Institution: The University of Manchester

Unit of Assessment: 3

Title of case study: Drug Development: Influences on Regulatory Policies and Industrial Practices (*ICS-11*)

1. Summary of the impact

Drug development is a highly regulated environment. Identifying the need for an independent, academic-led centre of excellence in research and training of pharmacokinetics, we established the Centre for Applied Pharmacokinetic Research (CAPKR) to engage in problems of generic interest to the Pharmaceutical Industry. CAPKR has been highly influential by informing regulatory practice in Europe and the USA, by establishing and optimising industrial practices related to drug development, particularly those related to drug-drug interactions, by reducing the usage of animals in research and by allowing the commercial development and extensive use of simulation software tools for quantitative prediction of pharmacokinetics in order to improve patients' safety.

2. Underpinning research

See section 3 for references [1-6]; see section 5 for corroborating sources (S1-S9); UoM researchers are given in bold. In REF3a and REF5 this case study is referred to as ICS-11.

The impact is based on research in Manchester from 1993-date.The key researchers within CAPKR are:

- **Malcolm Rowland** (Professor, 1975-2002; Emeritus Professor, 2002-date) – CAPKR founder
- **J.Brian Houston** (Senior Lecturer, 1986-1996; Reader, 1996-2002; Professor, 2002-date, CAPKR Director)
- **Leon Aarons** (Senior Lecturer, 1991-2002 ; Reader, 2002-2005 ; Professor, 2005-date)
- **Aleksandra Galetin** (Research Associate, 2002-2011; Senior Lecturer, 2011-date)
- **Amin Rostami-Hodjegan** (Professor, 2009-date)

Prediction of human drug metabolism and pharmacokinetics (DMPK) in drug discovery and development impacts on the use of medicines in all diseases. By developing methodologies for prediction of pharmacokinetics, we have pioneered the movement away from traditional, essentially empirical approaches. Mechanism-based prediction strategies avoid the previously common failure of drugs due to poor PK properties and increase the efficiency of clinical trials. Our premium position is underpinned by CAPKR, a consortium which has involved 14 research-led Pharma over its 16 year history (membership income has totalled >£8m plus >£3m associated income). CAPKR undertakes interdisciplinary applied generic research. Activities involve basic mechanistic studies of metabolism/transporters, physiologically-based pharmacokinetic (PBPK) modelling and clinical trial design and simulation. It focuses on the development, evaluation and implementation of human prediction approaches.

The PBPK models developed operate in conjunction with *in vitro – in vivo* extrapolation (IVIVE) techniques which allows the prediction of *in vivo* kinetic properties of drugs. These methodologies have accelerated the discovery and development of better and safer drugs and have dictated the evolution of best practices recommended by the regulators and subsequently widely adopted across the pharmaceutical industry. The models also result in a marked reduction in usage of laboratory animals, greatly advancing implementation of the "3Rs" principles (Replacement, Refinement and Reduction of Animals in Research).

The key lines of research have been:

1. Quantitative drug metabolism: evaluation and implementation of *in vitro* and *in silico* approaches for predicting human pharmacokinetics [1,2,5]. Systems and strategies to maximise the utility of *in vitro* methodologies for drug uptake and metabolism have been explored; in particular the issues of systematic under-prediction of clearance, inter-individual variability between livers and enzyme-transporter interplay complexities have been addressed. For drug-drug interaction

(DDI) prediction, a generic framework that uses in vitro kinetic data, together with perpetrator PK characteristics, has been established to qualitatively zone and quantitatively predict the likely severity of a DDI involving drug metabolising enzymes and uptake/efflux transporters.

2. PBPK model development [3,4]. Whole body and minimal PBPK models have been developed and evaluated as a systems approach to the prediction of pharmacokinetic behaviour, including DDIs. Particular attention has been placed on model development, and use of drug specific physicochemical, *in vitro* and nonclinical data, together with physiological data, incorporating variability and uncertainty. This activity integrates and complements with the above theme.

3. Statistical modelling methodology: optimal design and PK/pharmacodynamics (PD) modelling to support clinical pharmacology in the areas of paediatrics, cardiovascular disease, oncology and malaria [6]. Novel methodology has been developed and applied to achieve optimal design of PKPD experiments, with the aim to maximize information from these studies. Also integrates with the above themes.

3. References to the research

CAPKR research was published in leading journals, including the top journals in the field of Pharmacology and Pharmacy (SCI).

