

# **DRUG RESEARCH AND DEVELOPMENT**

**– CASE SCENARIOS, DEVELOPMENT PROCESS, RISKS AND BENEFITS**

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A Doctoral Thesis at a university in Sweden is produced either as a monograph or as a collection of papers. In the latter case, the introductory part constitutes the formal thesis which summarizes the accompanying papers. These have either already been published or are manuscripts at various stages (in press, submitted, or in manuscript).

*To Marion, Lea & Liam*



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## **ABSTRACT**

**BACKGROUND AND AIMS.** Drug development has been classically associated with large pharmaceutical companies developing ‘blockbuster’ drugs aimed at large patient populations through high market penetration and multiple indication life cycle management. Higher costs and lower output have rendered this model inefficient and unsustainable. The aims of this thesis were to assess: suitability of test procedures, benefit to risk profile during development, importance of stages of discovery and development for benefit/risk and entrepreneurship, expert judgement in making ‘go/no-go’ decisions, and implications for innovation.

**METHODS.** Literature review was used to identify why drugs fail and characterise drug regulation history. Examples of drugs in different development stages were critically reviewed for choice of test procedure and assessment of benefit/risk in context with knowledge and scientific expertise today. An 18-step model of drug discovery and development was defined. Using web-based questionnaires, health experts were asked the importance of each step for assessing benefit/risk, and entrepreneurial input. Individual judgement using real drug case scenarios was studied by scoring ‘go/no-go’ decisions on a Likert scale. Relative importance of assessment of risk versus entrepreneurial need was compared on the model. Influence of entrepreneurial characteristics on the expert assessments and on decision making was explored.

**RESULTS.** Drugs failed development for inefficacy and toxicity. Choice of test procedure confirmed anti-hypertensive and anti-asthmatic efficacy of K<sup>+</sup> channel openers in the laboratory, but these models were poor predictors of clinical potential. Alternative indications and potential routes of administration were left unexplored. Advances in molecular biology and screening have still failed to yield a product with full clinical potential. Retrospective case studies and prospective multicentre studies for an approved immunosuppressant proved valuable approaches for assessing risk of malignancy and risk during pregnancy. Identifying risk factors helps patients and carers in counselling to reach better outcomes. Health experts perceived toxicology, clinical trials, and pharmacovigilance most important for benefit/risk assessment. In contrast, drug discovery and later phases of development were of entrepreneurial importance. Results modelling revealed in-house entrepreneurial ‘core’ and external outsourcing opportunity. Experts showed marked variability in individual judgement for making ‘go/no-go’ decisions despite having the same information. Expert risk perception and decision making were not consistently influenced by entrepreneurial character. Optimised decision making was identified to be critical for effective drug development.

**CONCLUSIONS.** These findings reinforce the opinion that restructuring and opening up drug discovery and development to more external input is likely to increase the innovative capacity and efficiency of the whole drug discovery and development process.

**KEY WORDS:** drug discovery and development, benefit and risk, decision making, entrepreneurship, open innovation

## LIST OF PAPERS

This thesis is based upon the following papers which will be referred to in the text by their Roman numerals:

I. Paciorek PM, Burden DT, Burke YM, Cowlrick IS, Perkins RS, Taylor JC, Waterfall JF. Preclinical pharmacology of Ro 31-6930, a new potassium channel opener. *Journal of Cardiovascular Pharmacology* 1990;15:188-197.

II. Paciorek PM, Cowlrick IS, Perkins RS, Taylor JC, Wilkinson GF, Waterfall JF. Evaluation of the bronchodilator properties of Ro 31-6930, a novel potassium channel opener, in the guinea-pig. *British Journal of Pharmacology* 1990;100:289-294.

III. Kainz A, Harabacz I, Cowlrick IS, Gadgil SD, Hagiwara D. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. *Transplantation* 2000;70:1718-1721.

IV. Cowlrick I, Delventhal H, Kaipainen K, Krcmar C, Petan J, Schleichner S. Three-year follow-up of malignancies in tacrolimus-treated renal recipients - an analysis of European multicentre studies. *Clinical Transplantation* 2008;22:372-377.

V. Hedner T, Cowlrick I, Wolf R, Olausson M, Klofsten M. The changing structure of the pharmaceutical industry – perceptions on entrepreneurship and openness. In “Entrepreneurship and Technological Change”, Eds. Cassia L, Paleari S, Minola T. Edward-Elgar Publishing, in press (2011).

VI. Cowlrick I, Hedner T, Wolf R, Olausson M, Klofsten M. Decision Making in the Pharmaceutical Industry: Analysis of Entrepreneurial Risk and Attitude using Uncertain Information, accepted for publication (2011).

# POPULÄRVETENSKAPLIG SAMMANFATTNING

## LÄKEMEDELSUTVECKLING - Scenarier, utvecklingsprocess, risker och fördelar

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### BAKGRUND OCH MÅL

Läkemedelsutveckling har traditionellt skett på stora läkemedelsföretag där fokus huvudsakligen varit på att utveckla "blockbuster" läkemedel riktade till stora patientgrupper med hög marknadspenetration och lång livscykel. Stigande kostnader och lägre produktivitet har gjort att denna modell har blivit allt mer ineffektiv och ekonomiskt ohållbar. Syftet med denna avhandling var att bedöma prövningsprocessens ändamålsenlighet, fördelar med en riskvärdering under utvecklingsprocessen, vikten av nytta/risk bedömningar och entreprenörskap i olika stadier i forskning och utveckling, experters förmåga att göra "go/no-go" bedömningar i beslutsituationer och konsekvenserna av detta för utvecklingsprocessen.

### METODER

Litteraturstudier användes för att identifiera varför utveckling av läkemedel ofta misslyckas och för att närmare identifiera varför forsknings- och utvecklings (FoU) processen inte resulterar i registrering av nya läkemedel. Ett antal läkemedelskandidater i olika utvecklingsstadier användes som fallbeskrivningar i ett testförfarande för bedömning av nytta/risk. En 18-stegs modell för läkemedelsforskning och läkemedelsutveckling definierades. Olika experter på läkemedelsutveckling ombads svara på en web-baserad enkät, där de för varje utvecklingssteg bedömde betydelsen för risk/nytta, respektive betydelsen av en entreprenöriell inställning. Vidare gjorde experterna individuella "go/no-go" beslut genom poängsättning på en Likertskala. Den relativa betydelsen av risk kontra nytta i utvecklingsprocessen jämfördes i modellen. Inverkan av entreprenöriella karaktärsdrag på experternas bedömningar och deras beslutsfattande undersöktes.

### RESULTAT

I flera av studierna av olika läkemedelskandidater misslyckades utvecklingen på grund av bristande effekt eller toxicitet. Använda tester bekräftade den blodtryckssänkande och antiastmatiska effekten av  $K^+$ -kanal kanalöppnare i laboratoriestudier, men dessa modeller visade sig vara dåliga prediktorer för den kliniska effekten. Alternativa indikationer och potentiella administreringsvägar lämnades utforskade. Framsteg inom molekylärbiologi och substansscreening har fortfarande inte bidragit till utveckling av en produkt inom detta område med full klinisk potential. Retrospektiva fallstudier och prospektiva multicenterstudier för en godkänd immunosuppressiv substans visade sig vara en värdefull metod för att bedöma risken för maligniteter och risk under graviditet. Möjligheten att tidigt identifiera riskfaktorer visade sig kunna hjälpa patienter och sjukvård för att nå bättre resultat. Läkemedelseexperter uppfattade att toxikologiska studier, kliniska prövningar och säkerhetsövervakning av registrerade läkemedel var viktigast för att göra bedömningar av nytta/risk för olika läkemedelskandidater. Vidare ansågs en entreprenöriell attityd viktig i såväl de tidiga som de senare delarna av utvecklingsprocessen för nya läkemedel. Resultaten påvisade betydelsen av en intern "kärna" av entreprenöriellt fokus och externa möjligheter till outsourcing av vissa utvecklingssteg. Olika experter skilde sig markant i sina bedömningar avseende "go/no-go" beslut i de individuella läkemedelsfallen trots att experterna gjorde sina bedömningar på samma informationsunderlag. Experternas perception av risk och deras beslutsfattande var inte kopplade till entreprenöriella karaktärsdrag. En optimerad modell för beslutsfattande är kritisk för effektiv läkemedelsutveckling.

**SLUTSATSER**

Avhandlingens resultat understryker betydelsen att omstrukturera nuvarande modell för läkemedelsutveckling och att öppna upp processen i samarbete med externa aktörer. En mer öppen process för läkemedelsföretagens utvecklingsprocess kan ge möjligheter till att öka innovationsförmågan, vilket skulle kunna ge patienter nya möjligheter till effektiv läkemedelsbehandling vid allvarliga sjukdomar.

**NYCKELORD:** Läkemedelsutveckling, fördelar och risker, beslutsfattande



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## ABBREVIATIONS & DEFINITIONS

ACE	Angiotensin converting enzyme
ATP	Adenosine triphosphate
Big Pharma	Large influential pharmaceutical companies
Blockbuster	Drug with annual sales in excess US\$1 billion
BK	Big conductance potassium channel
$\beta$ 2	$\beta$ 2-adenergetic (receptor)
CNI	Calcineurin inhibitor
CTD	Common Technical Document
EBPG	European best practice guidelines
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FK506	Tacrolimus (twice daily and once daily formulations)
FKBP	FK506 binding protein
GLOBOCAN	WHO cancer incidence and mortality worldwide database
H1	Histamine H1 (receptor)
5-HT	5-hydroxytryptamine (receptor)
ICH	International Conference on Harmonisation
IND	Investigational new drug
IK	Intermediate conductance potassium channel
LTD4	Leukotriene D4 (receptor)
MMF	Mycophenolate mofetil
NDA	New drug application
NME	New medical entity
NICE	National Institute for Health and Clinical Excellence (UK)
NO	Nitric oxide (vasodilator)
NTPR	National transplant pregnancy registry
PER	Pregnancy exposure registry
PRA	Panel reactive antibody
PGD2	Prostaglandin D2 receptor
R&D	Research & Development
SD	Standard deviation
SPC	Summary of Product Characteristics
SUR2B/Kir6.1	Subtype of (ATP)-sensitive potassium channels
T-cell	T lymphocyte
TxA2	Thromboxane A2 (receptor)
WHO	World Health Organisation



## INTRODUCTION

'Drugs: Supply running low' was the title of an article in the Financial Times, 9 February 2011 (Jack, 2011) and 'Drug firms face billions in losses in '11 as patents end' was another article in the New York Times, 6 March 2011 (Wilson, 2011). That the pharmaceutical industry is in crisis is evidenced by huge cost cutting measures like the closure of the Pfizer research laboratories in Kent, UK (Jack, 2011). A drought of big drug breakthroughs, pressure to hold down prices, regulatory vigilance and spiralling costs, government investigations, thousands of layoffs, patent expiries, dwindling productivity, diminishing drug approval...the list makes a depressing read about an industry that has been renowned for being highly productive and of high value to society. The pharmaceutical business is all about making critical decisions involving billions of dollars and years of development with the hope that these decisions will benefit patients with new drugs and generate return on investment to fund further research. These were the very reasons that this thesis was undertaken to afford better insight into an industry that was once an example to all other sectors but has recently stalled in its mission to deliver.

