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AN EVALUATION OF EFFICIENCY AND PRODUCTIVITY OF THE INTERNATIONAL PHARMACEUTICAL INDUSTRY AND ITS SUSTAINABILITY IN THE 21ST CENTURY

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ABSTRACT

Throughout the last two decades the global pharmaceutical industry has been one of the most successful and profitable industries. However, a decline in the number of new product launches coupled with exponential growth in R&D investment has led to questions about the sustainability of the industry. In this thesis, five dynamics of pharmaceutical R&D productivity have been investigated in detail, i.e. cycle times, success rates, volume, expenditure and value, to assess how this can be improved upon. For this, data were collected directly from the pharmaceutical industry for the period 1998-2002 through longitudinal surveys.

The outcomes of the studies reported in this thesis suggest that with current R&D practices it is unlikely that the industry will be able to produce sufficient output, both in terms of numbers and value, to deliver the growth that stakeholders have come to expect and to support future R&D. Although a continuing increase was observed in the proportion of biotechnology products reaching the market, this was not sufficient to halt the industry's declining NME output. Statistically significant differences were demonstrated between the pipeline composition of therapeutic areas in terms of compound type ($p<0.01$), novelty ($p<0.01$) and origin ($p<0.001$). Therapeutic area differences were also observed in clinical success rates ($p<0.05$) and development times, with development of nervous system indications taking significantly longer than for other indications ($p<0.001$). These differences suggest that focusing on a smaller number of therapeutic areas might prevent an organisation's resources to be spread too thinly.

During the 1990s the impetus was on speeding up the development process which has resulted in a considerable decrease in overall development time for major pharmaceutical companies. The continuous decline in success rates, however, illustrates the need to focus efforts on improving all parameters of R&D productivity.

The findings of this thesis include signs that R&D practices are changing, with companies moving away from the fully integrated company model by building up external networks which will provide them access to resources and skills not available in-house. Small improvements in late stage success rates and the increasing number of NASs in preclinical development suggest that the industry's efforts to improve productivity are starting to produce results. It will take time for this to be translated into an improvement in the industry's output, the measure most frequently used to assess the industry's performance. Therefore it is important for the industry to manage the expectations of its stakeholders and to supply them with clear and objective information on temporary indicators of efficiency and productivity.

It is hoped that the findings of this work would stimulate discussions within the industry as well as with external stakeholders, leading to a greater understanding of the risks and issues involved in drug development, and ultimately to a higher degree of control over pharmaceutical R&D efficiency and productivity.

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GLOSSARY OF ABBREVIATIONS

ADME: Absorption, Distribution, Metabolism and Excretion

ANOVA: Analysis Of Variance

ATC code: Anatomical Therapeutic and Chemical code

bn: Billion

CMC: Chemistry, Manufacturing and Control

CMR International: Centre for Medicines Research International

CNS: Central Nervous System

CRO: Contract Research Organisation

CT supplies: Clinical Trial supplies

EU: European Union

FDA: US Food and Drug Administration

FTC: US Federal Trade Commission

FTE: Full-time Equivalent

GLOBEX: Global R&D Expenditure Database

GPEC: Greater Phoenix Economic Council

GU: Genito-Urinary

HIV: Human Immunodeficiency Virus

IBS: Irritable Bowel Syndrome

IMMED: International Marketed Medicines Database

IND: Investigational New Drug

IT: Information Technology

Mn: Million

NAS: New Active Substance

NBE: New Biological Entity

NCE: New Chemical Entity

NDA: New Drug Application

NME: New Molecular Entity

OECD: Organisation for Economic Co-operation and Development

OTC: Over The Counter

PBM: Pharmacy Benefit Manager

PK: Pharmacokinetics

R&D: Research and Development

TTP: Therapeutic Target Profile

Tufts CSDD: Tufts Center for the Study of Drug Development

WHO: World Health Organisation

GLOSSARY OF TERMS

Alliance expenditure: Amount of R&D expenditure allocated to alliances, including expenditure relating to work conducted in-house as part of formal alliance agreements, and management and negotiation costs, as well as payments made to alliance partners (including milestone payments, but not royalty payments). Alliances must involve shared technical, development or commercial risk and reward to all alliance partners. This does not include expenditure on in-licensed projects and outsourcing or "fee for service" contracts.

Biological: A substance isolated from animal tissues, e.g. vaccines, hormones, antigens.

Biotech product: A naturally occurring or modified polypeptide, protein, DNA or RNA product (produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals or transgenic plants), for therapeutic, prophylactic or in vivo diagnostic use in humans. The only vaccines included are recombinant vaccines.

Brand name: The accepted trade name of the active substance in each country.

Capital R&D expenditure: The total expenditure on equipment, land or buildings substantially devoted to pharmaceutical research and development activities relating to ethical pharmaceuticals.

Chemistry, Manufacturing and Controls (CMC) resources: Resources ($ and FTEs) allocated to pharmaceutical & chemical development, including, but not limited to, process research and development for drug substance and drug product, formulation, scale-up, technology transfer; analytical assessment, clinical supplies and compilation of technical regulatory dossier.

