Institution: University of Hertfordshire

Unit of Assessment: Panel A3A: Pharmacy and Pharmacology

Title of case study: Topical formulation development using *in silico* and *in vitro/ex vivo* models

1. Summary of the impact (indicative maximum 100 words)

The university's Pharmacy and Pharmacology unit has developed and validated novel *in silico* and *in vitro/ex vivo* models for use by the pharma industry to select drug candidates, optimise formulations, determine the posology for clinical trials and show bioequivalence. This resulted in: the approval of two products for actinic keratosis (Picato® and Zyclara®); a generic nail formulation approved for use based on the demonstration of equivalence using the *in vitro/ex vivo* models described with no clinical testing (the first time this has occurred); and the translation and commercialisation of two dermal drug delivery-based patented technologies (licensing deals with Sinclair IS and major pharmaceutical companies).

2. Underpinning research (indicative maximum 500 words)

One of the Pharmacy and Pharmacology unit's strategic foci has been to strengthen expertise in developing models and innovative technologies for topical drug delivery, and toxicological assessment using novel *in vitro/ex vivo* and *in silico* modelling approaches, leading to the development of several commercially exploited systems that predict the permeation and efficacy of topically applied formulations. This research, carried out in the Centre for Topical Drug Delivery and Toxicology, is led by Professor Marc Brown (Chair of Pharmaceutics (employed since 2006)), Dr Matt Traynor (employed since 2007), and Dr Liam McAuley and Dr Stewart Kirton (both employed since 2008)

The *in silico* and *in vitro/ex vivo* models, established between 2006 and 2013 by Brown and collaborators facilitate drug candidate selection and the design and optimisation of topical and transdermal medicines whilst reducing, refining and replacing the numbers of animals used during this development process. This was achieved with *in silico* modelling that incorporates innovative mathematical equations combined with *in vitro/ex-vivo* systems using excised human skin, human nail clippings, synthetic membranes or animal tissue combined. The models are designed to provide a more realistic measure of drug and product performance than previously available in a laboratory setting, thus reducing the risks of clinical trial failure. For example, the fungal-infected skin model inoculates excised human skin with fungi (such as those found in *tinea pedis*) to create a realistic diseased skin model. This is used in an adapted Franz cell such that a standard drug permeation study can be combined with an efficacy study to improve the *in vitro* assessment of drug delivery from the formulations and efficacy. In addition the ChubTur® and TurChub® cells were developed to aid the group's research into permeation of chemical compounds through and efficacy in nail sections. These systems predict with confidence the efficacy of ungual formulations and have demonstrated equivalence between a branded and generic nail product, resulting in marketing authorisation without needing any clinical evaluation; the first such approval. The *in vitro/ex vivo* models have been successfully used by Graceway Pharmaceuticals to optimise the formulation and posology of their next-generation imiquimod product, Zyclara. [text removed for publication] a formulation was produced which demonstrated the same efficacy as the existing product but with a considerably lower drug concentration, resulting in significantly reduced side-

effects and manufacturing costs. Similar models were used in developing and selecting the final formulation of Picato.

Technologies derived from the *in silico* and *in vitro/ex vivo* models have been exploited by many pharmaceutical companies in their drug candidate selection process. The novel self-assembling *Patch in a Can*® (MedSpray™) delivery system, developed by Brown with MedPharm funding, improves delivery of therapeutic compounds to superficial layers of the skin. This has been licensed to several pharmaceutical companies, with MedPharm Ltd now using MedSpray™ for developing treatment of athlete's foot (as well as other infections, pain relief and inflammatory skin disease). MedTherm [text removed for publication] a thermophoretic technology developed by Brown, Wood and McAuley, is licensed to a major international pharmaceutical company [text removed for publication]

3. References to the research (indicative maximum of six references)

Peer-reviewed Publications

1) M.B. Brown, R.H. Khengar, R.B. Turner, B. Forbes, M. J. Traynor, C.R.G. Evans, S.A. Jones. Overcoming the nail barrier: A systematic investigation of ungual chemical penetration enhancement (2009). *International Journal of Pharmaceutics* 370(1–2); 61–67. doi: 10.1016/j.ijpharm.2008.11.009

2) M. J. Traynor, R. B. Turner, C.R. Evans, R.H. Khengar, S.A. Jones and M.B. Brown. Effect of a novel penetration enhancer on the ungual permeation of two antifungal agents (2010). *Journal of Pharmacy and Pharmacology* 62(6); 730–737. doi: 10.1211/jpp/62.06.0009

– *REF2 Output*

3) M. B. Brown, C. H. Lau. S. T. Lim, S. Yi, N. Davey, G.P.J. Moss, S-H Yoo and C. De Muynck. An evaluation of the potential of linear and non-linear skin permeation models for the prediction of experimentally measured percutaneous drug absorption (2012). *Journal of Pharmacy and Pharmacology* 64(4); 566–577. doi: 10.1111/j.2042-7158.2011.01436.x

4) M. Brown, C. Evans, A. Muddle, R. Turner, S. Lim, J. Reed and M. Traynor. Efficacy, tolerability and consumer acceptability of Terbinafine topical spray versus Terbinafine topical solution: A Phase IIa, randomised, observer-blind, comparative study (2013). *American Journal of Clinical Dermatology* 14; 413–419. doi 10.1007/s40257-013-0031-y

– *REF2 Output*

Funding

1) M.B. Brown and M.J.Traynor. 'A fundamental study to determine the difference in barrier properties of healthy and diseased nail in order to aid the development of ungual drug delivery systems', BBSRC/ MRC, Sept. 2010–Sept. 2013, **£297,027**.