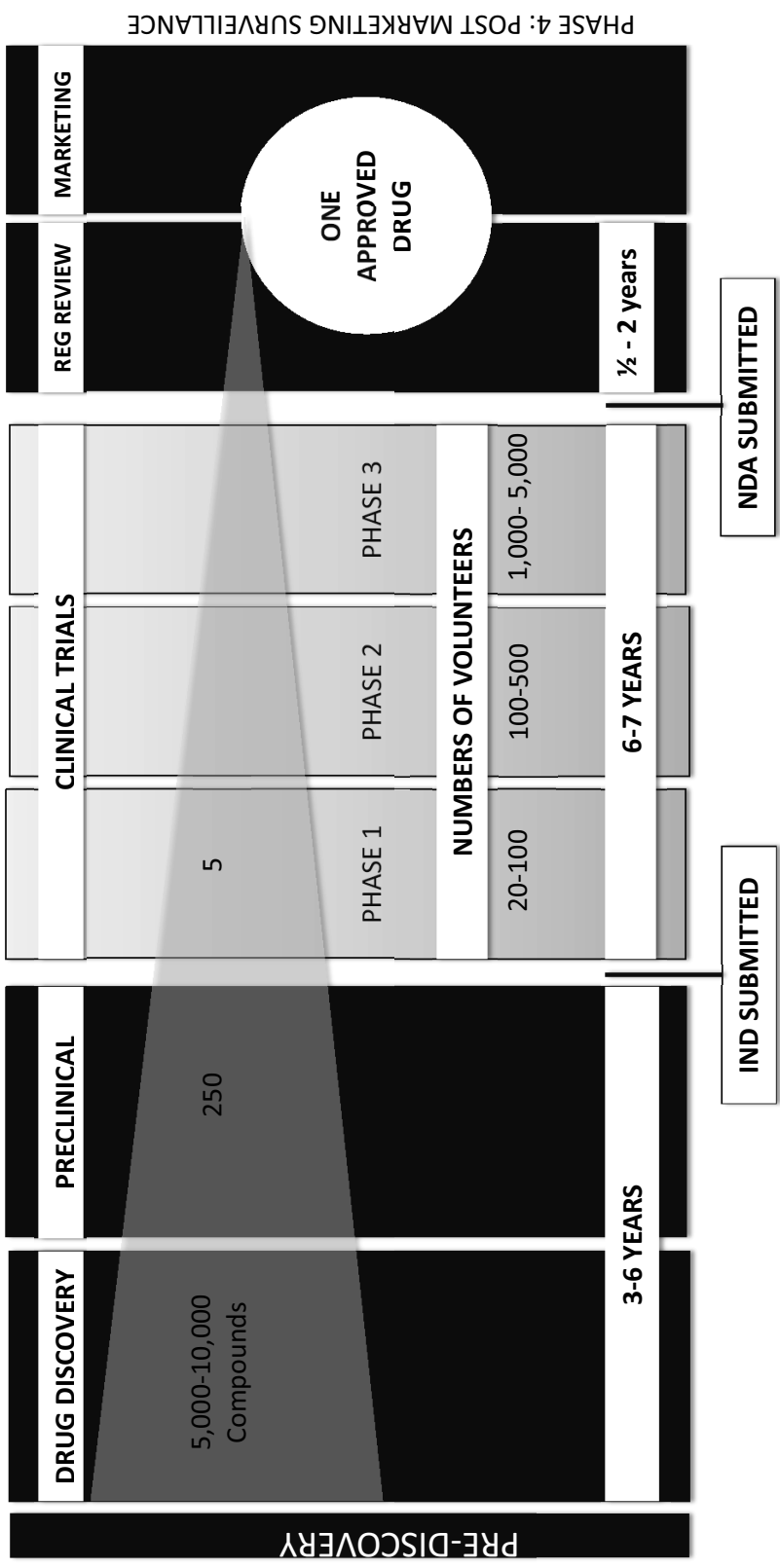
A drug can be considered as 'a substance or product that is used or intended to be used to modify or explore physiological or pathological states for the benefit of the recipient' (Hodges and Applebe, 1987). Drugs are also associated with side effects and risk to the recipient (patient), so drug use is regulated. Drug regulation began in the US and Canada with attention focused on adulteration of food, drink and drugs. The initial emphasis in Europe was to protect people from poisoning. The first law passed in the UK was the Arsenic Act in 1851 in response to poisoning from the uncontrolled sale of arsenic. Qualified personnel were then appointed to provide arsenic to adult men upon receipt of a signature (Bartrip, 1992). In 1868, the Pharmacy Act allowed only pharmacists to provide drugs. Following this early regulation, there has been a continued development of drug regulation to the present day (Hodges and Applebe, 1987; Hodges and Applebe, 1987a; Abraham and Lewis, 2000; Abraham, 2003; Abraham and Davis, 2006; Hedenmalm and Alvan, 2007). The current situation in the European Union for approval of medicinal products for human use follows Directive 2001/83/EC and its updates (Directive 2001/83/EC, 2001). Similarly in the US, the FDA detail application to market a new drug under 21CFR314.50 and its revisions (Code of Federal Regulations Title 21, 2010). The International Conference on Harmonisation (ICH) developed the Common Technical Document which is an internationally agreed format for

submission of medicinal product dossiers to the regulatory authorities in Europe, USA and Japan, according to Directive 2003/63/EC (Directive 2003/63/EC, 2003) and Notice to Applicants (Notice to Applicants, 2006; Horton, 2005). Drug regulation has evolved largely in response to drug disasters such as thalidomide and practolol which exposed inadequate safety testing (Abraham and Davis, 2006; Ray and Stein, 2006). There is a very high drop-out rate during drug development with market success rates as low as 0.01% of all candidates tested (Figure 1). Despite extensive regulations and a low success rate, the drug discovery and development process does not guarantee a supply of approved drugs which are efficacious and without risk. Candidate drugs continue to fail for reasons of inefficacy and toxicity during clinical trials prior to approval, and for toxicity during marketing (DiMasi, 2001; Schuster et al, 2005; Elias et al, 2006; Ray and Stein, 2006; Kola, 2008). These events result in significant patient morbidity and cost to society (Besag, 2007).

Drug research and development itself is a lengthy process typically exceeding 10 years. Before a drug can be brought to market, pharmaceutical companies are charged with collecting sufficient data on the efficacy, safety and quality of a product. Drug discovery usually starts with identifying a therapeutic goal or target disease, screening numerous drug candidates for activity, performing preclinical tests to assess efficacy and toxicity, assuring quality of manufacturing, and then collecting clinical data on safety and effectiveness from patients in clinical trials – informed and astute decision making throughout is imperative (Pritchard, 2003). These data make up the drug dossier which has to be submitted to the regulatory authorities. In trying to minimize the possible risk to the patient and target population, an acceptable balance of benefit to risk must be achieved before approval for use in humans is likely to be granted by the authorities. Even after years of development, there is still risk that unforeseen events will occur during increased patient use and exposure resulting in possible market withdrawal of the product and/or adverse morbidity and mortality. Definition of risk can be simply defined as potential loss or injury (Pritchard, 2008). However, understanding risk should be viewed from several stakeholder perspectives. Developmental risk is the fear that investment may result in failure and is central to owners and investors. Classical risk is understood to be risk to the patient whereas the patient sees the benefits in terms of improved health. Stakeholders for this balance of patient benefit to risk include pharmaceutical companies, investigators, ethics committees, and government regulatory bodies. Risk of therapeutic failure and termination of development is the concern of investigators and investors. Ironically, although innovative drugs with novel mechanisms

of action are attractive to all stakeholders, innovative drugs also bring the penalty of being unpredictable with unknown risk (Pritchard, 2008).

Some 25 years ago, Anker and Warrington described how a new chemical entity reaches the market (Anker and Warrington, 1987). Even then, it was evident that the time to reach the UK market had increased 4-fold from 1960 to 12 years in the late 1980's. There had been a shortening of the patent life accompanied by a 10-fold increase in development costs to US\$125 million. More recently, Hirako and colleagues collected data on over 1000 new drug submissions from 1997 to 2002 from the US, Europe, Canada, Switzerland and Australia (Hirako et al, 2007). Disturbingly, there had been a reduction in the number of drug submissions and approvals per year. In 2006, the US retail drug prescription market was estimated to be around US\$273 billion (Greenwood, 2008). In 2007, the EU market for prescriptions and non prescriptions was estimated at €214 billion or €430 per person (Pharmaceutical Sector Inquiry Report, July 2009). The stakes for the pharmaceutical industry are very high. However, if costs of drug failure and launch are included then overall development costs to enter the market (from 2000 to 2002) attain US\$1.7 billion (Mullin, 2003). The return on investment for industry from 1995 to 2002 fell from 9% to just 5% (Gilbert et al, 2003). DiMasi (DiMasi et al, 2004) showed that average time to drug approval from 1990 to 2000 was 90 months (range 62-115 months) and average return over the product life cycle in the year 2000 was US\$2.5 billion (range: US\$500 million for anaesthetics - US\$15 billion for cardiovascular and lipid lowering drugs). For every 5000 candidates considered for drug development only one gets approved (Robson, 2003; Figure 1).



**Figure 1**

The drug discovery and development process (adapted from Pharmaceutical Industry Profile, 2009)



A key driver of R&D overheads is the clinical trial, especially for Phase III studies. There is an increasing trend to conduct studies in countries like India and China where costs are lower (Cohen & Lowman, 2008). Since clinical costs contribute about 40% of total US drug R&D costs, savings of up to US\$250 million could be realised (Kermani & Narayan-Dubois, 2005). These increasing costs to around US\$55 billion per year (Greenwood, 2008) translated into just 19 drugs approved in 2007 (Pondrom, 2008). Classically, drugs capturing annual sales >US\$1 billion have been termed blockbuster drugs and have been the main source of revenues for drug R&D. The blockbuster model is characterised by investment in drugs for large patient populations, high market penetration through expensive promotional activities, and expansion of market boundaries by pursuing new indications (Lapuerta and Chen, 2002). However, the need to focus on safety following withdrawal of several drugs, increased regulatory burden, huge discovery and acquisition costs, and expensive clinical trials and marketing overheads have forced the conclusion that the global blockbuster model is dead (Numerof et al, 2006). Indeed, 3 to 4 new blockbusters per year would be required to continue blockbuster drug development with revenue growth of 10% per year (Rao, 2006). This situation is unsustainable. The present challenge is for companies to innovate and increase their risk-taking (Lapuerta and Chen, 2002). James Garnier (former CEO of GlaxoSmithKline) described an approach whereby efficiency can be raised by organization restructuring to create a more open business environment where workers in discovery and early development are empowered to take rapid decisions, remain passionate and motivated (Garnier, 2008). At the other end of the R&D continuum, Numerof and colleagues proposed a market-driven business model where the strategy rests on identifying new markets and testing new business models (Numerof et al, 2006). Initiatives from regulatory circles include the FDA's Critical Path Initiative in 2004 to work with industry towards a higher rate of approved innovative drugs in line with advances in technology in the past decade (US FDA, 2009). In 2005, the EMA published a 'Road Map' intended to improve the regulatory environment and help stimulate innovation, research and development in the EU (European Medicines Agency Road Map, EMEA/H/34 163/03). The Road Map was followed by a report on innovative development in March 2007 which outlined the initiatives and recommendations of the EU think-tank group (Innovative Drug Development Approaches, EMEA/127318/2007).

The significance of taking the right decisions at the right time can never be underestimated in any industry, not least in the health care environment (Pritchard, 2003; Mullin, 2003). These factors have significant implication for the drug developmental process, its innovative capacity, its organizational structure, and access to novel medicines in the future.

Using the author's own experience over the last 20 years of drug discovery and development, real case studies were chosen to critically evaluate the methodology in the light of what is known today. How did these studies affect the benefit to risk profile? How is this information used within drug R&D for making the appropriate development decisions?

This thesis was initiated to find out some of the reasons why drugs fail development.

## **AIMS OF THE PRESENT STUDY**

This thesis begins with the general hypothesis:

*'Over the last few decades there has been increased emphasis placed on drug safety (and efficacy) resulting in increased drug development costs which have forced the pharmaceutical industry to reconsider their role and approach in developing new chemical entities.'*

The questions under this general hypothesis define the scope of the present research:

- Were the choices of test procedures (preclinical test system and clinical trials) years ago appropriate for identifying/evaluating novel drugs and how do those processes compare with today?
- Which factors within drug R&D past and present confer increased knowledge and awareness for future drug research?
- What is the nature of risk for potential candidates in drug R&D based on real case scenarios?
- How important is innovation and entrepreneurship in drug discovery and R&D and which factors influence this perception?
- How are go or no-go decisions made during drug R&D?
- How can one consider value and benefit versus risk for new drugs against costs of development and other limiting factors?



## METHODOLOGICAL CONSIDERATIONS

### General approach

This thesis uses the whole drug discovery and development process as an axis for study. To try and answer some of the study questions it was first important to review the history of drug development and the regulatory framework that development candidates must pass through to be approved as having attained acceptable levels of effectiveness, safety and quality. Having identified some of the key drivers of drug regulations through literature review, investigation of why candidates fail the drug approval process was undertaken and some of the initiatives taken to remedy the present paralysis were examined. Some key findings are summarised in the Introduction. Armed with this knowledge, the author then selected drug development cases for which personal experience had been gained and the results were published. For each paper, the methods were considered in respect of what is known today. Comment was made on the appropriateness of the drug development processes and critique of the outcomes of each of the three drug development programs. These cases represented an antihypertensive drug from late preclinical development (Paper I), an anti-asthmatic drug passing from late preclinical to early clinical development (Paper II), and an immunosuppressive drug during the first few years post-approval (Paper III). In a new publication (Paper IV), the same immunosuppressive drug, but later in the drug life cycle, was assessed for safety as an example of an approved drug in longer-term use. A summary analysis was conducted from published clinical studies to determine the nature and magnitude of the risk of malignancy compared with the 'background population'.

