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@drugdiscoverytoday.com

Routine cognitive testing for all drugs? ▼

The past 20 years have witnessed the development of a more thorough understanding of cognitive abilities such as memory, attention and problem-solving skills. This enhanced understanding has been facilitated by improvements in computer technology, the use of which has simplified test administration and increased measurement accuracy.

Until recently, cognitive tests have been used to look at the efficacy of new drugs for dementia and occasionally for safety purposes or as experimental efficacy measures. This situation has changed markedly with the publication of several Committee for Proprietary Medicinal Products (CPMP) Efficacy Working Party (EWP) papers specifying the use of cognitive testing for the measurement of efficacy, safety and the monitoring of pharmacodynamic effects. As indicated in Table 1, the requirement for cognitive testing is currently restricted to diseases of the CNS. However, the recently published International Conference on Harmonization topic E11 document has specified that all drugs developed for use in children should be monitored for their effects on cognitive development.

Alzheimer's disease (AD) is currently the only indication in which cognitive testing is used as a primary efficacy endpoint. However, the recent successful development of cognition enhancing drugs has created the opportunity to ameliorate cognitive deficits in disorders such as Parkinson's disease and schizophrenia. Clearly, when the aim of a study is to show drug effects on cognition it is necessary to use cognitive test measures as primary endpoints.

The current cognitive 'gold-standard' for use in AD trials is the Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-cog) [2], the use of which has been criticised on several fronts [3]. One difficulty with the test is that it is actually 13 tests, scores for which are arbitrarily added together to derive a single, composite measure. This approach is unlikely to be helpful, because cognitive skills are extremely diverse and can be differentially affected by pharmacological interventions. Thus a composite score can obscure what is interesting about a drug.

An analogous situation would be to take a dozen biometric measures, such as enzyme level, blood pressure, temperature, and so on, and add them together in the hope of obtaining a meaningful indicator of a drug's effects. A further major difficulty with the continued use of the ADAS-cog is that it creates the need for protracted studies of large numbers of patients. The adoption of other cognitive outcome measures has the potential to reduce both the length and size of studies designed to show evidence of efficacy in AD.

Guidelines for multiple sclerosis (MS) and Parkinson's disease (PD) include provisions for reporting cognitive outcomes as secondary outcome variables. Cognitive deficits are seen in both these disorders and drugs that address the cardinal signs as well the cognitive deficits will probably prove popular. This is especially true for the pharmacological treatment of tremor in PD, because a known side effect of anti-cholinergic medication (still commonly prescribed for PD) is a measurable decline in cognitive function.

Table 1. CPMP Efficacy Working Party (EWP) cognitive testing requirements

Indication	EWP ref.	Document type	Adopted	In effect from
Alzheimer's disease[a]	553/95	Guideline	July 1997	January 1998
Schizophrenia[b,c]	559/95	Guideline	February 1998	August 1998
Parkinson's disease[b–d]	563/95	Guideline	December 1998	June 1999
Depression[b,c]	518/97	Concept paper	January 1998	–
Multiple sclerosis[d]	561/98	Note for Guidance	July 2001	January 2002
Epilepsy[b,c]	566/98	Note for Guidance	November 2000	May 2001
Bipolar disorder[b,c]	567/98	Note for Guidance	April 2002	October 2001

[a]Cognitive tests specified as primary outcome measures.
[b]Cognitive testing specified for measuring pharmacodynamic responses.
[c]Cognitive testing specified for use in monitoring for adverse events.
[d]Cognitive tests specified as secondary outcome measures.

1359-6446/02/$ – see front matter PII: S1359-6446(02)02151-1

Unfortunately, EWP guidelines are unspecific about which cognitive tasks should be used to assess drug effects. Good advice is hard to obtain, although an ideal source of assistance for companies wishing to select appropriate tests is psychologists with a thorough understanding of the drug development process. These individuals, although rare, can be invaluable in providing advice on the selection of reliable, valid and sensitive cognitive tests. However, in the absence of this expertise it is possible to identify tests appropriate for use in different disorders by reference to reviews of cognitive testing in neuropsychiatric disorders (e.g. [4]). Excellent guidance with respect to the qualities needed for a good cognitive test can be obtained from a recent position paper on objective psychometric testing [5].

Several companies have identified the potential value of routinely incorporating cognitive testing into their drug development protocols. Many cognitive tasks are highly sensitive to the effects of compounds crossing into the brain and so can provide useful evidence of brain penetration. It is clear that cognitive testing, when well conducted, has considerable value as a means of measuring the efficacy and safety of new compounds. Recent work has also indicated that cognitive test measures might find further use as biomarkers and surrogate endpoints [6].

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Gene patents: are they socially acceptable monopolies, essential for drug discovery? – reply ▲

Initial letter: Williamson, A.R. (2001) *Drug Discov. Today* 6, 1092–1093

Response from Richard Binns

Patent law does not have to be changed for gene patents

In a recent issue of *Drug Discovery Today* [1], Alan Williamson questions whether society benefits from gene patents. He proposes that patents should only be allowed for specified uses of genes with narrow claims. I entirely agree that unduly broad claims should not be granted by patent offices, but I believe this requires a change in patent office practice rather than in patent law itself. However, I would argue that claims in gene patents for DNA compositions and gene products should continue to be allowed, provided of course that they do not claim molecules in their natural state and are otherwise new, non-obvious and have an identified 'real world' use.

Are gene patents really so obvious?

Some of the earlier gene patents were granted at a time when the isolation and sequencing of DNA encoding virtually any gene was recognized as a major achievement. The work demanded perseverance and ingenuity and surely we should not introduce a rule that denies the validity of all these patents on the grounds of obviousness.

Even for more recent gene patents, although the generation of raw genomic sequence data might now be routine in many cases, identification and characterization of functional DNA can still present difficulties. Based on a comparative study which involved the European, Japanese and US patent offices, it is unlikely that homology data alone would be sufficient in Europe and Japan for the inventor to obtain a patent on DNA that encodes a putative gene. Other evidence will, therefore, have to be given to support an assertion of the DNA's use or function.

The US patent office took the view that patents that purport to demonstrate use or function by homology alone will be looked at on a case-by-case basis. Although this might be controversial, at least it does mean that in the absence of supporting evidence, such patents will be carefully examined by the US patent office. In addition, many patent applicants will still provide such supporting evidence to obtain patent coverage in Europe and Japan and to avoid the risk of rejection in the US.

Gene patents give early access to information

A patent must disclose sufficient details of how to perform the claimed invention. Patents are in the public domain and it has long been possible to search the patent literature. The disclosure requirement usually means, among other things, that full sequence information must be given in gene patents.

If a commercially minded inventor identified and isolated DNA encoding the gene for a drug target and could not patent this DNA, at what stage would the DNA sequence be disclosed to the public? A commercial organization might never publish the sequence, because in many cases it would be

  PII: S1359-6446(01)02150-X