Questioning models

The author explores validity and validation in *in vitro–in vivo* correlations

With most of the major pharmaceutical companies apparently appearing to be as interested in mergers or takeovers as they are in developing new medicines, and with the smaller companies attempting to avoid being subsumed, one wonders how much of this apparently frenzied activity is driven by the lack of lead compounds coming on stream.

Two articles in this issue of *Drug Discovery Today* suggest techniques whereby the time between discovery of a new chemical entity and its appearance as a marketed product might be accelerated. The two approaches are not only different, but because they can be applied to different stages of the development process, it is possible that some synergy could result from their contiguous application. Dr John Cashman deals with the concept of performing *in vitro* metabolism studies early in the development process, which not only would reduce the numbers of animals used in such testing but might also allow untenable candidates to be discarded at an early stage. Dr Manuel Navia and Dr Pravin Chaturvedi also deal with an aspect of selecting the optimum candidate molecule, but in this case, they discuss the development of a dosage form that can be administered by the oral route.

However, there is an element of commonality between the two approaches, in that both use *in vitro* models – albeit one being based on physicochemical techniques and the other on biological methods. The physicochemical approach has a more secure base, in that the *in vitro–in vivo* correlations have been established, whereas some of the biological techniques, especially those involving cell and tissue culture, are not so well validated.

Furthermore, although some physical tests have received compendial acceptance and, for example, dissolution tests are used extensively (but not exclusively) in the design of generic equivalents, they can never be considered to be totally predictive. A good example is provided by the *in vitro* tests that are used to evaluate pharmaceutical aerosol clouds. These involve the use of a number of impaction devices of varying sophistication and discriminatory ability. For example, such devices range from the relatively empirical two-stage impinger to a complex eight-stage device. It is usually accepted that the optimum particle size for deposition in the respirable airways is 1–6 μm, but this assumption is based upon mathematical modelling of the lung, and no study has so far shown that a high concentration of such particles in an aerosol cloud will lead to improved bioavailability. It now seems likely that a five-stage impinger will be selected as the device of choice, so perhaps it is fortuitous that the necessary correlations have not yet been produced.

> *'in vitro–in vivo* correlations will be further complicated as more of the products of biotechnology are developed'

The problems of producing *in vitro–in vivo* correlations will be further complicated as more of the products of biotechnology are developed. For example, peptide and protein drugs often exhibit nonlinear dose responses, complex pharmacokinetics and some, such as human growth hormone, need to be delivered in a pulsed manner rather than continuously. Nonconventional routes of administration will also need to be to be exploited, because the favoured oral route often produces bioavailabilities of the order of 1%. Interestingly, a commercial product containing a peptide has been marketed as an oral tablet even though its bioavailability is of this order.

Probably the next most popular alternative route involves the use of the nasal cavity, although some calcitonin products exhibit equally unimpressive absorption characteristics, and it may be that the animal model used may have overestimated the extent of absorption. Certainly, if reasonable blood levels are to be achieved following nasal administration, then it will either be necessary to prolong the residence time or to incorporate a penetration enhancer. In both cases, a range of models should be used in order to allow safe progression of the formulation into clinical trials. It is to be hoped that fast-track methods in the discovery and development process do not lead to compromised standards of safety; validation leads to registration.

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PII: S1359-6446(96)20005-4