In the final stages of the present thesis, it was investigated how health professionals perceive the overall drug discovery and R&D process as important for assessing drug benefit and risk, and how important is the need for entrepreneurship throughout the R&D process. Entrepreneurial attitude and intent of the employee as well as participation in entrepreneurship ventures were studied and discussed in context with creativity, openness and effectiveness of the organization (Paper V). For these purposes a model of drug R&D was developed by identifying key steps from drug discovery through to public perception of the commercially available preparation. This model was published but is not included as a paper in the present thesis (Figure 2; Cowrick et al, 2009). In Paper VI, the ability of health professionals to make critical go/no-go decisions in drug development was studied. Real-life

<b>Drug discovery</b>
<b>1) Selection and validation of target areas for drug research - how and why a certain drug mechanism or target is chosen and validated?</b>
<b>2) Drug synthesis and drug characterisation</b>
<b>3) Pharmacology: drug screening of potential development candidates, efficacy evaluation and preclinical safety</b>
<b>4) Drug formulation, analysis and stability for entry into man</b>
<b>5) Costs assessment - is there sufficient market potential and profit to justify drug development?</b>
<b>6) Toxicology of a drug including acute/subacute/chronic toxicology, teratology, mutagenicity, carcinogenicity</b>
<b>Drug development</b>
<b>7) Pharmacokinetics: preclinical (and later clinical drug absorption, distribution, metabolism and excretion)</b>
<b>8) Regulatory processes: conducting clinical trials, compiling drug dossier, submission, regulatory assessment</b>
<b>9) Phase 1 / First Time in Humans: pharmacokinetics, early pharmacodynamics</b>
<b>10) Phase II early: proof of concept and efficacy</b>
<b>11) Phase II late and Phase III: establishing dose relationship of effect and against comparator</b>
<b>12) Pharmaceutical processes: scale up, packaging and distribution</b>
<b>13) Sales and marketing of approved drug in the market place</b>
<b>14) Safety and pharmacovigilance of marketed drug</b>
<b>15) Post-marketing support of marketed drug with scientific and medical information</b>
<b>16) Publication of clinical experience with newly approved drug</b>
<b>17) Pharmacoeconomics of new drug, price reimbursement etc</b>
<b>18) Public's and patient's perception of new drug</b>

**Figure 2**

Drug discovery and development – 18-step model for analysis (Cowlrick et al, 2009)

drug scenarios based on Papers I to IV were placed before each employee and the variability in judgement for each go/no-go decision was assessed to see if it was influenced by any demographic factors or entrepreneurial characters. The findings were then reviewed in the light of how decisions are taken in industry and some of the options which are available to industry to optimise the decision making process to create more value.

## **Paper I**

### *Background*

Various preclinical models were used to determine the efficacy and cardiovascular pharmacology of a potent candidate from a new class of antihypertensives in early preclinical development. Ro 31-6930, a benzopyran, was developed following publication of the pharmacology of cromakalim, a novel K<sup>+</sup> channel opener and potent relaxant of smooth muscle. Enhanced potassium ion efflux results in hyperpolarisation of smooth muscle, opposing calcium entry through voltage operated channels making the tissue less responsive to vasoconstrictive agents effecting potent and sustained antihypertensive effects. The development candidate was initially evaluated in several preclinical pharmacological cardiovascular models for its efficacy and haemodynamic profile.

### *Test models to assess antihypertensive activity*

Following confirmation of the mechanism of action in *in vitro* screening systems and in the conscious spontaneously hypertensive rat (Cowrick et al, 1988; Paciorek et al, 1989), larger animal models were employed to define the cardiovascular profile of Ro 31-6930. Comparisons were made with cromakalim and the calcium antagonist, nitrendipine (Paciorek et al, 1990). For 24-hr acute experiments after oral dosing, mean arterial BP was recorded from conscious hypertensive rats directly from the carotid artery using restrainers to facilitate measurements. Three-week chronic antihypertensive effects in conscious hypertensive rats were assessed over 22 days of oral daily dosing by measuring systolic BP indirectly using the tail cuff technique. Blood pressure lowering studies were also carried out in conscious normotensive cats following oral dosing for up to 5 hours and full haemodynamic profiles including cardiac output and blood flow were completed in anaesthetised dogs with intravenous dosing.

## **Paper II**

### *Background*

The development of Ro 31-6930 as an antihypertensive as described above was abandoned. However, pharmacological studies showed that airways smooth muscle was also sensitive to

the hyperpolarising effects of K<sup>+</sup> channel opening drugs. It is possible to administer anti-asthmatic drugs to their site of action in tiny quantities using dose-metered inhalers. This approach limits the systemic exposure which would be encountered with oral administration and thus reduces potential adverse effects such as hypotension and tachycardia. It was an attractive idea to develop a novel therapeutic class for the treatment of asthma which had already begun with the lead competitor agent, cromakalim. Correspondingly, Ro 31-6930 was taken through a preclinical program to assess its bronchodilator properties.

### *Test models to assess bronchodilator activity*

Guinea pig isolated tracheal ring preparations *in vitro* were used to estimate the potency of Ro 31-6930 as a smooth muscle relaxant compared with cromakalim (standard K<sup>+</sup> channel opener), salbutamol (standard  $\beta_2$  agonist) and theophylline (standard phosphodiesterase inhibitor). Each drug was tested against spontaneous tracheal tone and agonist-induced tone in response to a range of added spasmogens (betahistine (H1), carbachol (cholinergic), 5-hydroxytryptamine, leukotriene LTD<sub>4</sub>, U46619 (thromboxane TxA<sub>2</sub> mimetic), and prostagalandin D<sub>2</sub>). An *in vivo* model of bronchoconstriction was set up using the ventilated anaesthetised guinea pig. Increased airways resistance to intravenously administered bronchoconstrictor agonists was observed as air overflow. All drugs were given intravenously in a cumulative manner to determine the degree of inhibition of the agonist-induced bronchoconstriction measured as a reduction in air overflow. In a final series of experiments, conscious guinea pigs were challenged with inhaled histamine aerosol to the point of respiratory distress (preconvulsive time). All drugs were administered orally to determine their ability to delay respiratory distress as assessed from histamine challenge every 30mins.



## **Paper III**

### *Background*

Tacrolimus (FK506), a macrolide immunosuppressant, was first discovered in 1984 in Japan and later became used as a primary immunosuppressant against transplant rejection (Peters, 1993). It belongs to the same class of drugs as ciclosporin, calcineurin inhibitors, which are both prescribed as primary agents in immunosuppressive regimens. Other concomitant or adjunct agents are used for induction immediately post-transplant or as add-on therapies which may be titrated downwards and discontinued as the risk of rejection recedes. Tacrolimus binds to its active site, FK binding protein, in target T-cells. This prevents T-cell proliferation following T-cell activation and protects the transplanted organ against cellular attack. Many other cells also contain FK binding protein so that its relative cellular concentration may influence potential drug toxicity of the tissues and organ. With time, tacrolimus became the drug of choice for many transplant recipients but its use during pregnancy for transplanted mothers was not recommended and there was very little published experience. Successful renal replacement for end-stage renal failure can restore fertility lost on dialysis. This gives female transplant recipients the option to consider becoming a mother. However, there is still considerable risk to mother and foetus. Appropriate counselling should be undertaken to enable mothers to understand the risk and make an informed decision whether to continue. Experience with tacrolimus during pregnancy was mostly limited to some case reports and registry data. Pregnancy exposure registries (PERs) offer an approach to perform pharmacovigilance and provide a basis for assessment of benefit and risk (Dellicour, 2008). The National Transplantation Pregnancy Registry (NTPR) in the US founded in 1991 is one of over 30 such registries indicated by the FDA (US Food & Drug Administration, 2011) to gather such information. Drug manufacturers also collect information on the drugs they market involving cases of exposure during pregnancy. This provides another approach for performing pharmacovigilance and carrying out benefit and risk assessments. As tacrolimus was not recommended during pregnancy, many prospective mothers underwent a change of drug therapy which is destabilising, increasing risk of rejection and graft loss. Thus, the goal here was to provide much needed information on the clinical course throughout pregnancy to address critical issues such as tacrolimus exposure, graft stability, risk of spontaneous abortion, perinatal organ failure, perinatal death, and malformations.

### *Methods to assess pregnancy outcomes*

From 1992 to 1998, information from transplant recipients who became pregnant while on tacrolimus therapy was collected on an in-house database. The data was performed retrospectively since pregnancy is very often an exclusion criterion in clinical trials. Data were collected on 100 pregnancies from 84 mothers treated with tacrolimus. Sources were registries, spontaneous reports, clinical trials and published literature. Summaries of the data were carried out to characterise demographics of the mother, time from transplant, drug therapy and exposure, complications during pregnancy, and outcome of the neonate including complications at birth. Statistics were restricted to descriptive analyses.

## **Paper IV**

### *Background*

Long-term administration of immunosuppressants to transplant recipients affords protection against rejection but brings the penalty of increased malignancy. This study represents an analysis of risk for a well-established drug, tacrolimus, with just 2-3 years to run before patent expiry. Risk of malignancy for any therapy is critical for assessing benefit for the patient. The description and assessment of risk of malignancy is typically based upon spontaneous/serious adverse event reports held by the manufacturer and registry data such as the Israeli Penn International Transplant Tumour Registry (Israeli Penn Registry, 2011). However, a more definitive assessment of the nature and incidence of malignancy with longer-term use of tacrolimus was considered to be of value to patient risk assessment. Tacrolimus was first marketed for the prophylaxis of allograft acute rejection in 1994 in Europe. Transplant patients on long-term immunosuppression are known to be at risk for an increased malignancy rate compared to the background population (Morath et al, 2004). Estimates of the nature of malignancy type and rates are typically estimated retrospectively from spontaneous reports and registry data which rely heavily on capturing these events. Thus, while large numbers of patients are available records may be incomplete. Multicenter studies in transplantation include relatively large numbers of patients. These patients are sometimes followed up closely for a defined period so that a more complete documentation is collected (Kaplan et al, 2003).

Tacrolimus has been investigated in a number of multicentre renal transplant studies and the aims of this work were to investigate the malignancy type and determine absolute incidences of de novo malignancies in European adult renal transplant patients longer-term (Cowlrick et al, 2008).

### *Methods to investigate de novo malignancies in renal transplant patients*

A literature search was employed using MEDLINE and EMBASE to identify published European multicentre renal transplant studies where tacrolimus was present in at least one treatment arm/regimen for at least 3 years follow-up (6 months to 1 year post-transplant is too short to estimate malignancies). Each study fulfilling these criteria was reviewed for number and type of malignancy and year of onset after transplant. Each study was also considered for tacrolimus dose/exposure and concomitant immunosuppressants. As part of the summary analysis, descriptive measurements were performed for incidences of malignancy type and confidence intervals were calculated for the more frequent malignancies. The findings were compared with the available experience in transplant recipients and against background incidences for the general population.

## **Paper V**

### *Background*

The costs of bringing a new drug to market have escalated in recent years. The likelihood of success and capturing sufficient return on investment to sustain the costs of R&D has come increasingly under question. Indeed, the classical model of drug discovery R&D appears unable to deliver the number of new medicines ideally needed to combat disease and also what is expected by society. There is an increasing focus on alternative business models. Amongst the many challenges facing industry are to improve selection and validation of novel targets, develop preclinical models that are better predictors of clinical efficacy, reduce escalating costs, expedite decision making to eliminate drug flops earlier, implement effective marketing strategy, and above all to recognise and reward talent (Ratti and Trist, 2001; Trim and Pan, 2005; Numerof, 2006; Rao, 2006). Organisations that have already restructured and begun to address these ideas tend to increase scientist and other professional

orientation towards entrepreneurial engagement which stimulates the emergence of more effective working relationships (Garnier, 2008). Historically the level of entrepreneurial activity in a company has been shown to be based on the behaviour of its entrepreneurial individuals (Miller and Friesen, 1982; Ajzen, 1991; Lumpkin and Dess, 1996). These entrepreneurial individuals are commonly the ones who pioneer R&D in new products or services, introduce new methods of production or pursue any other new activity that disrupts the prevailing market situation (Schumpeter, 1934). At the level of the firm, entrepreneurial organisations have also been described as those that encourage employees to take risks, favour change and act aggressively in the search for new business opportunities (Mintzberg 1973; Khandwalla, 1977; Miller, 1983). These still appear to be key fundamentals for entrepreneurs to become engaged, innovate and facilitate technological change. Of utmost relevance to the present discussion is to which degree is this entrepreneurial attitude and behaviour present, supported and encouraged within the environment of the pharmaceutical industry today?

### *Methods to assess entrepreneurship and openness*

A web-based questionnaire survey was used to investigate how health professionals from the pharmaceutical industry and allied health sectors perceived the importance of different steps within drug R&D for assessing the benefits and risks of developmental drugs. There were 18 steps identified by reference to European (EMA) and US (FDA) regulatory requirements for approving new medicines (Paper V, Appendix 1). The internet-based survey and the 18-step drug R&D model were tested and validated by experts in the field. This was a key initial step to establish the value of each step in the overall drug discovery and R&D process before the experts were asked to indicate how important entrepreneurial input was for each of the R&D steps. It was also examined how they perceived an entrepreneurial attitude and behaviour to be important for bringing new drugs to the market.

Initially personal details were recorded from all individuals invited to complete the questionnaire. Then, in the first part of the questionnaire (Part 1), each responder was asked to grade 18 steps (1 = not important through to 5 = absolutely essential) in the drug discovery and development process in terms of risk/benefit from discovery through to the marketing of a new drug. In Part 2, responders were asked how important (again grades 1 to 5) they perceived the need for an entrepreneurship attitude to be for each of the 18 steps. The

remainder of Part 2 contained additional entrepreneurial modelled questions to elicit information regarding entrepreneurial experience, behaviour, competences and perception of entrepreneurial attitude associated with managing a business at the employee level (Paper V, Appendix 2).

