J. Pharm. Pharmacol. 1999, 51: 899–903
Received September 18, 1998

Breaking out of the Ivory Tower: from Academia to Clinic

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Abstract

This paper considers the relationship between academic research and industry in terms of the commercial exploitation of product or process driven programmes originating in academic institutions. The commercial exploitation of pharmaceutical research is the only practical means of achieving the desired end-point of all research programmes in the pharmaceutical sciences—achieving patient benefits. The requirements for generating intellectual property rights (IPR), types of IPR likely to be encountered, time scales, costs, potential partnerships and commercial routes for exploitation are discussed. The ability to link up with industry to exploit new pharmaceutical products or processes is exemplified through two models. Model 1 involves out-licensing of IPR generated wholly within an academic setting and is illustrated by reference to the development of Ametop Gel, a novel percutaneous anaesthetic preparation. Model 2 involves a partnership with industry in a risk-sharing format, with both partners contributing expertise to the project. This latter model is illustrated by reference to a new controlled and sustained release intravaginal ring delivery system for oestrogen replacement therapy.

The ultimate goal of all research in the pharmaceutical sciences is to achieve patient benefits through improvements in the prophylaxis or therapy of disease states. It follows that the commercial exploitation of research findings will eventually be necessary in order to achieve this endpoint. It can be argued, therefore, that academic pharmaceutical research, in recognising this reality, has long since broken out of the ivory tower.

The progression of academic research to the clinic and, therefore, the market, frequently involves consideration of intellectual property rights (IPR). In examining models for the conversion of academic research into marketed products, it is necessary for researchers to be aware of the types of IPR that may be generated. Typically, these may include confidential information, know-how and patents. In the latter case, time scales, including obtaining a priority date, are particularly important to maximize value and increase the commercial attractiveness of the project.

This paper considers relevant aspects of IPR and presents two illustrated models for the commercial exploitation of novel drug delivery research carried out primarily within an academic setting.

Intellectual Property

IPR is commonly associated with patents but the term encompasses the expression of all ideas and information. Thus, IPR may involve confidential information and know-how, copyright, trade marks and design rights in addition to patents. A single project may generate more than one type of IPR and most types require a formal registration procedure.

Patents

Letters patent have been used since medieval times to protect a monopoly. The Patents Act 1977 is the current principal UK statute. In return for complete disclosure, the patent holder is granted a 20-year monopoly on the use of the invention. Commercial exploitation may be undertaken by the inventor or by a licensee who purchases rights to the invention from the patent holder. An idea or invention is patentable only if it meets certain criteria (Table 1).

Filing a patent application with the appropriate authority allows the establishment of a priority date, permitting the invention to be disclosed to

Table 1. What is patentable?

Criteria for a patentable idea or invention	Examples Of Non-Patentable Work
Industrially applicable	Scientific theory or mathematical method
New (different from what has gone before–prior art)	Artistic works
Not previously disclosed in any enabling form	Schemes or methods, e.g. of business
Not in the public domain	Anti-social inventions
Must have an inventive step–can be an incremental step rather than a quantum leap, e.g. process improvement	Methods of treatment or therapies (human or animal)
Must not be obvious (*to one skilled in the art*)	Some animal, plant or biological processes (but genotypes, cloned species and other biotechnology aspects may be allowed)
Not excluded by legislation	Computer programs

third parties. This is particularly important with respect to negotiations with potential licensees. Timing of the application is vital. Filing too soon risks early disclosure, whereas filing too late may result in competing or overlapping patents. In cases of dispute, where filings have been made for apparently similar inventions under different national or international authorities by competing researchers, complete and authenticated records of laboratory notebooks and other relevant material are vital to defend any claim to priority on the invention. This is well-known in industrial pharmaceutical research but its significance is rather less appreciated in academia.

The priority date provides an initial 12-month period during which technical and commercial exploration can continue. New data can be added and the patent application otherwise amended in this period. Thus, it is wise to restrict formal publication during this period. At the end of the 12-month period, it will be necessary to either proceed with a full application, usually involving more than one jurisdiction or, alternatively, to allow the application to lapse.

