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@current-trends.com

Oral drug absorption studies: the best model for man is man!

The oral route of drug administration remains the most popular option with patients and physicians alike. It is convenient in practice and enables the use of both immediate and sustained release formulations. Hence, when developing new drugs, pharmaceutical companies are increasingly aware of the need to assess the potential of a drug as an oral candidate at an early stage. Preformulation studies that provide data on drug solubility, partition coefficient and stability, plus *in vitro* permeability measurements (e.g. CaCo2 model) can be useful. Predictive computer models that provide supporting data on absorption are also available. The classification of compounds into four different biopharmaceutical categories is also helpful, e.g. class I (high solubility, high permeability drugs) are considered to be ideal with no perceived problems, while class IV molecules (low solubility, low permeability) are seen as major challenges[1].

Notwithstanding the availability of these different approaches, it is considered important to conduct *in vivo* studies in animal models to assess oral absorption as *in silico* and *in vitro* models do not provide information on regional drug permeability/metabolism nor on efflux systems. Moreover, in the development of a once-daily sustained or controlled release product, information on regional differences in drug absorption is essential[1]. It must be remembered that the total transit time for a drug product in the human gastrointestinal tract is approximately 24 h and, of this time, ≈80% will be spent in the colon rather than in the small intestines[2]. Hence, information on regional drug absorption from the jejunum, ileum, proximal and distal colon in a suitable animal model can be important in making early and accurate decisions in the drug development process. We are all well aware of the difficulty of dropping a lead candidate once it has entered the full development process. Fruitless effort to develop once-daily oral formulations of drugs that were unsuited for such strategies are the subject of anecdotal reports and examples have sometimes been described in the literature[3].

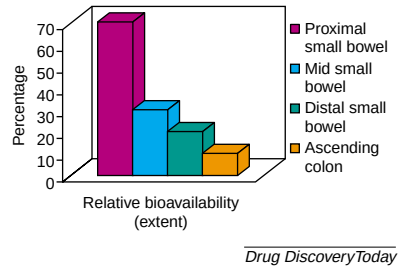

Figure 1. Results of an RDA (recommended daily amount) study in man with a proprietary molecule (n = 10 healthy volunteers).

The key question is what animal model? While the rat can be useful in providing important detail on extremes of drug properties, it does not always scale well to humans. The dog is a poor model of the human gastrointestinal tract[4], and while the pig has some advantages[5], we contend that the best model for the early evaluation of drug absorption in man is man! Today, such studies can be conducted by administering specially designed capsules to volunteers and can be triggered to release drugs in the desired part of the intestines. Such examples are the InteliSite capsule (Innovative Devices, Raleigh, NC, USA), Gastrotarget telemetric capsule (Gastrotarget, Tonawanda, NY, USA), Telemetric capsule (INSERM U61, Strasbourg, France) and the HF capsule (Battelle-Institute V, Frankfurt-am-main, Germany). Recent developments in 'intelligent' capsules have focused on technology that can deliver the drug in a wide range of physical forms into distal regions of the intestines and has led to the development of the Enterion Capsule by Phaeton Research (Nottingham, UK)[6]. These capsules can be loaded with drug solutions/suspensions, drug alone or formulated powder and their movement tracked using the product visualization technique of gamma scintigraphy.

Some results from a recent regional drug absorption study conducted in ten healthy subjects are provided in Fig. 1 for a proprietary molecule. The absorption is expressed in terms of relative bioavailability. The molecule was known to be highly water-soluble and Phase IIb studies had been conducted on the basis of a three times-a-day dosage regimen. However, the marketing department of the company required once-daily dosing. The drug

1359-6446/01/$ – see front matter PII: S1359-6446(00)01653-6

had a potential for sales in excess of $1 billion per year. Before outsourcing novel drug delivery technologies that might be capable of providing a once-a-day solution, it was decided to conduct a regional drug absorption study using these specially designed capsules. Poor absorption of the drug in the distal region of the gut was found that was sufficient to prevent the successful development of a once-daily product. Consequently, the sponsor was able to focus their development strategy on an achievable goal of a twice-daily product, which had support from the marketing team because the development problems had now been identified. Importantly, the development team could justify their new approach using data from humans and thereby avoid a culture of 'formulation failure'; it is very seldom in project teams that the drug is blamed for a lack of absorption!

