'…it is a medicine, not a molecule, that we are giving to the patient.'

editorial

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The lost science of formulation

Over the past 40 years the US pharmaceutical industry's inflation-adjusted research and development spend has increased from US$2.5 billion to US$27 billion. However, the number of new chemical entities (NCEs) produced per year in the USA has only doubled. In the early 1960s, this equated to an average of US$179 million per NCE compared with a conservative estimate of US$843 million per NCE in 2000. In addition, during the same period the 'time to market' has almost doubled to twelve years. As a result, drug company sales, which increased by 10–15% a year for most of the 1990s, have slowed to single-digit growth.

Many reasons have been suggested for this lack of productivity, including a more stringent and tightly controlled regulatory environment, increased competition and patent issues. It is also important to note that the effects of the recent multinational mergers, and the resultant so-called 'NCE pipeline consolidation', are yet to be seen. However, a striking observation is that this decline in productivity has coincided with multinational pharmaceutical companies beginning to search for, and spend vast amounts of money on, the identification of increasingly complex druggable disease targets. This often relies on genomics and the resultant development and validation of techniques like HTS, robotics, combinatorial chemistry and bioinformatics. In addition, although such techniques are producing an increasing number of potential drug candidates, the attrition rates of such molecules (resulting from problematic physicochemical properties, safety and efficacy) are also escalating. For example, at present it is estimated that for every 10,000 molecules screened during the discovery process, only one will gain regulatory approval in a medicine.

However, it is my opinion that these attrition rates could be reduced if formulation was considered earlier in the pharmaceutical development process. Currently 76% of the top 100 drugs are presented as oral dosage forms. Oral delivery is the industry route of choice because of the general simplicity and ease of manufacture of the dosage form as well as the convenience of administration and resultant increase in patient compliance. This is acceptable if the pharmaceutical company has a big library of drug candidates to choose from. But what if only one or two drug candidates are available, as with smaller companies, and the required bioavailability is not achievable orally? This is especially true within the biotech sector where it is uncommon for biologics to be delivered orally because of their inherent instability when administered by this route. Yet, anybody attending a biotech presentation will appreciate that such companies give little, if any, emphasis to

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preformulation and formulation development. Boardroom and commercial pressures often mean that biotech companies have to focus on identifying their 'active' molecule and then on preparing a simple injection formulation with sufficient stability data to allow them to get clinical data and thus attract the next round of funding. Alternative routes of systemic delivery, such as transdermal, pulmonary and nasal delivery, are given little consideration because of the belief that such approaches are problematic, time consuming and costly. In addition, local delivery directly to the pathological site is often not considered at all. Is it a coincidence that scientists are giving way to financiers in the boardroom?

The risk of such a short-sighted approach is that the formulation will not have been optimized for long-term drug stability, delivery, efficacy and safety. As a result, if the drug fails it is just as likely to be due to poor formulation and delivery as lack of efficacy. Even for successes it is likely that the formulation has to be developed further and optimized to produce a commercially viable and marketable medicine. Furthermore, significant changes in a formulation that has already been clinically investigated are frowned upon by the regulatory authorities. This often means that the human studies will have to be repeated with the new formulation, resulting in increased delays and costs and a possible loss of investor confidence. As a consequence, the smarter and more commercially viable biotech and pharma companies are beginning to realize the importance of formulation, and that it should be advanced in the pharmaceutical development process. However, for some of the reasons described above, this comes at a time when expertise in basic formulation and drug delivery is being lost. Therefore, large pharma are either rejecting drugs that cannot be delivered by so-called conventional routes or joining with more forward-thinking biotech companies and contracting this research out.

The current R&D outsourcing market is growing annually at ~15%, with a predicted market of US$36 billion by 2010. However, top tier contract research organisations (CROs) are attempting to transform their profitability by focusing on higher value-added services, such as preclinical and bioanalytical testing, laboratory services, drug discovery and informatics, leading to a shortage of high-quality formulation CROs. This comes at a time when the research councils' priority research areas are focused on molecular biology. As a result, academics working in schools of pharmacy in the UK are being forced away from research into formulation and drug delivery. Consequently, the number of classically trained formulators in academia continues to diminish as they retire without being replaced.