Data was collected from all responders and the mean ranking for each of the 18 steps for importance of benefit/risk was compared with the respective rankings for the need for entrepreneurship using exploratory statistical analyses (Student's t-test). Mean rankings were tested against demographic parameters to see if any significant relationships were present (Wilcoxon Rank sum test and Kruskal-Wallis test). Multivariate analysis was also carried out to determine if any combination of factors might be linked to mean rankings for the 18 drug steps.

## **Paper VI**

### *Background*

Development of a new drug from molecule to market is a complex logistic process which is dependent on multiple and repetitive expert input of knowledge from a wide range of specialists in various fields. Uncertainties and risks are prominent, in particular in early development of radically new medicines (Klofsten, 2005; Davidsson et al, 2006; Munos, 2009). Each drug discovery and development case represents challenges with previously unknown risks and potential benefits. Strategically, during the discovery and development processes, a series of go/no-go decisions have to be made at predefined process points that will determine whether or not to continue the discovery (from target selection to the IND) as well as development (from IND to NDA) processes (Pritchard et al, 2003) (Figure 3). These go or no-go decisions are based on judgement by a group of individual health experts with varying background knowledge and experience (Pritchard, 2008). Decisions are often made based on insufficient data, a high degree of uncertainty, time pressure, high economical stakes, and often in a competitive environment where several actors are competing to be first on the market with their specific drug candidate.

In order to investigate the entrepreneurial decision process in a drug development setting, a study was conducted using a web-based questionnaire aiming to investigate real-world judgement by employees in the pharmaceutical industry and allied sectors. Initially, coherence of judgement was assessed for a series of drug discovery cases which included early phases of target selection, pharmacology and toxicology as well as the latter phases of biopharmacy, galenics, clinical development, and introduction to the market. It was then examined if individual responder judgement was influenced by work experience and functional role, education or perceived entrepreneurial character. The main goal was to investigate the degree of coherence in judgements taken from real-world cases and see if any individual background factors could explain potential sources of variability.

### *Methods to investigate decision making process*

Health professionals from the pharmaceutical industry and allied health sectors were invited to complete the web-based questionnaire. These individuals were at least manager level and had to take responsibility for making decisions in their daily working practice. Real scenarios related to drug development from the pharmaceutical industry were selected in order to reflect variable uncertainties in terms of further development. The four drug cases selected represented key steps in drug R&D (Paper VI, Appendix 1) and the information provided in each case was provided to them to reflect the regulatory requirements during discovery and development set by the European Medicines Agency (EMA) and Food and Drug Administration (FDA). Each case scenario began with a short description of the development candidate with a question to be answered by the responder whether to continue or stop development – a go/no-go judgement. The response was graded according to a ‘Likert 11 point’ scale from -5 indicating definitely stop through 0 (undecided) to +5 indicating definitely continue. After each response, additional information on the case was revealed and the respondent was again asked to make a new judgement based on these new findings. Each case study was composed of 5 judgements taking the responder through an evolving scenario (Paper VI, Appendix 2).

Responders were then posed a number of questions to assess their entrepreneurial orientation. These included which career was most attractive to them, if they had been involved in any entrepreneurial activities or had entrepreneurial intentions, what did they believe their main competencies were to develop an entrepreneurial venture, had they tested a potential business

idea and did they work in an environment that supported entrepreneurship (Paper VI, Table 2). For data analyses, the primary output was the mean value for each decision at each of the 5 steps for all 4 drug case scenarios. Explanatory variables were the demographic variables and the entrepreneurial perception options. Descriptive analyses were carried out. Initially, for each drug case, the mean value for each step was compared with the previous step using paired t-test. The means for each step were also tested for any significance with demographic variables and the entrepreneurial options using student's t-test resp F-test. Logistic regression was also used to investigate the effects of more than one variable on the probability of continuing development from step 1 for each drug case. For this analysis, demographic variables and entrepreneurial options were tested as covariables for maximum likelihood estimates using Wald Chi-Square test for significance. Finally, the magnitude of the difference between steps 1 and 5 for each drug case and for all cases together was tested for any significant relationship to demographic and entrepreneurial variables using student's t-test resp F-test.

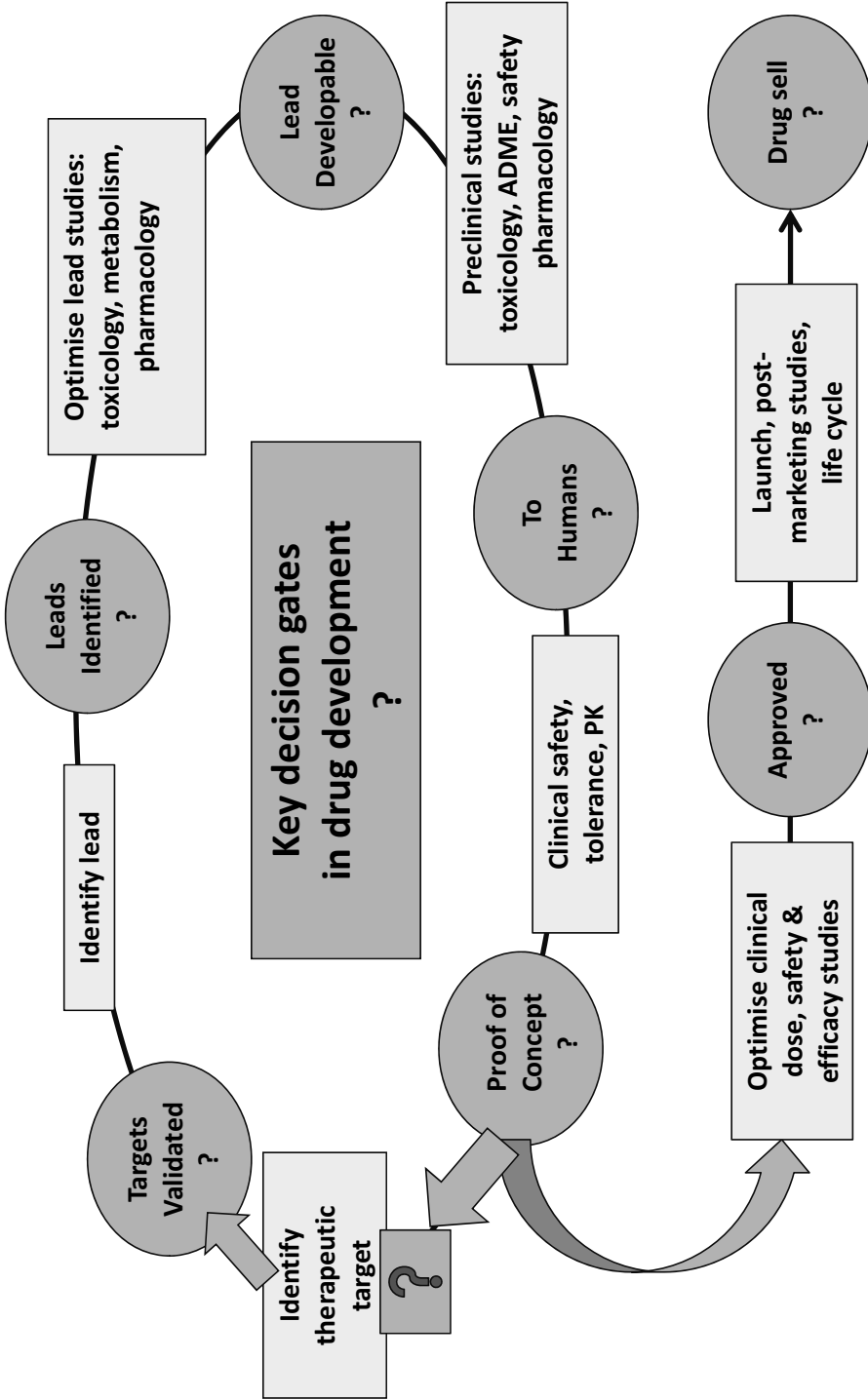


Figure 3

Key decision gates in drug development (adapted from Pritchard, 2003)



## RESULTS

### Paper I

Potent and long-lasting antihypertensive effects with Ro 31-6930 were confirmed both acutely (Paper I, Figures 2-4) and chronically (Paper I, Figure 5) over 22 days in conscious spontaneously hypertensive rats. Blood pressure was also lowered in conscious normotensive cats (Paper I, Figure 6) and anaesthetised dogs (Paper I, Figure 7). Reductions in blood pressure were accompanied with a marked tachycardia in conscious animals (Paper I, Figures 2-4 & 6). Haemodynamic analysis in the anaesthetised dog revealed a reduction in total peripheral resistance and an increased cardiac output due to an increased stroke volume without tachycardia (Paper I, Figures 9 & 10; Paper I, Tables 1 & 2). Nitrendipine also reduced blood pressure by reducing total peripheral resistance in these models but with little or no tachycardia. Ro 31-6930 was ten times more potent than cromakalim and 100 times more potent than nitrendipine as an antihypertensive. While both Ro 31-6930 and cromakalim reduced mesenteric and femoral vascular resistance, only cromakalim reduced renal vascular resistance (Paper I, Figure 11). The effects of nitrendipine reduced both renal and mesenteric vascular resistance but were not significantly different from pre-dose levels in any of the vascular beds.

### Paper II

Ro 31-6930 was effective at inhibiting a whole range of spasmogens used to induce either spontaneous (Paper II, Figure 1) or agonist-induced tracheal tone (Paper II, Table 1). In this respect it was more potent than cromakalim and theophylline and less potent than salbutamol. In ventilated anaesthetised guinea pigs, intravenous administration of Ro 31-6930 inhibited the air overflow resulting from increased lung resistance to the intravenously administered bronchoconstrictor agonists 5-hydroxytryptamine (Paper II, Figure 2) and histamine (Paper II, Figure 3). The rank order of potency of the bronchodilators in this model was similar to the *in vitro* data. In conscious guinea pigs challenged with inhaled histamine aerosol, oral administration of all drugs effectively prolonged the time to respiratory distress maintaining the same order of potency and exhibiting dose-related effects consistent with all test procedures (Paper II, Figures 4-7).

### **Paper III**

The majority (66%) of the population were liver recipients with 27% being kidney recipients. The mean maternal age was 28 years at conception and the time from transplant to conception was approximately 2 years. Tacrolimus dose and exposure remained stable throughout pregnancy (Paper III, Tables 1 & 2). Organ rejection (9 cases), preeclampsia (8 cases), and renal impairment (7 cases) were the most common maternal events (Paper III, Table 3). All rejection episodes were reversed by steroid bolus. Most deliveries were live births and most were premature (<37 weeks) (Paper III, Table 4). Nearly all neonates were born with growth status appropriate for gestational age. Two thirds of neonates were without complications. In the remaining third, the most frequent complications were hypoxia (9 cases), hyperkalaemia, and renal dysfunction (8 cases each) (Paper III, Table 5). There were 4 malformations without any consistent pattern representing 4% of all babies and 5.6% of all deliveries. Recorded adverse events for mother and foetus were not unexpected.

### **Paper IV**

The overall incidence of de novo malignancy up to 3 years post-transplant was 3.4% (Paper IV, Figure 1) in 5 multicentre studies (1993 to 2007) which fulfilled the search criteria (Paper IV, Table 1). In these 5 European multicentre studies, there were 9 treatment arms containing tacrolimus as the baseline immunosuppressant. Of the 83 patients experiencing a malignancy from a total of 2435 patients exposed to tacrolimus, malignancies were represented by skin 37%, lymphoma 16%, and non-skin-non-lymphoma 47% (Paper IV, Table 2). Skin malignancies increased linearly with time while lymphoma and non-skin-non-lymphoma malignancies occurred mostly in the immediate year post-transplant (Paper IV, Figure 2). In the non-skin-non-lymphoma category, malignancies of the genitourinary system were most common followed by respiratory (Paper IV, Table 3). Despite the relatively low incidence of malignancies in each study, it was evident that the incidence and spectrum across all studies were fairly consistent. The incidence for each study was between 2.5% to 4.0% and 95% confidence intervals for the main types of malignancy were relatively wide (Paper IV, Table 4).

The malignancy incidences were consistent with the known experience with tacrolimus therapy and exceeded 'background' figures for the general population by 2 to 3-fold.

## **Paper V**

The response to the questionnaire was strong; 62% (52/84) and the majority (60%) was male. Average age was 47 years with a mean of 21 years working experience. Most responders (86%) worked for a pharmaceutical company with a fair balance between those employed in Preclinical and Clinical Research (56%) and employees from Pharmacoeconomics and Marketing areas (44%). Around half of all responders were employed as manager (48%), approximately one quarter at department head level (28%), and one quarter from group head and general manager level (24%). Over half (58%) of the study population had a higher degree. The distribution of employees across size of organization (defined according to <50, 50 to 5000, >5000 employees) was well balanced (Paper V, Table 1).