The Paris Convention gives mutual recognition of priority dates. The Patent Co-operation Treaty (PCT) simplifies the initial stages of patenting in more than one country. The European Patent Office (EPO) offers an optional route for a single application in up to 20 European countries. The PCT route essentially allows time to be bought before individual national applications must be made. It is at this stage that the costs associated with the patenting process will rise significantly, particularly where translations of the application must be provided to a national authority. Exploitation of IPR in the form of a patent generated wholly or in part by academic researchers is a vital aspect in progressing a research project from university laboratory through to the clinical setting. How such IPR is exploited depends on a number of factors.

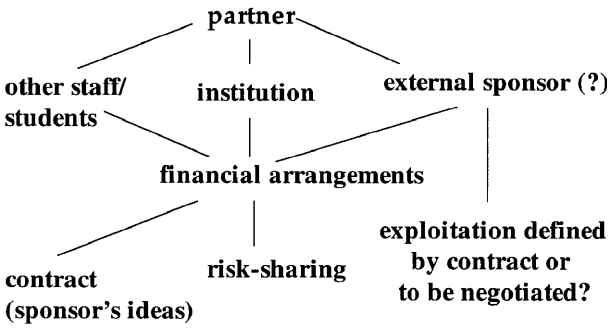

Figure 1. Possible partners to be considered in the commercial exploitation of research originating in an academic institution.

The IPR may relate to a putative drug or dosage form (product). Less dramatically, it may be concerned with, for example, an improved production process. Often, there are a number of partners to the development and complex financial arrangements may already be in place from the start of the project. Alternatively, the IPR may have been developed from a grant-aided project. Partners may thus include external sponsors (industry, government bodies or charitable trusts), university institutions and inventors, who may include academic staff, contract research staff and, possibly, research students (Figure 1).

There are various routes available for the exploitation of research originating in an academic institution (Figure 2). One such route may be through the formation of a company, particularly if the invention has a high potential future value and might generate a range of related products or services. Probably the best examples of this approach are to be found in the volatile biotechnology sector, where the involvement of venture capital is particularly significant. If, however, the IPR does not constitute the basis of a business, exploitation is typically either by outright sale of patent rights or, more usually, through out-licensing of the inven-

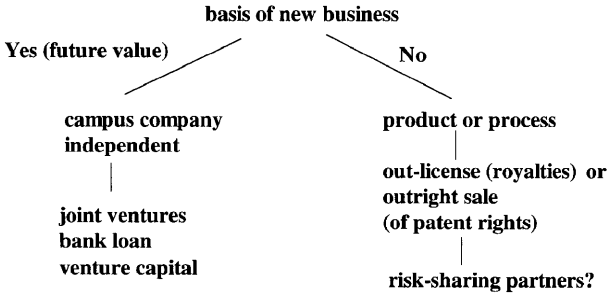

Figure 2. Potential routes for the exploitation of research originating in an academic institution.

tion in return for a proportional financial return based on sales (royalties). Two models for exploitation of IPR generated in whole or in part in an academic setting will now be considered to demonstrate possible routes from laboratory to patient. There are, of course, many variations on these models and, indeed, many other models that are applicable to the exploitation of research in the pharmaceutical sciences.

Model 1: Out-Licensing of IPR

Percutaneous local anaesthesia

In this model, there is no direct commercial sponsorship of the research programme, which is driven initially by academic curiosity or a perceived unsatisfied clinical need. The development of Ametop Gel (Woolfson & McCafferty 1993a; 1996) is a prime example of this model, involving university-industry technology transfer as envisaged in the 1993 UK Government White Paper, 'Realising Our Potential'. Ametop is an effective percutaneous anaesthetic that permits pain-free cutaneous procedures such as venepuncture and the harvesting of split skin grafts (Small et al 1988; Woolfson et al 1990). It is based on the discovery of the amethocaine (tetracaine) phase-change system (Woolfson & McCafferty 1993b) that allows the thermodynamic activity of a local anaesthetic base to be maximized within an aqueous delivery vehicle, resulting in a maximal drug flux through the stratum corneum such that rapid skin anaesthesia (within 30–45 min) of long duration (4–6 h) is achieved. The product, which is available commercially in the UK and internationally, was developed almost entirely within an academic setting and commercialised though an out-licensing arrangement of the associated IPR.