In instances where absorption in all regions from the gut is deemed essential for the success of a product from a therapeutic or marketing standpoint, then these 'clever' capsules can be used to deliver both drug and absorption promoting agents to selected regions of the gut to test novel strategies (e.g. bioadhesion, enhanced (para)cellular transport, inhibition of p-glycoprotein efflux).

Some might argue that such early studies in humans are not usually possible or appropriate because of limited toxicological data on the compound and/or limited quantities of available drug. In our experience, a suitable toxicology package is normally available for candidate systems or can be readily obtained (e.g. 14 days in two species). The drug can be loaded into the capsule requiring a small quantity of the compound and low (sub-therapeutic doses) can be used to evaluate regional differences in absorption; the amount selected will then depend on the detection limits of the chosen analytical method.

Interestingly, representatives of the regulatory authorities are now suggesting that regional absorption studies can play an important role in the development of sustained release products by characterizing the input rate function of the pharmacokinetic–pharmacodynamic relationship (Lesko, L.L. Immediate release-to-extended release: pharmacodynamics considerations. *Capsugel Symposium on Formulation Optimization and Clinical Pharmacology*, Tokyo, Japan, 23 April 1999, pp. 53–61).

We believe that time spent on developing new pharmaceutical products can be cut dramatically if an understanding of the absorption profile of a drug in the various regions of the gastrointestinal tract can be established or enabling technologies evaluated for their effect on drug absorption. However this needs to be primarily undertaken through absorption studies in man, not in the dog!

References

1 Wilding, I.R. (1999) Evolution of the Biopharmaceutics Classification System (BCS) to Oral modified release (MR) formulations; what do we need to consider? *Eur. J. Pharm. Sci.* 8, 157–159

2 Wilding, I.R. (2000) Site specific delivery in the gastrointestinal tract. *Crit. Rev. Therap. Drug Carrier Syst.* 17, 557–622

3 Wilding, I.R. *et al.* (1991) Relationship between the systemic drug absorption and gastrointestinal transit after the simultaneous oral administration of carbamazepine as a controlled release system and a suspension of ^{15}N-labelled drug to healthy volunteers. *Br. J. Clin. Pharmacol.* 32, 573–579

4 Davis, S.S. *et al.* (1993) Gastrointestinal transit of a putative bioadhesive matrix tablet: comparison of canine and human data. *Int. J. Pharm.* 94, 235–238

5 Gardner, N. *et al.* (1996) Development and validation of a pig model for colon-specific drug delivery. *J. Pharm. Pharmacol.* 48, 689–693

6 Wilding, I.R. *et al.* (2000) Development of a new engineering-based capsule for human drug absorption studies. *Pharm. Sci. Tech. Today* 3, 385–392

Stanley S. Davis and Ian R. Wilding
Pharmaceutical Profiles Ltd
Mere Way, Ruddington Fields
Ruddington, Nottingham, UK NG11 6JS
tel: +44 115 974 9000; fax: +44 115 974 8000
e-mail: iwilding@pharmprofiles.co.uk

Optimizing screening technology: how much to invest? – Reply ▲

Initial letter: Glickman, F. (2000) *Drug Discovery Today* 6, 73–74

Response from Kevin Oldenburg

The pressures faced by the pharmaceutical industry are not unlike those that have been faced by the electronics (chip) industries in past years. In both industries, there is a constant drive to develop new, faster and better products in increasingly shorter timeframes. In the electronics industries, the generation time of a microprocessor is approximately 6 months and the overall speed of a processor doubles every 12–18 months. The cost of building a new chip manufacturing facility is in the tens of millions of dollars.

In the pharmaceutical industry, the major pharmaceutical companies need to produce in the order of 2–3 new chemical entities per year to remain competitive. To do this, they have implemented new technologies that, it is hoped, will help speed up this endeavor. Both industries rely heavily on new advanced technologies, both are taking a risk that the new technologies will deliver what they promise, both have to weigh the potential advantages of the new technologies with the cost of capturing those technologies, and both have to worry that if they do not implement new technologies, their competitors will.