Individuals' risk/benefit perception of each drug R&D step (mean score) covered a relatively narrow range. The least important step was Pharmaceutical Processes (mean 2.6) and the most important were Toxicology (mean 4.4) followed by Phase II late / III, Pharmacovigilance, and Phase II early. In terms of the need for an entrepreneurial attitude, respondents judged that these qualities were particularly important in the late phases of R&D with an overall range of mean scores 2.8 to 4.1. Sales and Marketing was perceived to be the most important followed by Public and Patient Perception. Pharmacoeconomics and Post-marketing Support also scored highly. Entrepreneurship was also perceived to be highly important in the early strategic discovery phase of Selection and Validation of Therapeutic Target Areas, and for Costs Assessment. For nearly all R&D steps there was considerable and statistically significant divergence between the ranked importance for risk/benefit and entrepreneurship (Paper V, Figure 1). Those steps ranked highest in the risk/benefit assessment such as Toxicology, Pharmacology, Safety and Pharmacovigilance and Clinical Trials were ranked much lower for entrepreneurship. Conversely those R&D steps ranked highest for entrepreneurship such as Sales and Marketing, Public and Patient Perception, Costs Assessment and Pharmacoeconomics were ranked lower in the risk/benefit assessment.

The respondents had a positive attitude to embark on an entrepreneurial venture with 36% expressing this option. About half of the respondents expressed a corporate career as the most attractive of the options provided. A slight majority (55%) expressed that they worked in an environment that was generally supportive for entrepreneurship. Nearly all individuals (96%) expressed competences to develop an entrepreneurial venture demonstrated by their belief in having the interest, drive or the necessary business, technical or financial skills. Three in four respondents responded as having had entrepreneurial intentions in the form of a new project, licence, new firm or some other form of engagement. Nearly two thirds (64%) of the study population had been engaged in entrepreneurial activities. For example, encouraging somebody to assess the commercial potential of a new idea (36%) or giving advice for a new company (31%) or encouraging somebody to start up a new company (29%). Nearly one half (47%) had already tested a potential business idea and just over half (56%) felt it important to work in an entrepreneurial environment (Paper V, Table 2).

In the final results section, responders indicated how they perceived personal attributes to be weakly to strongly associated (5 point scale) with managing a small business. To rank these perceptions the attributes with the highest percentage of responders selecting 'strong' and 'very strong' were determined accordingly: creativity (95%), hard work (95%), independence (92%), opportunity exploitation (91%) and risk taking (90%) as the highest ranked attributes from the 26 given options (Paper V, Figure 2).

## **Paper VI**

Demographics of the population are summarised in Table 1 in Paper VI. For all four drug cases there was considerable change in decision direction depicted by movements in the step mean value between continue to stop (Paper VI, Figures 1a to 1d; Drug figures W, X, Y, Z). The changes in mean value were nearly all significant when each step was compared with the previous step showing the study population was able to take quite different decisions to the varying information presented (Paper VI, Table 3). The variability in the judgement expressed by the magnitude of the SD about the mean was large especially for two of the drug cases. Increasing age and experience were two demographic variables which reduced the mean judgement scores for two of the drug cases suggesting greater tendency to stop development. The competencies drive, and interest perceived as being important for an

entrepreneurial venture tended to reduce mean scores while the competencies for business, and for financial increased the mean score and likelihood to continue drug development (Paper VI, Table 4).

Nearly all entrepreneurial traits were tested to be unlikely to increase the probability of continuing drug development. The only three reaching significance were each valid for just one drug case and did not present any pattern. These were: entrepreneurial career being attractive, never having tested a potential business idea, and *not* having the competence business skills. Demographic variables found to have a significant influence on increasing variability were men versus women, increasing age, increasing experience, and working in pharmacoeconomics and marketing versus preclinical & clinical development.

Entrepreneurial orientation of the study population was described by around two thirds of the group as having had prior engagement in entrepreneurial activities. However, less than half had had previous intentions to start a new project. Nearly half of the group chose a corporate career to be most attractive. Drive, interest, and business skills were the most frequent competencies selected as being important for developing an entrepreneurial venture. Just over half of the population felt it was important to work in an environment supportive of entrepreneurship and over half felt they did work in such an entrepreneurial environment (Paper VI, Table 2).



## DISCUSSION

This thesis shows that invited healthcare experts used their *intuitive* judgement to make go/no-go decisions for real-life drug case scenarios. There was considerable variability for individual judgement which could not be consistently explained by the known demographic factors or entrepreneurial characteristics tested. Decision making in drug discovery and development is also made from incomplete information, there is likely to be considerable variability, and this uncertainty calls for opening the decision process to include additional expert input. Decision making for all stakeholders can take many styles. As drug candidates mature through company discovery and development processes then so the stakeholder groups making decisions will tend to include more external and regulatory influence (see Figure 3).

This thesis also describes how drug disasters have resulted in complex drug regulation to try and make drugs safer. Society has a model of drug discovery and development which is very expensive, produces very few novel drugs – in its present form is inefficient and unsustainable. Critical review of the methodology adopted in earlier drug development shows that the test procedures confirmed preclinical efficacy but were poor predictors of clinical value. The full potential of drug candidate indications and possible routes of administration were largely left unexplored. Further review of possible approaches used to assess safety for established drugs testifies to the utility of retrospective case studies and prospective multicentre studies in arriving at a more informed position for counselling patients on benefit and risk of the medicines they are prescribed. Identifying risk factors also helps patients and carers to attain better outcomes.

Investigation of individual health expert judgement for ‘go/no-go’ decision points throughout drug discovery and development using real drug case scenarios showed marked variability between individuals in the face of unknown information. However, optimised decision making is considered to be a pillar for effective drug development. Experts also indicated the importance of various stages of drug R&D, within a model of drug discovery and development, for assessing benefit and risk and for entrepreneurial input. These findings reinforce the opinion that restructuring and opening up drug discovery and development to more external input is likely to increase the innovative capacity and efficiency of the whole process.

The discussion that follows takes each of 6 papers in turn before addressing the original hypothesis and questions which initially defined the scope of the present work. These 6 papers cover the whole drug discovery and development process. Papers I and II study a drug candidate which was in preclinical and early clinical development for the indications of hypertension and asthma. Papers III and IV take another drug for the indication of prophylaxis of transplant rejection. This drug was studied during the early and late phases of the life cycle after approval. Paper V investigates the entrepreneurial characteristics of health experts and their perception of drug discovery and development for assessing benefit/risk and need for entrepreneurship on a model of drug discovery and development. Finally, Paper VI uses real, but modified, drug case scenarios to study individual expert judgement, and possible influential factors, in making 'go/no-go' drug development decisions along the drug development.

## **Paper I**

The paper published by Paciorek and colleagues in 1990, presented the preclinical pharmacological results of a promising antihypertensive candidate from a new class of drugs, the K<sup>+</sup> channel openers. These experiments established the potent and long-lasting antihypertensive effects of oral administration of Ro 31-6930 in hypertensive rodent and normotensive non-rodent animal models. However, like the comparator K<sup>+</sup> channel opener cromakalim, these blood pressure lowering effects were accompanied with a marked tachycardia in conscious models which was far less evident with the calcium channel blocker, nitrendipine. In investigational studies, prior administration of the beta-adrenoceptor blocker, propranolol, prevented the tachycardia to Ro 31-6930 showing it to be reflex in nature as was similarly demonstrated with another K<sup>+</sup> channel opener pinacidil using metoprolol to block the beta-adrenoceptor reflex pathway (Goldberg, 1988). Toxicological studies in rats and monkeys indicated that the reflex tachycardia to Ro 31-6930 caused myocardial lesions in higher-dose groups. This was explained by a combination of hypotension and tachycardia resulting in reduced cardiac perfusion and hypoxia (unpublished observations). These effects were also blocked by propranolol suggesting that the lesions were secondary to pharmacodynamic effects rather than drug class-specific toxicity. Although lower doses of Ro 31-6930 were free of these toxicological effects, the indication for hypertension was



discontinued. An indication for bronchodilation in asthma was later pursued as also occurred with the competitor candidate, cromakalim.

It is relevant to mention that clinically available antihypertensives, (pinacidil and nicorandil), also possessed K<sup>+</sup> channel opening properties (Goldberg, 1988). This suggests that this class of drugs did have clinical potential at the time. In retrospect, perhaps a more careful assessment of efficacy and toxicity against lower dose titration was warranted before abandoning this indication. Contrary to this approach was the challenge of a very steep dose response curve characteristic of this class of drugs. A back-up analogue less potent than Ro 31-6930 but with a very similar pharmacological profile was also abandoned. In essence, the final decision to stop drug development of Ro 31-6930 as an antihypertensive was, not for potency, not for formulation considerations, but primarily for safety reasons.

With regard to methodology used to assess the pharmacological activity of lead candidates, screening was performed using *in vitro* rat portal vein. Some 3 or 4 candidates could be tested daily. Virtual screening is now able to predict K<sup>+</sup> channel opening activity although high-speed assays are still difficult to perform. Thus, despite the great value of computer guided virtual modelling today, the use of time consuming cell preparations and animal models are still required (Hong et al, 2007). In this context, the appropriate choice of animal model, ethical considerations, study design, and above all, the relevance to the target disease are critical strategies towards eliminating drug failures early (Andes and Craig, 2002; Pritchard, 2003). The animal models used in the Paciorek series of studies clearly indicated that marked tachycardia was of clinical adverse potential. The experimental models were also robust showing consistent efficacy across all species. Developing a new class of drugs, such as K<sup>+</sup> channel openers to treat hypertension, was considered most desirable at the time. Hypertension which is of very high prevalence in society has been managed using a similar approach for many years and still relies heavily on first line use of ACE inhibitors, calcium channel blockers and diuretics which are all old classes of drugs (NICE clinical guideline 34). As noted above, pinacidil was a K<sup>+</sup> channel opener approved as an antihypertensive and it caused reflex tachycardia in the clinic. Lower doses of pinacidil, however, were without marked tachycardia and were considered to have a positive benefit to risk profile (Goldberg, 1988). In addition, nicorandil, a coronary vasodilator, has both K<sup>+</sup> channel opening properties and NO-mediated coronary vasodilatory properties (Schmid and Schroeder, 2005). Nicorandil has found its place in the clinic for chronic stable angina. It is devoid of the

undesirable tachycardia characteristic of older drugs like the vasodilator, hydralazine. Newer, effective drugs like ACE inhibitors do not cause tachycardia in the clinic. Thus, development of a new antihypertensive without tachycardia is important.

In 1990, the biology of K<sup>+</sup> channels was far less understood than today. During the time that has elapsed studies of chemistry and structure-activity relationships have dramatically opened this field of research (Lawson, 2000). Wang published the results of an agent, iptakalim, representing a new class of K<sup>+</sup> channel openers as effective antihypertensive agents in several models of hypertension and almost devoid of reflex tachycardia (Wang et al, 2005). This result was achieved after careful structure-activity relationship development of 10 different structural types of K<sup>+</sup> channel openers which demonstrated that so much structural diversity still conferred affinity at the active site. Whereas, Ro 31-6930 is a member of the benzopyran pyridines, iptakalim belongs to a novel group of aliphatic amines (ATP sensitive K<sup>+</sup> channel opener, subtype SUR2B/Kir6.1) selectively dilating resistance vessels without affecting conductance vessels. Iptakalim is reported not to lower blood pressure in normotensive preclinical models and in humans (Pan et al, 2010). A novel therapeutic goal may have finally been realised.

In summary of discussion of this paper, Paciorek and colleagues described the actions of Ro 31-6930 and cromakalim which were both members of a new class of drug at the time, K<sup>+</sup> channel openers (Paciorek et al, 1990). The antihypertensive properties were confirmed by conventional procedures which also revealed hypotension in the normotensive situation and a troublesome reflex tachycardia. Since the publication, a multitude of K<sup>+</sup> channels has been characterised and a number of different chemical groups developed which confer better selectivity and promise more therapeutic potential. Ro 31-6930 represents a drug case which demonstrated excellent efficacy but concomitant toxicity in late preclinical studies and can be classified under drug failures in the 'fail early' class. In essence, the benefit to risk balance for Ro 31-6930 was considered negative and the antihypertensive development was stopped before Phase I healthy volunteer studies were initiated for safety reasons. The case of Ro 31-6930 is returned to below where the pharmacological profile is considered in terms of its potential in asthma.