2) R. Chilcott, M.J. Traynor, M.B. Brown. 'Skin absorption of nano particles using a flexing skin model', Health Protection Agency, Feb. 2010–Feb. 2013, **£110,000**.

3) From 2007 to 2013, a further 16 grants totalling c.£577,023 were awarded to the group by pharmaceutical companies [text removed for publication]

4. Details of the impact (indicative maximum 750 words)

Technologies derived from our *in silico* and *in vitro/ex vivo* models have been exploited by several pharmaceutical companies [text removed for publication] in their drug candidate selection process. *Patch in a Can*® (MedSpray™) improves delivery of therapeutic compounds to superficial layers of the skin. Unlike current marketed patches, the spray is manufactured as a solution but during dose actuation assembles into a microfine occlusive film. This provides a highly thermodynamically active system that dramatically increases drug release. The technology enables the potency of certain drugs to be increased without having to increase the dose, thus reducing side-effects. As such, the MedSpray research has been used nationally and internationally by the pharmaceutical industry.

Specifically, our research tested and optimised MedSpray formulations, including terbinafine (TerbiMed), for the treatment of athlete's foot; TerbiMed received regulatory approval for Phase II clinical trials in 2009. The formulation demonstrated complete mycological cure in 83% of patients after a single application. The technology demonstrates good patient acceptability and is well tolerated with low rates of reoccurrence. This indicates a significant improvement in management of the disease, which affects about 15% of the population and is present in about 40% of all patients who attend clinics for any medical concern. It is an important and a significantly prevalent infection, with chronic episodes common in patients with concomitant diabetes and immunosuppression. The existing standard treatment regimes involve the application of topical antifungals for up to 4 weeks, which can cause issues of compliance and might be one reason why the condition has had a high rate of recurrence (c.35%). TerbiMed now provides a formulation that has been shown clinically (2009) to cure the infection after one treatment, and the product was subsequently licensed to Sinclair Pharmaceuticals in 2010 (Section 5, Ref. 1); [text removed for publication]

The successful clinical trial also resulted in the MedSpray technology being licensed to six other global pharmaceutical companies for different applications; for reasons of confidentiality, further details cannot be disclosed. The technology is, however, used with a number of topical and transdermal drugs. MedTherm (developed with MedPharm funding; [text removed for publication] a thermophoretic technology developed by Brown, Wood and McAuley, is licensed to a major pharmaceutical company and commenced preclinical Proof of Concept studies in 2013. [text removed for publication]

The predictive models used on behalf of Graceway Pharmaceuticals generated an effective lower strength imiquimod formulation, with predicted lower incidences of side-effects, and expedited their formulation development process. This allowed them to make considerable savings on product development. Further, our research data directly influenced their decision-making on the final composition of the marketed product. The data we generated was included in the documentation submitted to the FDA, and the new product (licensed April 2010: NDA 022483), known as Zyclara in the US, [text removed for publication]

Approximately 25–60% of adults have at least one actinic keratosis, and 5–20% of all untreated cases progress to squamous cell carcinomas, resulting in an estimated 3,000 deaths per annum in the USA. Similar models were used on behalf of Peplin Australia in developing and selecting the final formulation of Picato, which gained US regulatory approval in January 2012, and in Europe later the same year, for the treatment of actinic keratosis (NDA 202833). Peplin was acquired by Leo Pharma in 2009 for $287.5m, [text removed for publication]

Hertfordshire's fundamental research on nail formulations enabled [text removed for publication] to develop a formulation equivalent to [text removed for publication], resulting in a successful marketing authorisation application to the EMEA [text removed for publication].

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. MedPharm, 'MedPharm completes License Agreement with Sinclair Pharma for Terbinafine MedSpray®'. Press Release (06/12/2010) available at:
<www.medpharm.co.uk/uploads/media/101130_Terbinafine_Spray_Press_Release_FINALedit_02.pdf>

[text removed for publication]

5. 'LEO Pharma to Acquire Peplin for US$287.5m', news release, Leo Pharma website, 3 September 2009.
<www.leo-pharma.com/Home/LEO-Pharma/Media-Centre/News/News-2009/2009-sep-03-LEO-Pharma-to-Acquire-Peplin-for-US$287.5m.aspx>

Institutional Corroboration

Four of the companies discussed in this case study have provided documentation that corroborates key impact claims outlined in section 4. Details are provided separately.