1. **J.B. Houston**. 'Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance', *Biochemical Pharmacology*. 47, 1469-1479 (1994). DOI: 10.1016/0006-2952(94)90520-7
2. G.T. Tucker, **J.B. Houston**, S.M. Huang. 'Optimizing drug development: strategies to assess drug metabolism/transporter interaction potential-toward a consensus', *Clinical Pharmacology & Therapeutics* 70: 103-114 (2001). DOI:10.1067/mcp.2001.116891
   This article was also published simultaneously in 3 other journals by prior arrangement:
   Pharmaceutical Research 18 (8), 1071-1080, (2001). DOI: 10.1023/A:1010994022294,
   British Journal of Clinical Pharmacology 52 (1), 107-117, (2001). DOI: 10.1046/j.0306-5251.2001.temp.1441.x
   European Journal of Pharmaceutical Sciences 13 (4), 417-428, (2001) doi.org/10.1016/S0928-0987(01)00148-8
3. **M. Rowland**, C. Peck, G. Tucker. 'Physiologically-based pharmacokinetics in drug development and regulatory science', *Annual Reviews Pharmacology and Toxicology*. 51, 45–73 (2011). DOI 10.1146/annurev-pharmtox-010510-100540
4. T. Rodgers, D. Leahy, **M. Rowland**. 'Physiologically based pharmacokinetic modelling 1: predicting the tissue distribution of moderate-to-strong bases', *Journal of Pharmaceutical Sciences*. 94, 1259-1276 (2005). DOI:10.1002/jps.20322
5. **A. Galetin**, **K.Ito**, **D. Hallifax**, **J.B. Houston.** 'CYP3A4 substrate selection and substitution in the prediction of potential drug-drug interaction' (2005) *Journal of Pharmacology and Experimental Therapeutics*. 314, 180-190 (2005). DOI 10.1124/jpet.104.082826
6. S.K. Gupta, G. Sathyan, E.A. Lindemulder, P.-L. Ho, L.B. Sheiner, **L. Aarons**. 'Quantitative characterization of therapeutic index: application of mixed-effects modelling to evaluate oxybutynin dose-efficacy and dose-side effect relationships', *Clinical Pharmacology & Therapeutics*. 65, 672-684 (1999). DOI: 1016/S0009-9236(99)90089-9

4. Details of the impact

See section 5 for numbered corroborating sources (S1-S9).

Quantitative prediction of human PK has made huge strides over the last two decades, largely through the efforts of the CAPKR group (**Rowland, Houston, Aarons**). Pioneering work demonstrating how information gathered during *in vitro* studies in cell cultures or sub-cellular fractions obtained from human tissues can be routinely generated and employed within PBPK models continues to be carried out within CAPKR (**Houston, Rostami-Hodjegan, Galetin**). Mechanistic translation of preclinical data and prediction of human PK is fundamental for candidate drug selection, first-in-human dose projections, improved design of clinical trials and increased patient safety.

Pathways to Impact

A clear distinction evident in CAPKR research is its impact via its continuity and cumulative effect, rather than via sporadic and rare high impact articles. This has been possible through continuous support by industry both collaboratively and financially (>£11m) enabling the group to have long term plans to progress many different interconnected areas rather than focusing on isolated short term objectives. The scientific leadership has attracted one of the major commercial providers of simulation tools in the field of PBPK/IVIVE, Simcyp®, to seek input from the group in the form of Scientific Advisory Board chair and membership (**Rowland, Houston)** and part-time secondment for R&D Director (**Rostami-Hodjegan**).

Members of the group serve on European committees, various national medical research grant bodies and UK government Committee on Toxicity of Chemicals. Their views are sought by government regulatory organisations (e.g. FDA (Federal Drug Administration) and EMA (European Medicines Agency), responsible for producing guidance to the pharmaceutical industry on the conduct of appropriate safety and efficacy studies prior to licensing new drugs). One other notable output from CAPKR is the number of postgraduates and postdoctoral associates who have gone on to senior positions in the international pharmaceutical industry.

Reach and Significance of the Impact

The high volume of research from the CAPKR consortium has provided the scientific basis of human PK prediction which has been adopted by leading scientists and maintained CAPKR's prominence as a centre of excellence in DMPK. The impact of CAPKR's body of work can be viewed at 3 levels:

1. **Government Agencies** responsible for registration and regulation of drugs in Europe and the USA. The modelling and simulation perspectives and predictive methodologies developed and expanded within CAPKR now form integral parts of new regulatory framework, including assessment of DDIs. Several recent publications by the FDA have been co-authored by CAPKR members (e.g. ref 2 above). Specific examples of impact are evident in numerous citations to our work in recent "position papers" from the FDA - 18 out of 45 references (40%) in the FDA authored PBPK paper, "*Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review*" (S1) and 5 out of 48 (10%) in the DDI paper, "*Predicting Drug–Drug Interactions: An FDA Perspective*" (S2). Supporting letters are provided outlining the CAPKR impact within policy making in the Medicines and Health Care Products Agency (MHRA)/EMA and the FDA (S3, 4). The letter from the Expert Pharmacokinetics Assessor at MHRA asserts CAPKR "*has supported and influenced European regulatory practice in a number of ways*…" and goes on to say "*the biggest impact that I notice on a daily basis is on the approach to evaluation of drug-drug interactions for new medicines*" (S4). The letter from FDA Deputy Director, Office of Clinical Pharmacology provides a breakdown of areas in which CAPKR work has influenced FDA and asserts CAPKR "*have greatly impacted the regulatory scientific approaches and review recommendations*" (S3).

2. Best practices within the **Pharmaceutical Industry**. In addition to letters supporting this case [S5,6], various contributions to joint working parties between the FDA and the pharmaceutical industry can be cited. In the "position paper" from PhARMA - Pharmaceutical Research and Manufacturing of America (S7), in relation to mechanism-based metabolic DDI, 11 out of 77 references (15%) are CAPKR publications. Also CAPKR's influence is evident through membership of expert panels, e.g. **Galetin** leads the International Transporter Consortium PBPK modelling group responsible for preparation of 'white' papers on best practice for transporter kinetics and translational modelling.

The paradigm shift in the way the pharmaceutical industry operates due to CAPKR's promotion of *in vitro* techniques for extrapolation to humans and other animal species has impacted substantially on the reduction in usage of animals in research (S8). This is manifested in the letter by the Vice President of Drug Metabolism and Pharmacokinetics in GSK when he says: "*The future drug metabolism and pharmacokinetic paradigm will be model first, experiment in vitro second,*

translate to humans and only as a last resource conduct animal studies. I believe CAPKR share this view and have been conducting the basic research that enables the building blocks for such a future" (S5).

3. **Spin out companies**. Initial applications of the above prediction and analysis methodologies were used in a spun out phase one contract research company, Medeval, initiated by **Rowland** under the auspices of the University. Medeval was eventually bought out by venture capitalists and then acquired by Icon Ltd, which has a strategic relationship with the University. Medeval was awarded a Queen's Award for Enterprise in International Trade in 2002. After 10 years of trading, it had a turnover of around £10.5m pa and employed 180 staff.

The implementation of PBPK modelling has provided opportunities for commercialisation and wider use of various software packages as simulation tools, in particular Simcyp®. Simcyp® employs 70 members of staff and was acquired by the translational life sciences company Certara™ for US$ 32m in 2012. It received the Queen's Award for Enterprise in International Trade in 2010 and an ethical science award 'Outstanding Scientific Contribution to Animal Replacements' from the Dr Hadwen Trust for Humane Research in 2009. This product is used by 18 of the top 20 Pharmaceutical companies. Predictive models developed in CAPKR are also incorporated into other widely used PBPK software such as GastroPlus™ (Simulation Plus), Cloe-PK (Cyprotex) and PK-Sim® (Bayer Technologies Ltd). A supporting letter outlining CAPKR's impact is provided by the Vice President of Technical Sales Support and Consultancy Services for Certara which states "*CAPKR's international reputation lead to the formation of Cyprotex which was spun-out and floated in 2001 and is now one of the world's largest in vitro DMPK screening CROs*" (S9).

5. Sources to corroborate the impact

S1 Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review, Zhao, P *et al.* Clin.Pharmacol.Ther. 89: 259–267 (2011).
S2 Predicting Drug–Drug Interactions: An FDA Perspective, Zhang, L *et al.* AAPS J. 11:300-306 (2009).
S3 Letter from Deputy Director, Office of Clinical Pharmacology, FDA
S4 Letter from Expert Pharmacokinetics Assessor, MHRA
S5 Letter from Vice President of DMPK, GlaxoSmithKline
S6 Letter from Director, Pharmacokinetics, Dynamics & Metabolism, Pfizer, La Jolla, & President of the International Society for the Study of Xenobiotics (ISSX)
S7 The Conduct of in Vitro Studies to Address Time-Dependent Inhibition of Drug-Metabolizing Enzymes: A Perspective of the Pharmaceutical Research and Manufacturers of America, Grimm, SW *et al.* Drug Metab.Dispos. 37:1355–1370 (2009).
S8 http://www.nc3rs.org.uk/page.asp?id=1426 (Reduction of animal research)
S9 Letter from Vice President of Technical Sales Support and Consultancy Services, Certara Limited (Simcyp®)