## Paper II

In this paper, Paciorek and colleagues were able to salvage a drug failure and re-evaluate it for another indication. New indications are typically added once a drug has been approved for an initial indication. Therefore, the case of Ro 31-6930 represented a different situation, a significant change of direction within the R&D laboratories, and a rapid application to new preclinical models of disease. The models selected in this paper showed that Ro 31-6930 was efficacious and an effective bronchodilator both *in vitro* and *in vivo*. Ro 31-6930 inhibited a range of spasmogens known to be involved in asthma. The selected preclinical models were all valid models of disease in as much that they were sensitive to the bronchodilator activity of different pharmacological classes of drugs,  $\beta_2$ -agonist and phosphodiesterase inhibition, which had proven utility in the management of asthma. As a bronchodilator, Ro 31-6930 compared favourably with the class competitor, cromakalim, and was more potent (Paciorek et al, 1990a). In another preclinical paper, it was shown that Ro 31-6930 was able to inhibit allergen-induced bronchoconstriction in anaesthetised guinea pigs and cats (Paciorek et al, 1991). This work was important because it demonstrated efficacy in an additional animal species and efficacy in animal models of bronchoconstriction following exposure to allergen. The majority of asthmatic patients are allergic and those that are not allergic still present with the same underlying inflammatory processes (Barnes, 2009). In view of these findings, the authors suggested that Ro 31-6930 would also have clinical potential in the treatment of asthma (Paciorek et al, 1991).

Development of Ro 31-6930 proceeded in healthy volunteers but the therapeutic index separating the minimally effective dose relaxing airways and doses producing adverse cardiovascular side effects was too narrow (unpublished observations) and similar to other reports for this class of drugs (Barnes, 2009). A clinical pharmacology review on K<sup>+</sup> channel openers in 1992 also noted that ‘the available drugs did not have sufficient tissue selectivity to be useful therapeutic options’ (Andersson, 1992). The published literature for cromakalim suggested hypotension barely occurred in healthy volunteers, but it was masked by marked reflex tachycardia (Donnelly et al, 1990). Furthermore, adverse clinical evidence in 1993 showed that oral administration of the active enantiomer of cromakalim was unable to inhibit histamine and carbachol-induced bronchoconstriction in asthmatic patients and caused headache in most patients (Kidney et al, 1993). These findings ended the enthusiasm for developing these drugs as bronchodilators at that time.

From around 2003, a new probe called Proteomics from Lectus (Lectus Therapeutics, 2007) was developed. This probe can be used as a tool to identify specific accessory proteins belonging to individual ion ( $K^+$ ) channels in different tissues. With demonstrable binding and drug modelling for target sites, tissue specificity has been made more likely.  $K^+$  channels are known to be heterogenic across a whole range of excitable tissues and epithelium in various organs throughout the body (Quast, 1996). In a similar manner to the work from Wang and colleagues above (Wang et al, 2005), many different chemical classes of agent have been developed which are known to modify the activity of  $K^+$  channels (Mannhold, 2006). Disappointingly, a recent review of patents for which  $K^+$  channel modulators were targeted for respiratory diseases such as asthma indicated that not one of the original pioneer  $K^+$  channel modulators ( $K^+$ <sub>ATP</sub> openers) has been developed, notably for lack of specificity (Nardi et al, 2008). In fact, most research emphasis has been placed on big-conductance  $K^+$  (BK) channel openers. The only candidate in a Phase I asthma study was an intermediate-conductance  $K^+$  (IK) channel opener named senicapoc (ICA-17043, Icagen). In 2010, a review of  $K^+$  channel openers in airways disease reported another agent in clinic, andolast, a BK channel opener, to show promise. Andolast possesses anti-inflammatory, mucosal protective and anti-secretive properties (Malerba et al, 2010).

An important issue in the present review of studies with Ro 31-6930 to treat asthma is the emphasis on the acute symptoms of the disease. In the longer term, an underlying inflammatory scenario occurs with remodelling of the airways. Steroid preparations are often reserved for the treatment of severe asthma but chronic administration may be required to obtain long-term benefit but with the penalty of many side effects (Szeffler & Leung, 2001). Present approaches to the cure of asthma reflect the complexity of the disease with so many different drug classes and multiple mechanisms of action: new corticosteroids, mediator antagonists (inhibitors of histamine, prostaglandins, leukotrienes, interleukins, and tachykinins), anti-inflammatory agents (phosphodiesterase inhibitors, transcription factor inhibitors, adhesion molecule blockers), and anti-allergics (IgE blockers). Despite this avalanche of research,  $\beta_2$  agonists as bronchodilators and steroid treatment directed at the underlying inflammation continue to be effective and central for the management of asthma (Barnes, 2009). The possible therapeutic effects of Ro 31-6930 in managing the long-term development of asthma and underlying inflammation were never tested by Paciorek and colleagues (Paciorek et al, 1990a; Paciorek et al, 1991). However, by 1993 the therapeutic potential of  $K^+$  channel openers for hyper-reactivity characteristic of chronic asthma was

reviewed showing this class of agents to be worthy of such research (Cook and Chapman, 1993). In the discussion above, it is evident that early examples of  $K^{+}_{ATP}$  openers failed to yield clinical potential.

It is highly relevant to the discussion to comment on the choice of animal models to evaluate therapeutic lead candidates. Asthma itself is characterised by reversible airflow obstruction and non-specific airways hyper-responsiveness in up to 10% of the population. Airways smooth muscle activity is also characterised by both obstruction and hyper-responsiveness. Thus, resistance to airflow and airways pathophysiology are critical to the evaluation of new drugs for asthma. Earlier attempts to find some new drugs to treat asthma relied on the observation that candidates relaxed vascular smooth muscle (as was the case with the  $K^{+}$  channel openers) which introduced unwanted side effects once candidates were tested in *in vivo* models of asthma. Procedures to investigate the actions of new agents against asthma should, of course, include models of small airways but this is not always done (Janssen, 2009). The most effective way to deliver drug to the site of action and spare systemic side effects is by inhalation (Barnes, 2009). This route of administration was not explored within the study package described by Paciorek and colleagues. The emphasis on specific receptor mechanisms can also be misleading because bronchoconstriction is the net result of many mediators. Furthermore, concentrations of these mediators that isolated tissue preparations are exposed to are probably way in excess of a physiological role and render test models of low therapeutic relevance. Human tissues for study, when available, might also confer better predictability of clinical outcomes (Janssen, 2009). Against this background, the preclinical evaluation by Paciorek and colleagues remains robust with respect to: the ability to show inhibition of many different mediators implicated in asthma, inhibition of smaller changes in the airways, the inhibition of both agonist and allergen-induced airways constriction *in vitro* and *in vivo*, and the use of *in vivo* procedures assessing the function of small airways (Paciorek et al, 1990a; Paciorek et al, 1991). Finally, models of asthma which target therapies at the intracellular level to modulate the excitation-contraction coupling of airways smooth muscle have been proposed to have great promise (Janssen, 2009).

In summary of this paper, Ro 31-6930 failed drug development (as a bronchodilator) in early clinical trials for safety concerns. Lack of efficacy and drug safety complications do not provide a robust platform for further clinical development. Animal models of asthma confirmed Ro 31-6930 to be a potent relaxant of airways smooth muscle in more than one

species. Ro 31-6930 afforded protection against agonist- and allergen-induced bronchoconstriction (Paciorek, 1990a, Paciorek, 1991). However, animal models are not always good predictors of efficacy in clinical asthma (Barnes, 2009). This class of drugs and K<sup>+</sup> channels have undergone considerable research without much success in launching a drug formulation (Nardi et al, 2008). It is debatable whether all the preclinical studies would be performed in-house today. Attention to the underlying disease and development of models to assess inflammation are appropriate regarding the known properties of the various structures of K<sup>+</sup> channel openers (Malerba et al, 2010). Delivering minute quantities of drug via inhaled aerosol to the target site is a speciality science but offers specificity of action. These techniques were not fully explored prior to drug discontinuation and could have been assessed with external partners.

### **Paper III**

In this paper, the safety of a marketed drug was studied within the very sensitive setting of pregnancy for the critical indication of transplantation. Tacrolimus had been marketed for several years but data supporting continued administration during pregnancy was very limited and very much needed. The additional information offered from this retrospective analysis of 100 transplant patients from Kainz and colleagues suggested that pregnancy outcomes in transplanted mothers maintained on tacrolimus-based therapy were little different to reports already available with other immunosuppressants (Kainz et al, 2000).

Regarding the collection and publication of data for the Kainz review, anonymity of mother and child was maintained regardless of data source. Data was collected by the Sponsor from various sources but had(s) the weakness that much of the data is missing. However, this weakness was overcome to some extent in that this cohort was of considerable size and the next largest published number of patients was from Pittsburgh in 2000 with just 27 pregnancies (Jain et al, 1997). Thus, this experience brought important information and represented a valuable resource for counselling before, during and after pregnancy. Separate assessments for liver and kidney recipients would provide a better reference for counselling transplant mothers as performed elsewhere (Coscia et al, 2008) but kidney recipient numbers were too few (22 mothers) to undertake any reliable analysis.

The experience from Kainz et al showed that outcomes were little different to those with the use of ciclosporin-based therapy which had been the standard of care for over 19 years (Lamarque et al, 1997). In trying to minimise risk, favourable pre-conception criteria had been defined as good transplant graft function, no evidence of rejection, minimum 1 to 2 years post-transplant and no or well controlled hypertension. For these women, pregnancy had been shown to proceed without significant adverse effects for mother and child (Armenti et al, 1998). The Kainz experience did not make any comparisons of risk for early and late conception after transplant, but the findings did not contradict those from Armenti and colleagues. In addition, the malformation rate of 4% was similar to 3% reported in non-transplant individuals (Armenti et al, 1998). In its entirety, the data from the present review provided data to support change of the wording under pregnancy in the tacrolimus labelling. Thus, rather than tacrolimus... 'should not be used in pregnant women unless the perceived benefit justifies the potential risk to the foetus' as in the year 2000, the equivalent text in 2007 was... 'Pregnancy and Lactation: Tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus' (Tacrolimus Summary of Product Characteristics, 2007). This reflects a reduced perception of risk, with expanding experience, to mother and foetus in the setting of pregnancy following transplantation.

The limited amount of literature published in the last 10 years on pregnancy in transplant recipients includes a review on data from 1996 to 2004 from the NTPR registry (Grimer, 2007). This experience covering 1430 outcomes offers suggestions rather than guidelines for pregnancy during transplant because the data is not based upon prospective clinical studies. Pregnancy is usually an exclusion criterion from clinical trials. The suggestions for clinical care are largely based on the experience gained in patients treated with the calcineurin inhibitor immunosuppressant, ciclosporin. Important information, not covered in the Kainz cohort, drew attention to the increased risk of graft loss up to 2yrs after delivery for renal recipients. Graft rejection in the Kainz paper was noted with tacrolimus during pregnancy although no case resulted in graft loss. Of note, however, the majority of patients were liver recipients. Another guideline published in 2002, The European Best Practice Guidelines (EBPG Expert Group on Renal Transplantation, 2002), reaffirmed the necessity to check drug exposure and if necessary adjust immunosuppressive dose during pregnancy to reduce the risk of acute rejection. Adverse events typically occurring such as preeclampsia in the mother necessitate bi-weekly checks of weight, blood pressure, and renal function. This guideline

confirmed that immunotherapy based on ciclosporin or tacrolimus with or without steroids and azathioprine can be continued during pregnancy. This again supports a shift in the balance of benefit and risk in favour of tacrolimus administration.

Moving to the risk to the new born, the present labelling for tacrolimus does not recommend breast feeding because of passage into maternal milk (Tacrolimus Summary of Product Characteristics, 2007). In the 100 pregnancies described by Kainz, an estimate of tacrolimus in maternal milk was not carried out. However, in the publication from Jain et al, 1997 information from 10 mothers showed tacrolimus to be in maternal milk (0.6ng/ml) at some 40% of that in maternal plasma (1.5ng/ml) indicating a considerable degree of tacrolimus exposure to the new born. In a later review, tacrolimus was found to be low in mother's milk and this group stated breast feeding was possible (Ostensen et al, 2006). Furthermore, follow-up of mothers who did breast feed did not reveal any complications in 64 transplanted mother births (Coscia et al, 2008). The appropriate decision whether to breast feed or not is a question of benefit versus risk. Some transplant centres in Sweden consider that the balance favours breast feeding during tacrolimus therapy (Olausson, personal communication 2009).

In a comprehensive overview of this subject at WebMD (Mukherjee, 2009), balanced information on the management of transplant recipients during the course of pregnancy is given by transplanted organ and for the foetus. Of utmost significance is the discussion on the change in the prescribing information for an increased risk for foetus with mycophenolate mofetil (MMF). Notably, in renal recipients MMF is often given in combination with tacrolimus. In November 2007, the FDA changed the pregnancy category of mycophenolic acid (active metabolite of MMF) to pregnancy category D, meaning evidence of human risk. The NTPR registry revealed a 42% miscarriage rate and a 27% incidence of structural malformations, typically of the ear, in transplanted woman treated with MMF. It is now recommended that MMF is stopped prior to conception (Louden, 2009). For those pregnancy cases where the immunosuppression was recorded in the Kainz cohort, MMF was not included in the regimen.

