of the genomics revolution. The root of personalized medicine is based on extensive studies showing that individual variations in response to drugs are caused, at least partially, by genetic polymorphisms. This field, also called pharmacogenetics, is undergoing rapid progress, fueled by the decoding of millions of single nucleotide polymorphisms (SNPs) across the human genome. SNPs are the most frequent polymorphisms in the human genome and recent research has established that these polymorphisms can provide crucial links to disease-causing genes and drug-response genes [2].

When used properly, pharmacogenetics can clearly deliver improved health benefits to the patients while realizing cost savings. One of the most widely used pharmacogenetics tests in the clinical setting is anti-retroviral drug resistance testing for the clinical management of AIDS patients. Considering the growing evidence of linking HIV1 mutations with antiviral therapeutics failure, Durant *et al.* clearly demonstrated that genotypic-resistance testing has a significant benefit on the virological response when choosing a therapeutic alternative in a prospective clinical trial [3]. Also from the same study, genotypic-guided treatment was shown to achieve cost effectiveness. The additional expense of genotyping appeared to be offset by the savings obtained in drug costs [4]. A result of this study (and others) is the rapid adoption of routinely conducting HIV genotyping for drug resistance, in clinical practice, before prescribing antiviral therapies.

In addition to monitoring the therapeutic efficacy, many researchers are also looking for ways to predict drug toxicity using genotyping. As an example, abacavir is a commonly used nucleoside analogue reverse-transcriptase inhibitor against HIV1. About 5% of patients treated with abacavir develop a hypersensitivity reaction that could be fatal. Recent research has linked the abacavir hypersensitivity reactions to the human major histocompatibility complex class I, B (HLA-B) region [5,6]. Further validation of these results in large clinical cohorts will be needed before being implemented as a routine clinical test for prescription guidance.

With the fast advancement of enabling genotyping technologies, pharmacogenetics will fundamentally

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change the practice of medicine by providing physicians with essential information to precisely prescribe the appropriate drugs according to patients' genetic make-up and will provide enormous health benefits and cost savings to the public.

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Michael M. Shi
Sequenom
3595 John Hopkins Court
San Diego, CA 92121, USA

Meeting the challenges in screening

Jack Elands* and Matt P. Botwood, IDBS, 2 Occam Court, Surrey Research Park, Guildford, GU2 7QB, UK; *tel: +44 1483 688 325, *e-mail: jelands@id-bs.com; tel: +44 1483 595 000, e-mail: mbotwood@id-bs.com

The theme of this year's Society for Biomolecular Screening Eighth Annual Conference, held in The Hague (The Netherlands; 22–26 September 2002) was *High Information Content Screening*. The conference was attended by approximately 2000 delegates.

Novel screening methods with high information content

Sheri Miraglia (Applied Biosystems; http://www.appliedbiosystems.com) chaired the *Novel Screening Methods With High Information Content* session. She introduced the theme with the analogy of travelling by plane or on foot: whereas aeroplanes do not enable anyone to observe fine details of the area over which they fly, huge amounts of detail can be observed when walking; however, this is not practical for significant distances. The answer might lie in specialized technologies such as spy satellites, which offer both speed and accuracy.

The speakers broadly covered two topics: high content screening (HCS) for the determination of multiple factors in a single assay system, and parallel, multiplexed assay systems.

Co-chair Len Pagliaro from BioImage (http://www.bioimage.com) likened HTS to sitting in an early plane, from which one could only see blue (sky) and green (land). Today, we try to derive a single value from all the instruments in a modern cockpit, which is unrealistic. Although many of the data are irrelevant provided they are within a certain specification, some data are extremely useful for characterizing the interaction between a compound and target.

Image based HCS

Kurt Scudder of BioImage described how HCS could be used to measure multiple parameters of a single, cell-based assay system. Primarily, this is used to measure a main event, such as the translocation of a protein. To assess the validity of the main result, other parameters are recorded (for example, instrument failure, fluorescent compounds, artifacts caused by toxicity and too-low cell count). The main result can be qualified using multivariate analysis and extra parameters (for example, principal component analysis). Manual analysis is incredibly valuable; to exploit this information fully, machine vision, imaging-based clinical diagnostics and remote sensing, or satellite imaging, are considered useful. Stefan Prechtl from Schering AG (http://www.schering.de) described a similar use of different labels to detect multiple subcellular components.

Yan Feng from the Institute of Chemistry and Cell Biology (Harvard Medical School; www.iccb.med.harvard.edu) took the concept of HCS a step further, showing examples of measuring incomplete nuclear separation during cell division, and discussed several translocation and protein distribution assays.

A different perspective on HCS

Screening using *Candida elegans* was described by Gerhard Weidner from EleGene – now at Protodyne (http://www.protodyne.intranets.com). This organism is well understood and models of several human diseases have been characterized. Several targets have been explored using a fully automated imaging system, and additional information, such as toxicity and drug availability, is inherently derived from this assay.

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