Intact, healthy human skin presents a natural barrier to topically applied drugs, including local anaesthetics. Therefore, the formulation of an effective percutaneous local anaesthetic product presents a difficult challenge. For the local anaesthetic drug to reach its target site of action, the pain receptors (nociceptors) that lie within the viable skin tissue, it must first penetrate through the outermost skin layer, the horny layer or stratum corneum. The stratum corneum, which is essentially lipophilic (fatty) in nature, constitutes the major resistance to drug penetration through healthy intact skin (Wiechers 1989). If this barrier layer is impaired, for example, by skin disease or by the presence of an open wound, the rate of drug absorption will be substantially greater, increasing the risk of significant systemic absorption of the applied local anaesthetic agent, an undesirable event. Hence, Ametop gel is designed for application only to healthy intact skin where the external barrier layer is intact.

Since the skin barrier is essentially lipophilic, it follows that the lipophilic form of a local anaesthetic agent is required to achieve penetration of, and diffusion through this barrier. Lipophilicity of a local anaesthetic base is also directly related to its pharmacological potency (Covino 1986). It is clinically desirable to achieve skin anaesthesia with as short an application time as possible. Thus, the use of a potent local anaesthetic is advantageous, as less drug has to accumulate at the pain receptors in order to elicit the desired pharmacological response. Amethocaine, in its free base form, is an ideal local anaesthetic for percutaneous delivery (McCafferty et al 1988). As a highly lipophilic agent, it will readily diffuse through the skin barrier and, as a further consequence of its lipophilicity, amethocaine base is both potent and long-acting.

To promote the maximum partitioning of amethocaine from the product into the skin, the delivery vehicle in Ametop Gel is an aqueous gel. There are no lipophilic components in this vehicle, hence partitioning of amethocaine into the skin is favoured. Amethocaine is released from a boundary layer at the skin surface and drug release takes place from a saturated aqueous solution of amethocaine base. This boundary layer is constantly replenished with drug, enabling the penetration process to continue throughout the application period. Drug replenishment of the aqueous boundary layer is achieved from fast-dissolving amethocaine oil droplets suspended homogeneously throughout the product. The oil droplets of amethocaine are present because of a unique phase change that takes place when Ametop gel is applied to the skin site, the drug forming a metastable hydrate in the presence of water that melts at approximately 30°C, just below skin temperature (Woolfson et al 1991). It is this unique phase

change at skin temperature which is the basis of the intellectual property relating to Ametop.

Unusually for a drug delivery development arising from university-based research, it was possible to obtain significant supporting clinical data before formal clinical trials (Woolfson et al 1990). This provided proof of concept during the licensing phase and also a body of supporting, non-pivotal clinical data for regulatory purposes. The clinical efficacy of the system and its ease of testing were, perhaps, unique to this development and it remains one of the few examples of a pharmaceutical product taken from university laboratory to the clinic and through to the marketplace (Woolfson & McCafferty 1996).

Model 2: Co-Development with an Industrial Partner: Risk-Sharing

Development of an intravaginal drug delivery system for oestrogen replacement therapy

Steroids, in general, including oestrogens, are efficiently and rapidly absorbed through vaginal mucosal epithelium (Chien 1992). The vaginal route avoids undesirable first-pass hepatic metabolism and delivery of oestrogen by this route is therefore analogous to secretion of oestrogen into the systemic circulation by the ovaries.

Oestrogens may be administered intravaginally by the use of creams, solutions or vaginal tablets. However, to achieve controlled-release of the oestrogenic agent, sustained over a period of months in order to enhance both patient compliance and convenience, an intravaginal device in the shape of a ring (IVR) and fabricated from an elastomeric polymer such as polydimethylsiloxane, is the most suitable drug delivery device (Englund et al 1981). The intravaginal ring can be self-inserted high into the vagina where it is held in place due to its shape and inherent elasticity.

It is now widely understood (Stumpf 1982) that the desired drug to be administered in hormone replacement therapy is 17β-oestradiol, the naturally occurring and most potent human oestrogen. However, when hydrophobic devices such as an IVR are used to deliver 17β-oestradiol, a number of difficulties arise. Primarily, the drug is too polar in its chemical character to be practically delivered in sufficient daily quantities to alleviate all of the clinical symptoms typically associated with postmenopausal human females requiring replacement therapy with oestrogen. These difficulties mean that a daily drug release in excess of 50 μg 17β-oestradiol, as determined in-vitro, an amount clinically acknowledged as the minimum necessary for effective oestrogen replacement therapy (Lieveritz 1987), cannot be practically achieved since the narrow sheath surrounding a large diameter core is difficult to mass produce reliably and a high drug concentration is required in the core section of the device, which consequently must be of large diameter.