It is pertinent to note that registry sources are just one source of information. Ideally, each transplant recipient considering becoming or who has become pregnant should be advised and counselled as an individual according to specific comorbidities, immunosuppression, and other characteristics with all available data sources (Coscia and Armenti, 2010). For example, an individual's serum creatinine level prior to pregnancy and the increase during pregnancy



have been shown to be predictors of graft dysfunction after birth in renal recipients (Coscia, 2008). In this sense, the Kainz analysis does not include any data on creatinine levels or analysis of predictors of renal dysfunction. Information is limited to rejection in 9 mothers, renal impairment in 7 mothers, and renal dysfunction in 8 neonates. The report of this cohort is also deficient in providing follow-up data for neonates which can provide long-term reassurance for mothers (Coscia, 2008).

In summary of this paper, this is an example of a recently marketed drug for which the risk to mother and foetus was assessed from information collected several years after drug approval. The approach inherits weaknesses that it is retrospective, provides incomplete information, lacks longer follow-up, but nevertheless overcomes ethical issues of including pregnant women in prospective clinical trials. Counselling, guided by data available, is an invaluable part of transplant pregnancy management (Mukherjee, 2009). Since the original publication, the data from the Kainz study has been reviewed by other parties; shifted the balance of risk in favour of benefit, accepted as supporting evidence by the regulators supporting a change of text in the labelling, and cited by professional groups charged with creating guidelines for transplant care (EBPG Expert Group on Renal Transplantation, 2002; McKay, 2006; Grimer, 2007). Finally, it is reinforcing to read that the first child born to a transplant recipient celebrated his 53<sup>rd</sup> birthday on 10 March 2009 (Khedmat et al, 2009).

## **Paper IV**

This study assessed risk for a well-established immunosuppressive product (tacrolimus) which was late into the product life cycle for the indication transplant rejection. Transplant patients are exposed to an ever increasing risk of malignancy with time (Ju et al, 2009). It has been estimated that a reduction in cardiovascular events through aggressive treatment of hypertension and hyperlipidemia will make malignancy the leading cause of transplant death (Buell et al, 2005). To quantify the magnitude of this risk, a summary analysis of clinical studies was carried out where the exact number of patients treated with tacrolimus per study was known. This is more reliable than relying upon registry data sources where the denominator is unclear and the chance of unreported malignancies is higher. Search criteria in the present summary analysis included only multicentre clinical studies in Europe which were prospective, randomized, controlled and comparative. These data provide very strong medical evidence to make claims of efficacy and safety. However, the goal was not to make

comparisons with other drugs but to more clearly characterise the longer-term risk of malignancy with the use of tacrolimus-based therapy. An inherent weakness in this approach is that clinical studies preselect the population under study introducing bias. Notably, estimates of the risk of malignancy for transplanted adults within a study might not be representative for comparisons with the total adult transplant population and non-transplant adults, not least because malignancy risk increases with age at transplant (Ju et al, 2009) and with age in non-immunosuppressed individuals (CancerStats, 2011). In the present analysis, one study excluded transplant recipients >60 years and one excluded patients >65 years.

Limited space is often a restriction to providing sufficient methodological detail in publications. It is enlightening to look a little more closely at study entry criteria and study design to appreciate the scope of the present analysis (Cowlrick et al, 2008). In Table 1 of Paper IV, studies were summarised for number of patients, mean age, initial dose of tacrolimus, adjunct immunosuppressant, and number of study centres with participating countries. Tacrolimus exposure was detailed in the text. However, it is also useful to know that very few living donors were included; nearly all patients were cadaveric kidney recipients. Glomerulonephritis (30%-40%) was the most common reason for transplantation and retransplantation was <10% in any study treatment arm. High-risk patients with high panel reactive antibody (PRA >50%) were limited to just one treatment arm which contained no more than 11% patients. Patient survival was high ranging from 88% to 97%. The monitoring of all studies followed an ethics-approved protocol with an adequately powered primary endpoint. All studies were open in nature as blinded studies in transplantation are almost never performed. Importantly, no study was powered for malignancy – this was retrospectively assessed as an adverse event. Analysis of malignancy incidences was descriptive with simple means and percentages calculated over the three years of tacrolimus exposure. Confidence intervals were determined for only the most frequently occurring malignancy types. Multivariate analysis to try and correlate risk of malignancy with demographic parameters or any other metric was not performed. Thus, this study population represented a low to medium risk population for rejection and graft loss. The population was rather homogenous with similar patient demographics for all 5 studies across Europe (Cowlrick et al, 2008).

The main findings of the study are consistent with other published data (Kauffman et al, 2006). In that review of several studies covering the same time period 1995-2004, data based

upon 5 registries and 5 transplant centres show the malignancy rate was approximately 1% per year after transplant and almost identical to the current study. This incidence continues to reflect malignancy rates 2 to 3-fold higher than statistics for the general population in Europe (Ferlay et al, 2008).

The predominant malignancies following transplant have been recorded from registry sources as non-Hodgkin lymphoma, malignancies of the skin and lips, malignancy of the vulva/perineum, Karposi's and renal cell carcinoma (Penn, 1994). Immunosuppression increases the risk of skin and lip cancers. While many cancers in the general population are not increased, rarer malignancies may be increased such as lymphomas (Penn, 2000). The type of malignancies recorded in the present analysis support high frequencies of skin cancer and lymphoma.

The nature of malignancy typically varies with regard to geography and other factors, not least, duration of immunosuppression (Ju et al, 2009; CancerStats, 2011). Ju and colleagues found that malignancy incidence rates 0-3 years post-transplant were some 2 to 3-fold the rate seen in non-transplant adults and this increased to 30 fold at 15-18 years post-transplant. The weakness here of the present study is insufficient follow-up to explore this effect but there is no reason not to expect higher malignancy rates with longer exposure to tacrolimus which was evident for the three years of follow-up, especially for skin cancers. Exposure to different risk factors in Europe such as life style, weather patterns, and different approaches in national health management and diagnosis are able to account for some of the variation in malignancy type and incidence (CancerStats, 2011). If non-melanoma skin cancers are excluded then bowel, breast, lung and prostate cancers account for about half of the malignancy incidence and half of the mortality for the general population in Europe (CancerStats, 2011). In the present study, these four malignancy types made up approximately 35% of this same cancer spectrum. The tendency for some malignancies to occur earlier after transplant is due to the increased susceptibility to infection. Causative agents are known to include human papillomavirus, Epstein-Barr virus, hepatitis C, and HIV possibly transmitted from the donor graft and during the surgical procedures. Other causative factors, non-viral in nature, include sunlight and tobacco smoke (Vajdic et al, 2006). It is difficult to speculate in the present study to the precise nature of causative factors over time because of the relatively short follow-up but the limited data did show that most of those lymphomas recorded occurred during the first year after transplant (Cowlrick et al, 2008).

Qualitative comparison between the various treatment arms, utilising different adjunct immunosuppressants, did not reveal any change in the overall spectrum of malignancies. In a much earlier publication (Gruber et al, 1994), malignancies in renal recipients treated with ciclosporin increased with time but were no different compared with non-ciclosporin therapy based on azathioprine, steroids and antibodies. The increased risk of malignancy in transplant recipients compared with the background population is probably more dependent upon cumulative exposure rather than specific type of immunosuppression. This has been described as an impaired immunosurveillance and compromised anti-viral activity which might exacerbate cellular injury to harmful insults like sunlight. Immunosuppressive drugs and transplant procedures interfere with the immune response and introduce infection (Webster et al, 2007). Identifying and quantifying risk factors enables implementation of more effective measures to contain malignancy and enhance counselling. Specific risk factors for malignancy have been identified as age while diabetes mellitus as primary disease (reason for transplant) reduced risk. Reduction of immunosuppression (overall load) and thorough screening of patients are some of the available approaches to reduce risk of morbidity and mortality after transplant (Webster et al, 2007). Reduction of immunosuppression is also consistent with the longer-term experience with tacrolimus. More recent clinical studies tend to employ lower initial doses and target lower exposure (Paper IV, Table 1). As noted above, avoidance of sunlight reduces the incidence of skin cancer and effective use of prophylactic anti-viral measures also helps to contain risk of malignancy (Penn, 2000). The utility of sirolimus for its anti-neoplastic effects are also being explored. The authors review individual potential carcinogenic profiles of the various immunosuppressants, notably higher risk with lymphocyte-depleting antibodies (Domhan et al, 2009). These agents were not employed in the present summary analysis (Cowlrick et al, 2008).

In summary, the present analysis provides absolute estimates and confidence intervals of the various malignancies experienced by adult renal recipients exposed to tacrolimus for up to 3 years post-transplant. The investigation of a well-defined population in large prospective, controlled, European multicentre studies adds to the strength of these data. The findings reflect an increased risk of malignancy in immunosuppressed individuals consistent with other reports. This experience provides more detailed information to that available in the labelling, and serves as a robust basis for future comparisons and for counselling patients. It is suggested that this approach could be extended to additional populations such as adult liver

recipients and paediatric recipients, and where clinical studies permit, applied through longer follow-up.

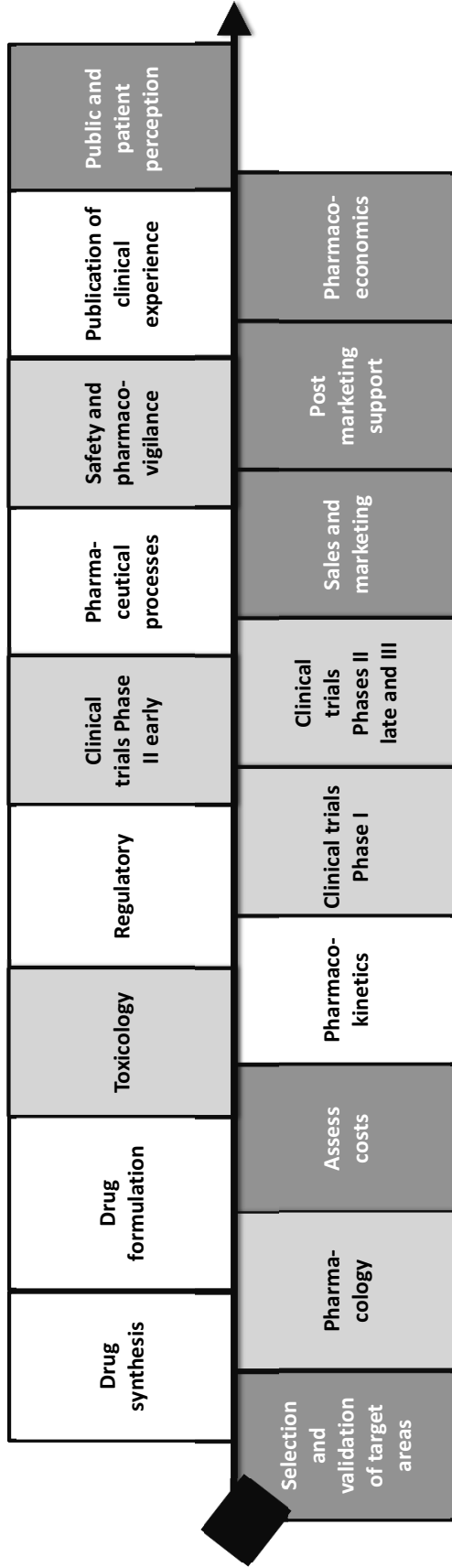
## **Paper V**

For this study, some of the outcomes from the methods analyses and assessment of benefit and risk from the former papers were put into context with the overall drug discovery and development process to investigate entrepreneurship. First of all, an 18-step model of drug discovery and R&D was defined (Figure 2; Paper V, Appendix 1) and over 50 health professionals were then invited to answer a number of entrepreneurial questions within a web-based survey. These experts perceived Toxicology, Pharmacovigilance, and Clinical Trials as the most important parts of the drug R&D process for the assessment of drug benefit and risk. This perception matched the areas where drugs typically fail development and were also areas which are highly regulated (DiMasi, 2001; Schuster et al, 2005; Elias et al, 2006; Ray and Stein, 2006; Kola, 2008). These are also areas which a company could contract out to external specialised units.

When the same professionals were asked which of the 18 drug R&D steps were important for requiring an entrepreneurship input, they identified quite different steps. First, steps above of importance for assessment of drug benefit and risk scored quite low for entrepreneurship. Secondly, the steps rated highest needing entrepreneurial input, Sales and Marketing, and Public and Patient Perception, were of quite low importance for assessing benefit and risk. Further, the higher rated steps for entrepreneurship input tended to belong to the latter stages of R&D with the exception of Selection and Validation of Target Areas for Research as shown in Figure 1, Paper V. The authors are not aware that a need for entrepreneurship has been recognised as being so important in the latter stages of the drug R&D processes before. However, some of these characteristics are similar to that described by Ratti and colleagues where marketing is an activity retained as a core skill in-house. In their model, preclinical and clinical development are controlled by the source organization but can be contracted out (Ratti and Trist, 2001). Other development processes identified by our study population as being important for assessment of benefit and risk are also processes that can be carried out by other specialized parties while it would be desirable to retain some areas demanding a strong entrepreneurial input. On this basis, a working model in Figure 4 is presented which

represents one such option. The ability of the study population to differentiate the importance of benefit/risk from the need for entrepreneurship input for the various steps in this drug R&D model may also have other implications for marketing strategy and marketing modelling. Notably, strong entrepreneurship was identified as key for early selection and validation of target areas and then again throughout the latter R&D processes. It has become increasingly evident that a marketing strategy developed to ensure a successful drug launch should integrate earlier events and processes to differentiate products and define competitive advantage as soon as possible (Trim and Pan, 2005; Hemels et al, 2009). Characterisation and positioning of the drug candidate begins during drug discovery and continues throughout the development. The better the clinical predictability of early tests of effectiveness then the more likely it is that a successful candidate with economic viability can be identified. The use of model based drug development can contribute significantly to this process and enhance decision making throughout development (Zhang et al, 2008). The entrepreneurial qualities required in this context are critical to smart drug development, confer competitive advantage, and ought to be considered as core skills to retain within the organization.