This trend creates a major dilemma. If the required dosage form is not to be delivered orally or by injection, where can basic preformulation and formulation work for drugs applied to the skin, nail, airway and mucous membranes be performed? Admittedly, with the market for such systems expecting to reach US$102 billion in 2006, numerous companies are promoting their own drug delivery technologies. Nevertheless, what if a simple bespoke formulation is required by a company that does not want to pay or cannot afford the costs, milestone and royalty payments associated with many of the more promising drug delivery technologies?

A good example of a sector of the pharmaceutical industry that requires such highly specialised formulation skills is dermatology. The global dermatology market for prescription and over-the-counter topical medicines includes a wide range of products to treat not only diseases of the skin, but also the effects of aging. Currently, the whole field of dermatology is experiencing a busy and interesting period with a series of new and exciting products in development, which will result in delivery systems that will perform better than ever. Consequently, the global market for prescription dermatological products reached nearly US$6.9 billion in 2001, growing at a rate of 9% from 1996 to 2001. Prescription anti-acne, anti-fungal and anti-hair-loss medications had the most dramatic growth during this period, with growth rates between 16.5% and 54.9%. By contrast, sales of prescription dermatitis, eczema and psoriasis medications experienced a slower growth rate over the same period because many of the drugs are older and have lost patent protection. The rate of growth is considered to be sustainable and the total sales are predicted to reach US$10.6 billion by 2006. This is obviously a large market, yet there are very few CROs that can offer specific topical formulation expertise.

Nevertheless, UK-based MedPharm is one company that is looking to re-educate the pharma industry on the importance of formulation development in drug delivery using alternative routes, such as the skin and nose. Established in 1999, with specific expertise in topical formulation, the company currently employs 35 staff. The contract development services laboratories are based in London and the corporate head office is in Charlbury, Oxfordshire. MedPharm also has a good manufacturing practice facility in Livingston, Scotland, where the pharmaceutical manufacturing services division is located for the production of clinical trials supplies.

Initially, and understandably given my earlier observations on the lack of priority placed on formulation, our experience was that relatively small feasibility projects grew by extension and expansion as customers came to value our input, so that eventually we ended up delivering full-scale packages. At the other end of the scale, we often found ourselves being brought in to rescue products by developing new optimized formulations. Now I am pleased to say that our success has led to us being included at a much earlier stage in planning future projects. Currently, MedPharm works on formulation projects across a wide range of disease areas with both large and small pharmaceutical organisations based in Europe, Australia, Japan and the USA. Success has enabled us to put to the test our belief that formulation is central to effective drug delivery.

We are now moving beyond providing only contract services and using our unique bank of *in vitro* disease models of the skin, mucous membranes, nose and lungs as a basis to develop a range of novel delivery systems.

One prime example is the new MedNail program aimed at providing novel topical delivery systems for ungual (nail) drugs. The work is boosted by the award of a grant from the UK Biotechnology and Biological Sciences Research Council, which recognises the UK company's leading work in this growing US$1 billion market for primarily treating onychomyosis and nail psoriasis.

Onychomyosis is the most prevalent disorder of the nail, affecting up to 10% of the general population and continuing to increase. If left untreated, the condition can result in some serious health problems, especially in diabetics and immune-suppressed individuals. Although oral therapeutics are effective, their toxicity is often reported to have considerable side effects. This has led to problems with patient acceptance and a corresponding reluctance by physicians to prescribe even mild oral treatments. At MedPharm, we believe topical formulations are a much more acceptable form of treatment; however, the excellent barrier properties of nail keratin present a problem. Currently, drugs can only be applied this way chronically, leading to ineffectiveness, with success rates as low as 10%, and thus poor patient compliance. The MedNail research project is now focussing on gaining a better understanding of the barrier properties of the nail and thus finding ways of improving drug penetration using novel formulations and application techniques.

We initiated a project intended to offer biotech and pharmaceutical companies a real alternative to conventional topical cream formulations. The culmination of these efforts, MedSpray™-enhanced drug delivery, has already been demonstrated to deliver significantly more drug compared with currently marketed topical formulations. Not only does MedSpray™ give more dosage flexibility, but it is also ideal for both immediate and controlled local delivery. Furthermore, research shows that patients often prefer sprays over more conventional topical formulations due to their ease of use, and for cosmetic and aesthetic reasons.

In these ways my company is fighting to keep both the art and science of formulation alive, in the belief that successful formulation is the key to successful delivery. We should never lose sight of the fact that it is a medicine, not a molecule, that we are giving to the patient.

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