The use of oestradiol prodrugs with enhanced hydrophobicity is one aspect of overcoming these difficulties. However, a highly hydrophobic precursor may not give detectable blood levels of 17β-oestradiol in the human female when delivered intravaginally from an elastomeric ring since its solubility in the aqueous diffusion layer between device and epithelial tissue is too low (Woolfson et al 1997). Hence, suitable ester prodrugs of 17β-oestradiol were identified such that an adequate balance between aqueous and lipid solubility was achieved, thus permitting effective sustained and controlled oestrogen replacement therapy from an IVR. The project combined the GMP manufacturing capabilities and clinical expertise of the partner company with the research experience and facilities of a University drug delivery laboratory.

Polydimethylsiloxane elastomer was blended with n-propylorthosilicate (cross-linker) and 10% w/w of 17β-oestradiol or an ester prodrug, the mix being activated with 0·5% w/w stannous octoate. A drug-loaded core was prepared by injection moulding of this mix, with curing at 80°C for 2 min. A rate-controlling membrane was similarly prepared, without the active agent, by injection moulding of the mix around the active core. IVR devices were of cross-sectional diameter 9 mm, outer diameter 54 mm, with core cross-sectional diameter of 2 mm and core length varied as required. The rings were tested in-vitro for their release characteristics in 250 mL of each of the following media: 0·9% w/v saline, 0·133% w/v aqueous benzalkonium chloride (BKC) and 1·0% w/v aqueous BKC. IVR devices ($n = 4$) were suspended in individual capped flasks at 37°C with constant shaking, the release medium being replaced every 24 h. Analysis was by HPLC using an ODS column (15 cm), mobile phase acetonitrile/water 50 : 50, UV detection at 235 or 281 nm, as appropriate.

Drug release from a cylindrical device such as an intravaginal ring can be described by Crank's equation (Chien 1992), which relates the daily drug release rate under sink conditions to the solubility and diffusibility of the drug in the polymer matrix, its partition characteristics between the polymer matrix and the aqueous dissolution medium and the ring dimensions. Table 2 shows the mean in-vitro

Table 2. Mean daily release rates of 17β-estradiol (μg per day, n = 4) and certain ester prodrugs from intravaginal rings into various media. Rings were 9 × 54 mm containing a drug-loaded core of full length (141 mm) and having a cross-sectional diameter of 2 mm.

Compound	Release medium		
	0·9% w/v saline	0·133% w/v BKC	1·0 % w/v BKC
17β-Oestradiol	8	–	–
17β-Oestradiol-17-valerate	–	365	550
17β-Oestradiol-17-propionate	26	112	218
17β-Oestradiol-17-acetate	24	56	96
17β-Oestradiol-3-benzoate	< 5	42	66
17β-Oestradiol-3-acetate	350	700	850
17β-Oestradiol-3-propionate	–	–	1200

daily release rates of 17β-oestradiol and certain ester prodrugs from intravaginal rings into various media. Rings were 9 × 54 mm containing a drug-loaded core of full length (141 mm) and having a cross-sectional diameter of 2 mm. Sink conditions were evident for the 17β-oestradiol precursors in 1·0% BKC. The low release rates in saline of the most lipophilic 17β-oestradiol precursors, the valerate and benzoate esters, were due to their intrinsically low aqueous solubilities. The best release rates under sink conditions, in combination with substantial aqueous solubilities as indicated by the release rates into saline, were observed for the acetate and propionate esters. The ability of a particular 17β-oestradiol precursor to achieve substantial release from an intravaginal ring into saline may be regarded as a significant indicator of its likely in-vivo absorption characteristics. Thus, in particular, 17β-oestradiol-3-acetate exhibited substantial release, in both sink conditions and in saline, from intravaginal rings of dimensions as described in Table 2. The solubility characteristics observed with 17β-oestradiol-3-acetate are particularly interesting when compared with its 17-acetate analogue and these observations represent the basis for exploitable intellectual property arising from this research.

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