Institution: University of Sheffield

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Commercial and health impacts of drug modelling tools

1. Summary of the impact

Research at the University of Sheffield developed pharmacokinetic tools that enable prediction of drug absorption, distribution, metabolism and excretion, and potential drug-drug interactions. In 2001 the University created a spinout company, Simcyp Ltd, to commercialise the technology. The impacts are:

- Commercial: the company was awarded the Queen's Award for Enterprise in Innovation in 2010 and in February 2012 was sold for $32M to Certara, a leading provider of drug discovery and development software.
- Commercial: the Simcyp population-based Simulator is now used in drug development by many of the world's leading pharmaceutical companies, saving them time and millions of dollars through more efficient and targeted testing.
- Health: human and animal test subjects have benefitted by optimisation of the design of trials to minimise unnecessary drug exposure.
- Health: the Simcyp Paediatric module has improved the care of children by providing reliable evidence to better guide dosage.

2. Underpinning research

The handling of a drug by the body can be very complex, as several processes (such as absorption, distribution, metabolism, and elimination) work to alter drug concentrations in tissues and fluids. The perceived failure of new drug development has been blamed in part on deficiencies in understanding how human populations handle such drugs.

Prior simulation of the potential exposure of different individuals to a given dose of drug and how they metabolise and react to this drug might help to improve the design of clinical trials. Simplifications of body processes are necessary to predict a drug's behaviour in the body. One way to make these simplifications is to apply mathematical models and computer simulations to the various processes.

Professors Tucker (UoS 1972-2009) and Rostami-Hodjegan (UoS 1996-2009) were interested in clinical trial simulation and developed computer programmes to assess how drugs were metabolised in human populations. Using programmes that were developed using FORTRAN they attempted to simulate pharmacokinetic (what the body does to the drug) behaviour in 'virtual populations' taking into account demographic, physiological and *in vitro* biochemical data (R1, R2).

In 1999, they started to incorporate their algorithms into Windows-based software as part of the Simcyp Simulator Project. The project was a cooperative venture with a consortium of pharmaceutical companies. It had the objective of developing a user-friendly programme and database with simple visual outputs that could be used to predict *in vivo* pharmacokinetics in virtual adult patient populations (R3). This was also extended to pharmacokinetics in children (R4).

The Simcyp Simulator (R5) has evolved to include extensive demographic, physiologic and genomic databases that have allowed the development of algorithms which account for patient variability. This enables drug companies to predict drug behaviour in the virtual patient population, as opposed to a virtual reference man, allowing individuals at extreme risk to be identified. This has facilitated decision making in the early clinical stages of drug development and also minimises

unnecessary drug testing on humans and animals. The Simulator continues to evolve and is now used in the investigation of pharmacodynamics (what the drug does to the body, R6).

3. References to the research

R1. Rostami-Hodjegan A, Nurminen S, Jackson PR & Tucker GT. Caffeine urinary metabolite ratios as markers of enzyme activity: a theoretical assessment. Pharmacogenetics. 1996; 6: 121-49. doi: 10.1097/00008571-199604000-00001

R2. Rostami-Hodjegan A, Peacey SR, George E, Heller SRR & Tucker GT. Population-based modeling to demonstrate extrapancreatic effects of tolbutamide. Am J Physiol. 1998; 274: E758-E771. PubMed ID: 9575839

R3. Moghadamnia AA, Rostami-Hodjegan A, Abdul-Manap R, Wright CE, Morice AH, Tucker GT. Physiologically based modelling of inhibition of metabolism and assessment of the relative potency of drug and metabolite: dextromethorphan vs. dextrorphan using quinidine inhibition. Br J Clin Pharmacol. 2003; 56: 57-67. doi: 10.1046/j.1365-2125.2003.01853.x

R4. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clinical Pharmacokinetics. 2006; 45: 931-56. doi: 10.2165/00003088-200645090-00005

R5. Jamei M, Marciniak S, Feng K, Barnett A, Tucker G & Rostami-Hodjegan. The Simcyp population-based ADME simulator. Expert Opin Drug Metab Toxicol. 2009;5 :211-223. doi: 10.1517/17425250802691074