Advancement versus cost

So, where is the point that the advantages of advanced screening technologies are outweighed by their cost of implementation? This, however, is not a simple question to answer and instead, maybe we should ask where, practically, we need to be with our screening technologies to move the

'bottleneck' downstream from the primary screening process. This is a somewhat easier question to answer. Let us make some simple assumptions. First, let us assume that a chemist will not want to look at more than 10,000 'hits' from a primary screen. Second, let us assume that the average 'hit' rate from a primary screen is approximately 0.5%.

Based on these two assumptions, the maximum library size should be in the order of 2 million individual compounds. However, let us now assume that with some 'advanced technology', those 10,000 initial 'hits' from the primary screen could be ranked in order of potency and that computer programs were available that could segregate the compounds into family classes. This would mean that the initial 10,000 hits could be segregated into a much smaller number of structure–activity relationship groups. If this were true, then the initial number of compounds that could be tested (i.e. the 2 million) could be expanded rather dramatically.

In the past 5 years, screening has progressed from 96-well plate (100–200 μl) assays to 384- (50–100 μl) and to 1536-well plate (3–10 μl) assays. There are several advantages to miniaturization to the 1536-well stage. First, there are dramatic cost reductions due to miniaturization. Second, with the reduced reagent consumption, it now makes sense to test the compounds in the primary screen in triplicate – something that is not typically performed in either the 96- or 384-well plate formats. This has two major repercussions for the pharmaceutical industry. Mainly, that many more compounds can be tested for the same or reduced cost than was previously done in the 96- or 384-well plate formats. Furthermore, much more information can be generated in the primary screen. Not only can a compound be identified as 'active' in the primary screen, but its relative potency can be assessed. Thus, we have now met the criterion discussed above.

With this one small advance, more compounds can be tested in a primary screen and those compounds can be ranked in order of potency. This means that the chemist has much more information at hand when determining which of the compounds to take forward. In essence, a relatively straightforward technology (miniaturization to 1536-well plates) has enabled much of what was previously considered 'confirmation and follow-up analysis' to be moved into the primary screen. Not only can we screen more compounds in a shorter time, but we can get more information about those compounds at the same time!

When is enough, enough?

Do we really need to test more and more compounds – when is enough, enough? One of the major arguments for small directed libraries and directed screening is that if you find one member of the 'family', then through combinatorial or medicinal chemistry, most members of the 'family' can be found. However, the assumption here is that we know what constitutes a 'family'.

For example, compare two compounds with which we are all familiar, testosterone and estrogen (estradiol). These two compounds, for all intents and purposes, would be suitable as representatives of the steroid 'family', as they only differ by a methyl group and a couple double bonds (most computer-based similarity searches declare these molecules highly similar). Unfortunately, if testosterone was chosen as the representative of the 'family' and tested in a typical primary screen, it would not be shown as active against the estrogen receptor and hence, the estrogens would not be discovered. The same is true if one started from estrogen and tested it against the testosterone receptor. This simple example demonstrates that until we have a better understanding of what actually constitutes similarity, it would be wise to test as many compounds as practical.

The dilemma of the viscous circle! If a molecules' activity cannot be predicted *a priori*, then its activity cannot be assigned based on its molecular 'family' and therefore it necessitates the screening of increasing numbers of compounds. This naturally leads to increased costs, but to lower these costs, additional miniaturization must be implemented. As additional miniaturization technologies are implemented, more compounds can be tested for the same or less cost and consequently, more compounds are added to the library. It is a viscous circle, but is this not what science is all about? – balancing what we can do today with what we would like to do tomorrow?

If a technology simply increases the speed of screening, little has been gained except to move the bottleneck downstream. While this might be good for the screening group, it does not serve the company as a whole as well as it could. A new technology needs to be placed in context as to how it will benefit the company as a whole. Currently, 1536-well plate technology should suffice for the foreseeable future. However, just like managing your financial portfolio, some of your investment should be in established companies (e.g. 96-well and 384-well plate technologies), some invested in new markets (technologies such as 1536-well plates) and a small quantity in high-risk endeavors (cutting-edge new technologies).