Clinical research resources: Resources ($ and FTEs) allocated to clinical studies in volunteers and patients, pre- and post-marketing.

Clinical trial: Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product, and/or to identify any adverse reactions to an investigational product, and/or to study the absorption, distribution, metabolism and excretion of an investigational product, with the objective

of ascertaining its safety and/or efficacy.

Collaboration/sponsored research: An NAS discovered as a result of research carried out in collaboration with, or sponsored by, another: company, a university, government agency or an individual.

Compound type: See *new chemical entity*, *biotech product*, *biological*, and *gene therapy product*.

Discovery resources: Resources ($ and FTEs) allocated to all basic research, synthesis and screening (including biological and pharmacological screening) and ADME (absorption, distribution, metabolism and excretion) studies.

Efficiency: A measure of how much output (e.g. number of new product launches) can be generated per unit input (e.g. $) and differs from productivity by not taking into account any quality aspect of input or output.

Established mode of action: A compound with the same mode of action as this NAS has been previously marketed.

Ethical pharmaceuticals: Any medicinal chemicals, biologicals, products of biotechnology or in vivo diagnostics which are intended for the cure, alleviation, treatment, prevention or diagnosis of diseases of humans and are, or will be, available as 'prescription-only medicines'.

First approval: Issue of technical approval letter from the regulatory authority to first approve the active substance.

First human dose: The administration of the first ever human dose.

First patient dose: The administration of the first dose to the first patient for the target indication.

First pivotal dose: The administration of the first dose in the first pivotal safety and efficacy trial for the active substance.

First submission: Submission of the first registration dossier for the active substance.

First synthesis: The first synthesis or isolation of the NAS. Alternatively, for biotech NASs the first cloning or compound code assignment, if deemed more appropriate.

First toxicity dose: The administration of the first dose in the first animal toxicity study required for the first ever administration of the compound to humans.

First world marketing: First launch of the NAS on any country i.e. the NAS goes on sale for the first time.

Full-time equivalent (FTE): Someone employed by the company to work full-time in R&D. Someone working part-time is counted as a fraction of an FTE (for example someone employed to work 3 days a week would be 0.6 FTE.). This includes contractors included in the internal salaries or operations expenditure.

Gene therapy product: A gene or oligonucleotide produced by recombinant DNA technology delivered using a non-endogenous vector.

Generic name: The accepted name (or company code if unassigned) of the active substance.

Innovation: Introduction of a new idea into the marketplace in the form of a new product or service, or an improvement in organization or process

Investigational new drug (IND): An application that a drug sponsor must submit to FDA before beginning tests of a new drug on humans. The IND contains the plan for the study and is supposed to give a complete picture of the drug, including structural formula, animal test results, and manufacturing information.

Last visit last pivotal study: The last visit of the last patient in the last pivotal study for inclusion in the first major regulatory submission for the active substance.

Licensed-in or acquired: An NAS that is licensed, purchased or otherwise acquired from outside the developing company (e.g. from another company, a university, government agency, or an individual).

Line extension: Chemical, biological or radiopharmaceutical substance that has been previously available for therapeutic use in humans and is destined to be made available as a 'prescription only' medicine, to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of disease in humans and for which both clinical work (clinical trials and/or bioequivalence studies) additional to that conducted for the original product and a regulatory submission for approval to market are required. This definition includes: new combinations of marketed active substances; new pharmaceutical formulations; new routes of administration; new indications; new patient populations. This definition excludes: changes to

manufacturing and control methods; changes to container and packaging and changes to labelling other than those relating to new indications, formulations, dosage schedules and strengths patient population or route of administration.

Miscellaneous resources: R&D resources ($ and FTEs) not classified as discovery, non-clinical, clinical, CMC or regulatory resources. This includes, but is not limited to: project management, R&D management, R&D IT, library and information services, administrative support.

New active substance (NAS): A chemical, biological or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans. The term NAS also includes: 1) an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available; 2) a biological substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process; 3) a radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.

New chemical entity (NCE): a new entity (excluding new salts or esters) produced by chemical synthesis.

New drug application (NDA): An application requesting regulatory approval to commercially market a new drug for human use.

New molecular entity (NME): A product (including new chemical entities, biological products, vaccines and products of biotechnology) that has not been previously available for therapeutic use in man and is destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in man. New salts, pro drugs and esters of existing products and certain biological compounds (e.g. antigens) are excluded. Combination products are also excluded unless one or more of the active constituents has never been

previously marketed.

Non-clinical safety evaluation resources: Resources ($ and FTE) allocated to toxicological, safety and associated kinetic tests in animals.

Novel mode of action: A compound with the same mode of action has not previously been marketed.