The experts invited to participate in the present study were evenly distributed across small, medium and large companies with the majority from the pharmaceutical industry. As a group, they can also be characterised as managers, middle aged, well qualified with considerable work experience. Their replies to a number of entrepreneurial questions are summarised in Paper V, Table 2 and support the observation that the study group had a positive attitude towards entrepreneurship. In terms of involvement and participation in development of entrepreneurial activities there was a positive response. Entrepreneurial engagement and intent were also indicated by most individuals. Reference to Figure 2 in Paper V shows that key attributes strongly associated with entrepreneurship and small business management included creativity, hard work, independence, individualism, intellectual challenge, opportunity exploitation, risk taking, leadership, self-development, control of one's own life, and finally team work. It is suggested that models of drug discovery and development which strive to include these qualities might be innovative and provide greater opportunity. Outsourcing more processes frees companies to focus on core skills consistent with an entrepreneurial orientation and more efficient value creation (Garnier, 2008, Hedner et al, 2011a).



**Figure 4**

A model of drug discovery and development showing outsource potential and core processes

(Overlapping boxes represent drug discovery, development and marketing processes indicating these processes are non-discrete often running in parallel. Dark grey boxes with white text are those processes perceived to be highly important for entrepreneurial attitude and light grey boxes with black text are those processes perceived to be highly important for assessment of benefit and risk. Dark grey boxes/processes might be considered core/in-house skills while light grey boxes/processes are well regulated, are often the reasons why drugs fail, and some can be outsourced.)

To summarise the present work, it has been shown that employees have a positive attitude to entrepreneurial skills and an entrepreneurial career. The majority has entrepreneurial intent and has been engaged in entrepreneurial projects. They also recognise the required competences and attributes associated with entrepreneurship and are able to identify which steps of the R&D process need an entrepreneurial input. These findings at the employee level are key considerations for smaller more specialized innovative organizations and their business interrelationships both internally and externally. Implications are also discussed for more open models of drug discovery and R&D (Hedner et al, 2011 in press) to increase the organizational entrepreneurship orientation as a more likely mechanism of increasing NME output and overall value (Munos, 2009). This thesis continues to place emphasis on optimal decision making by investigating individual judgement of drug development go/no-go decisions in the next paper.

## **Paper VI**

In this final paper, the ability of health professionals to make critical go/no-go decisions in drug development was studied. To simulate real world judgement, drug case scenarios based on the drug cases studies in Papers I to IV with other examples were selected to represent preclinical development, clinical development, and marketing stages of drug development. In the face of this uncertain information, the degree of coherence in individual judgement was investigated, and whether any known individual demographic or entrepreneurial factors could explain potential sources of variability.

The study group indicated their assessment for 5 decision points for each of 4 drug case scenarios, named W, X, Y and Z as represented by the group mean decisions on an 11-point Likert scale in Figures 1a – 1d, Paper VI. In light of these results, Hypothesis 1 for case judgement is accepted, ‘experienced employees can make go/no-go decisions (and exercise their case judgement) based on real-life drug discovery and development case scenarios’. The drug case scenarios caused considerable change in direction of go and no-go for each case. These judgements reflected marked variability between individuals reflected by the extended whisker plots and the large standard deviations in Table 3, Paper VI. On this basis, Hypothesis 2 for decision coherence is rejected, ‘there is limited variability in experts’ judgements in go/no-go decisions through phases of drug discovery and development’.



It is important to note the study design set no threshold to accept or reject any of the hypotheses. Indeed, much discussion derives about appropriate use/abuse of statistics with regard to the use of Likert scales, especially whether the data are parametric or just assumed to be (Jamieson, 2004). However, the SD typically ranged from 1.5 to 3.0 around typical mean values 0 to 3.0 (Table 3; akin to parametric analysis), and the range and inter quartiles around the median (Figures 1a – 1d; more akin to non-parametric analysis) were very large supporting the decision to reject Hypothesis 2.

To account for the marked variability in the results, the known demographic factors and entrepreneurial options were tested for their influence as reported in the results and discussed in the present paper (Cowlrick et al, 2011). In short, no consistent finding or explanation across all factors and drug scenarios could be offered based on the series of tests undertaken. On this basis Hypothesis 3 for judgement variability is rejected, ‘differences in judgement between respondents can be explained by functional role, education, experience, area of expertise or other data captured’. Similarly, Hypothesis 4 for influence of entrepreneurial traits is also rejected, ‘variability in individual judgements given by the respondents could be influenced by their perceived entrepreneurial character’.

Individuals in this study exercised judgement based on incomplete knowledge with many unknowns resulting in marked variation between individuals. It is rather surprising that no consistent influential factor was found to account for the individual variability but this does not exclude the possibility there are such factors. Factors such as gender with women tending to rate some health risks higher than men (Slovic et al, 2007), and increasing age have been shown as possible explanatory variables to account for variability (Cowlrick et al, 2009). Personal bias in different forms was also suggested in the discussion as a possible explanatory variable. Decision making in the pharmaceutical industry during drug development is critical to patient safety and to ensure outcomes are maximised for all stakeholders. Increasing the number of individuals or experts, as per the ‘wisdom of crowds’ (Surowiecki, 2004), may help informed decision making to reach better coherence. Importantly, this study looked at individual variability in judgement without cooperation between individuals. In real-life situations, groups of experts may use techniques to reach consensus such as decision analysis, marketing models, risk analysis models, or human judgement which is by far the most frequently used technique in both preclinical and clinical situations (CMR International, 2008). In addition, a particular style might be most suitable:

directive styles in small specialized start-up discovery units, consensus styles under leadership influence in large pharmaceutical companies, and democratic styles by majority vote within regulatory bodies (Pritchard, 2008).

Optimal decision making is also driven by the criteria set for the drug target and business profiles (Pritchard, 2003). An increased probability of success should be achieved by asking:

- Is there a need for a drug molecule with this therapeutic target?
- Are preclinical models predictive of activity in man?
- Does the endpoint measure clinical efficacy and does this have therapeutic value?
- Is benefit to risk favourable and risk manageable?
- How does this drug profile compare with other drugs on the market?

Appropriate go/no-go decisions are especially critical at Phase II ‘proof of concept’ study to prevent poor candidates consuming valuable resources. Inability to realistically assess go/no-go decisions against the benefit to risk ratio has been shown to be a key reason for drugs failing to win regulatory approval. Even when drug approval is granted, there is still significant risk so that continued drug surveillance is necessary (Maniglia, 2007; Hemels et al, 2009).

In summary, it is suggested that decision makers should be more objective, representative of the intended disease target population, and balanced with regard to potential influential factors such as gender. These individuals/groups might also benefit from additional decision making techniques. This is an important avenue of research towards optimising decision making throughout drug discovery and development and needs further studies.

## CONCLUDING REMARKS

The thesis began with the general hypothesis:

*‘Over the last few decades there has been increased emphasis placed on drug safety (and efficacy) resulting in increased drug development costs which have forced the pharmaceutical industry to reconsider their role and approach in developing new chemical entities’.*

The information gathered from literature review, summarised in the Introduction of this thesis and later discussed, strongly supports this hypothesis. Worse still, drug development appears critically ill and inefficient. The present model of drug development no longer delivers new medicines capable of providing return on investment to fund future research. In an effort to restructure, industry has preoccupied itself with mergers and acquisitions which provide stakeholders with short-term benefit. Longer-term, at best, innovation remains flat. Industry has also begun to open up with increased outsourcing and partnerships. However, the model proposed for drug development in the present work suggests industry can go much further. As part of this change, the entrepreneurship potential of researchers and other professionals could be nurtured and strengthened, not least in drug discovery and during the latter stages of sales, marketing and pharmacoeconomics. Opening the whole process to increased external expert input also arms decision makers with the knowledge and wisdom to adopt more objective strategies to address drug target and business profiles. This thesis shows that drug regulations have developed largely in response to drug disasters. Despite the complex nature of these regulations, drugs still frequently fail for reasons of inefficacy and toxicity prior to approval, and for toxicity during marketing. Regulatory agencies have also acknowledged ‘delivery failure’ by taking initiatives to address this situation. They stand as a key stakeholder and agent of change if patients are to be provided with novel and effective medicines.

The following questions were set under this general hypothesis:

- Were the choices of test procedures (preclinical test system and clinical trials) years ago appropriate for identifying/evaluating novel drugs and how do those processes compare with today?

Critique of the methodology adopted to evaluate drug candidates (K<sup>+</sup> channel openers as anti-hypertensives and anti-asthmatics) over the last 20 years using real examples shows that the models were appropriate to demonstrate efficacy in the laboratory. However, the predictive clinical value of these procedures is far from ideal. R&D units are under pressure to produce a lead candidate quickly so that appropriate disease models may not be optimally developed, and potential indications and routes of administration left unexplored. Technology has advanced and with it a better understanding of molecular targets and drug discovery. However, this improving scenario has still failed to yield an increase in clinically valuable products today although some candidates look promising. Review of the methodology adopted to assess safety of immunosuppressants during pregnancy and for malignancy risk after drug approval showed the approaches to be simple, effective and to enhance the balance of benefit to risk assessment favouring benefit for patients. This underlines the role and value of continued surveillance, retrospective case studies and prospective clinical trials.

- Which factors within drug R&D past and present confer increased knowledge and awareness for future drug research?

Drug development has successfully been built upon a 'blockbuster model' for many years whereby a 'me-too drug' or a drug with a new indication was aggressively marketed to large patient populations and rewarded by handsome returns on investment. Despite advancements in molecular biology and characterisation of target receptors, new drug indications have become difficult to exploit. This could be because new indications are more difficult to develop than before and/or perhaps the innovative potential has largely disappeared. This work suggests some of the latter and that stakeholders need to address this deficit. The present findings also argue that opening the whole drug development process up to more external influence will result in better decision making for future research.

- What is the nature of risk for potential candidates in drug R&D based on real case scenarios?

The nature of risk should always be balanced against benefit in context with the target disease. In particular, the risk of cardiovascular events was considered too great for drug candidates studied in this thesis. Conversely, transplant offers much benefit and a medical solution for end-stage organ failure despite a greatly increased risk for malignancy with life-long immunosuppression. The challenge to decision makers is to assess the net benefit

(against the risk) as early as possible in drug development and develop the best drugs further. The resultant should be a more efficient drug process which society can afford.

- How important is innovation and entrepreneurship in drug discovery and R&D and which factors influence this perception?

Without innovation and entrepreneurship industry would die. This thesis suggests that this is indeed the case. Invited experts, as decision makers for several drug case scenarios, also indicated that drug discovery and the latter stages of development especially require entrepreneurial input. Many small R&D units appear more efficient than fewer larger 'Big Pharma' players. Proposals to correct this inefficiency are restructuring of Big Pharma R&D, exploitation of open innovation, returning power to entrepreneurs, and enabling more objective decision making. There is already considerable evidence that these changes are taking place and do improve efficiency.

- How is a go or no-go decision made during drug R&D?

Effective go/no-go decisions are the pillar of efficient drug development. Despite identification of a drug target profile and business profile, decisions must be made with incomplete information and with many unknowns. The present drug case scenarios show that this process involves marked individual variability in judgement. Techniques are available to facilitate group decision making but human judgement is the dominant technique exercised by most companies. Companies, regulatory bodies, and other stakeholders might prosper by opening their doors to others gifted with more magical insight.

- How can one consider value and benefit versus risk for new drugs against costs of development and other limiting factors?

One can argue that faced with life-threatening disease, for drugs which are highly efficacious, costs become increasingly less relevant. One should also never forget that no drug comes without the risk of side effects. There are a number of methods used to assess or even justify cost of therapy which were not considered in this work. Evidence in this thesis does support that clinical efficacy, therapeutic index, and tolerability are important drug profile properties to consider for candidate development. The medical need and the potential market should also be evaluated. Drug development is so costly that the candidate profile should

continuously be addressed against the target criteria throughout the development process. Stakeholders and society at large are under enormous pressure to review how drugs are developed to restore innovation and efficiency. Changes in legislation and changes in patent regulation are two of the many areas open to debate if patients are to continue to receive novel therapies for acute and chronic diseases.

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