R6. Dickinson GL, Lennard MS, Tucker GT, Rostami-Hodjegan A. The use of mechanistic DM-PK-PD modelling to assess the power of pharmacogenetic studies -CYP2C9 and warfarin as an example. British Journal of Clinical Pharmacology. 2007; 64: 14-26. doi: 10.1111/j.1365-2125.2007.02850.x

4. Details of the impact

The Sheffield research, via the spin-out company Simcyp, has delivered commercial and health impact worldwide, thanks largely to its innovative and firmly user-driven business model. Since its inception, all customers have directly steered product development through the Simcyp Consortium, voting on priorities for annual upgrades to ensure the product remains current and closely matched to end-user needs. Consortium members also provide routine data from their own trials, keeping the simulator as accurate as possible through the addition of large volumes of real test data. The accuracy and reliability encouraged several national regulatory bodies to accept Simcyp's modelling as evidence in licensing new drugs. This combination of user-focus, accuracy and regulatory recognition, coupled with the significant commercial benefits described below, has attracted more than 20 of the world's top 25 pharmaceutical companies to buy licences, including AstraZeneca, Eli Lilly, Johnson & Johnson, Merck, Novartis and Pfizer.

Commercial

Simpcyp was spun out from the University of Sheffield in 2001 (S1). Turnover in 2006 was £1M increasing every year to £4.7M in 2010. This was associated with a £0.2M post-tax profit in 2006 rising to £1.9M in 2011 (S2). It was 15th fastest growing UK company in 2009 (S3) and as at 31 July 2011 the number of employees was 47 (S2). In 2012 Simcyp was sold to Certara for $32M (S4, S5).

The company also delivers significant benefits for its industrial customers. It can take 12 years and £1 billion to bring a new drug to market. Simcyp allows manufacturers to eliminate dangerous or unsuitable compounds at an early stage and focus solely on potentially viable drugs. By cutting short the early testing phase, they can save time and many millions of dollars that they would otherwise spend testing drugs that would later fail in clinical trials.

Simcyp won the Queen's Award for Enterprise in Innovation in 2010 (S6).

Health and Wellbeing

The extensive use of Simcyp by the industrial pharma community has delivered two distinct impacts on health and wellbeing.

Firstly, by optimising the design of trials it has minimised unnecessary drug exposure among human volunteers and animal test subjects. Its contribution to humane research was recognised in 2009 with an OSCAR (Outstanding Scientific Contribution to Animal Replacement, from the UK's leading non-animal medical research charity, The Dr Hadwen Trust for Humane Research [S7].

Secondly, the Simcyp Paediatric Simulator provides valuable information relevant to first-time dosing decisions and the design of clinical studies in infants, neonates and children. It also helps pharma companies meet their obligations under EU regulations. A Senior Pharmacist at Sheffield Children's Hospital and Senior Scientist at Simcyp outlines the tool's value:

> "*Traditional dosing decisions have often been taken under the false assumption that young children are simply little aduts. This model takes into account the many changes in pharmacokinetics which occur as a result of organ maturation and changes in body composition and drug elimination pathways. Fewer than 50% of children's medicines have actually been tested in an appropriate age group. Simpcyp Simulations allow a clinical study in children to become 'confirmatory' rather than 'exploratory', reducing unnecessary drug exposure. This is crucial now that EU regulations insist that paediatric data be included in all applications for new medicinal products."*

5. Sources to corroborate the impact

S1. Simcyp website gives details of company's history: http://www.simcyp.com/

S2. Simcyp turnover, post-tax profit and employee number figures 2006–2010 from Operations Director, Fusion IP available on file.

S3. Reference to 15th fastest growing UK company in 2009. The Business XL Top 50 Rising Stars is an annual ranking of UK-based fast growing companies reporting turnover of between £2.5 million and £100 million and profits of at least £300,000 (http://tinyurl.com/pwhomqz).

S4. Certara media release announcing acquisition of Simcyp (http://tinyurl.com/phthryg).

S5. Acquisition for $32m confirmed in press (http://tinyurl.com/n3xbcor).

S6. Media release from Fusion IP announcing award of Queen's Award for Enterprise in Innovation to Simcyp: (http://www.fusionip.co.uk/simcyp-wins-queens-award/).

S7. Media release from Simcyp confirming the award of the OSCAR (http://tinyurl.com/modur97).