Kevin R. Oldenburg
Managing Director
MatriCal
6 LaFayette Place
Chadds Ford
PA 19317, USA

Optimizing screening technology: how much to invest? – Reply ▲

Initial letter: Glickman, F. (2000) *Drug Discovery Today* 6, 73–74

Response from Paul England

Fraser Glickman is of course correct in his assertion that one can reach a point of diminishing returns on investments in HTS equipment, once HTS itself is operating at a much higher efficiency than other steps in the drug discovery process. This is particularly so for those processes that feed HTS (target validation and expression, combinatorial chemistry) and the downstream process of lead optimization. However, many of the very largest pharmaceutical companies are now planning to routinely screen 50–100 targets against 500,000–1 million compounds a year and, for this, a capacity of up to 2 million assays per week is necessary. To achieve this throughput, automation beyond standard 384-well formats and simple linear track robots or semi-automated workstations will be required, and reagent supply can become a significant factor driving miniaturization. For these companies, remaining with existing 384-well technology is not an option, and Glickman's arguments are open for discussion. In particular, the need for higher density and more miniaturized formats such as 1536 or 3456-well plates, coupled with automation that enables rapid plate processing in parallel, is obligatory for achieving the throughput that large pharmaceutical companies are planning over the next 1–2 years.

However, rather than focus this response on arguments of HTS capacity only, I would like to raise the issue of how investments in advanced HTS equipment can be employed over and above the improvements in screening of primary targets to generate additional or novel information much earlier in the drug discovery process, and hence lead to overall improvements in efficiency and success.

He correctly identified that screening against the primary therapeutic targets for many assays is not limited by quantities of chemical or biological reagents or HTS capacity, particularly if investments have been made in automation. However, screening against primary targets is only one part of lead discovery, and much effort is required to characterize the hits obtained, not only in terms of their specificity against related targets, but also in terms of their potential to be suitable lead structures for real drugs. This latter point implies an understanding at an early stage of the many different properties of hit molecules, including solubility, adsorption, metabolism and excretion (ADME), toxicity and, for significant numbers of targets, the ability to cross the blood–brain barrier. Because most of these properties require direct measurement, as does information on selectivity, obtaining the relevant information can become the rate-limiting step in converting hits to leads and permitting fully informed decisions on which molecules to take forward into lead optimization.

Investment in higher throughput and miniaturized HTS automation, which Glickman characterizes as having 'questionable practical value', can provide the wherewithal to obtain this key secondary information on many hits, or even with sufficient throughput, the whole of a company's compound library. With the recent development of HTS assays for some ADME and toxicology properties, it is now feasible with appropriate HTS capacity to screen either the whole or a major subset of a compound library up-front, independent of compounds being identified as hits in particular therapeutic target screens. This can significantly aid the selection of leads, and shorten the whole hit-to-drug process by the early provision of important information on the properties of hits. Equally importantly, such information can be used to decide on the quality of existing compound collections, and can be used either to remove compounds from screening collections that have undesirable properties, or to make decisions on purchase or synthesis of additional compounds.

Glickman implies that technology geeks are driving HTS automation as an end in itself. This is of course always a danger, but additional HTS capacity, often coupled with miniaturization to reduce the cost of reagents and the use of compounds, offers a real opportunity to improve the efficiency of the whole drug discovery process by providing important information sufficiently early on the quality of leads to influence key decision points on the often tortuous route from hits to drugs.

Paul England
Aurora Biosciences Corp
11010 Torreyana Road
San Diego, CA 92121, USA
tel: +1 858 404 6650
fax: +1 858 404 6787
e-mail: EnglandP@aurorabio.com

Do you have an opinion about the articles published in *Drug Discovery Today*?

Do you have opinions about articles published in this journal? If so, you can communicate them to other readers by writing to Deborah A. Tranter, The Editor, *Drug Discovery Today*, Elsevier Science London, 84 Theobald's Road, London, UK WC1X 8RR. tel: +44 (0)20 7611 4400, fax: +44 (0)20 7611 4485, e-mail: DDT@current-trends.com