Origin: See *self-originated, licensed-in or acquired* and *collaboration/sponsored research.*

Outsourcing expenditure: Amount of R&D expenditure allocated as contracts to external organisations (e.g., for clinical trials, toxicology, formulation development, etc). NB: This does not include expenditure on joint ventures, e.g., with biotech companies, or expenditure on contracts to sister companies which are part of the company's legal entity.

Over-the-counter products: Pharmaceutical products that do not require a prescription

Patent priority date: The date of the first ever patent application for the NAS with a patent office.

Pharmacodynamics: Involves the study of the effect that a drug has on the body. This will include looking at what effect the amount of drug has, called a dose response, and will also look at the site of action of the drug, such as the kinetics of how a drug interacts with a receptor, known as receptor dynamic.

Pharmacokinetics (PK): Involves the study of the manner in which the body handles a drug. It looks at the rate at which drug concentrations change in the body, and is involved with analysing the kinetics of absorption, distribution, metabolism and excretion of a drug.

Pharmacological mode of action: The pharmacology of the NAS, e.g. selective 5HT2 antagonist.

Phase I: Initial safety trials on a new medicine, usually conducted in healthy volunteers. An attempt is made to establish the dose range tolerated by volunteers for single and multiple doses. Phase I trials are sometimes conducted in severely ill patients (e.g. in the field of cancer) or in less ill patients (e.g. metabolism of a new antiepileptic medicine in stable epileptic patients whose microsomal liver enzymes have been induced by other epileptic medicines). Pharmacokinetic trials are usually considered Phase I

trials regardless of when they are conducted during medicines development.

Phase II: Clinical trials (pilot and well-controlled) to evaluate efficacy (and safety) in patients with the disease or condition to be treated, diagnosed, or prevented. Objectives may focus on dose-response, type of patient, frequency of dosing, or numerous other characteristics of safety and efficacy.

Phase III: Clinical trials conducted in patient populations for which the medicine is eventually intended. These generate additional data on both safety and efficacy in relatively large numbers of patients in both controlled and uncontrolled trials. Clinical trials are also conducted in special groups of patients (e.g. renal failure patients) or under special conditions dictated by the nature of the medicine and disease. These trials often provide much of the information needed for the package insert and labelling of the medicine. Also includes trials that are conducted after the regulatory submission of a new drug application or other dossier, but prior to the medicine's approval and launch.

Pivotal study: Well-controlled trial to evaluate efficacy (and safety) in patients with the disease or condition to be treated, diagnosed, or prevented. These clinical trials usually represent the most rigorous demonstration of a medicine's efficacy.

Productivity: A ratio to measure how well an organisation (or individual, industry, country) converts input resources (labour, materials, machines, etc.) into goods and services. Productivity contains both measures of operational efficiency (e.g. number of studies conducted per resources consumed) as well as measures of value generation.

R&D expenditure: The total expenditure on all research and development activities relating to ethical pharmaceuticals. This includes salaries and all other personnel-related costs, costs related to consumable materials and supplies, and an appropriate share of overheads to cover administration, depreciation, space charges, rent, etc. The cost of R&D conducted by means of grants or contracts to other companies or institutions, and proportional costs for joint ventures should be included. This definition excludes capital R&D expenditure.

Regulatory marketing authorisation: The first marketing authorisation granted by the relevant national authority of each country, or by the European Commission through the Centralised procedure.

Regulatory resources: R&D resources ($ and FTEs) allocated to regulatory activities.

Regulatory submission: The first application for a marketing authorisation submitted to each country either by national application, or through the EU Centralised or Mutual Recognition procedures.

Sales: The income from sales of ethical pharmaceuticals. This includes finished products, bulk sales and royalties from licensed-out ethical pharmaceuticals.

Self-originated: An NAS discovered as a result of research conducted either entirely within developing company, by a wholly owned subsidiary of developing company, or by an entity that is wholly a part of the merged organisation.

Terminated NAS: An NAS for which the decision was made to stop all further development activities, either internally or within other organisations. As such, the definition excludes NASs that were subsequently licensed-out for further development by other organisations as well as marketed NASs that were subsequently withdrawn. NASs undergoing regulatory review were only considered terminated if the decision was made to abandon development. Therefore, NASs deemed 'non-approvable' by the regulatory authority or withdrawn from the regulatory review process by the applicant for which further development was ongoing (e.g. for alternative indications or to support re-submission of the dossier) were still considered to be in active development.

Termination date: The date on which the decision was made to stop all further development activities.

Termination reason – Clinical efficacy: Evidence that the clinical effect of the NAS is either therapeutically not meaningful, therapeutically not sufficient (compared to competitors) or not statistically significant.

Termination reason – Clinical pharmacokinetics/ bio-availability: The absorption, distribution, metabolism and elimination (ADME) characteristics in human subjects (patients and healthy volunteers),

suggests that the pharmacokinetic/bioavailability profile in humans precluded further development.

Termination reason – Clinical safety: The safety of the NAS, for example based on the benefit-to-risk ratio established during clinical development, was considered to be unacceptable.

Termination reason – Cost of goods: The cost of manufacturing and production of the NAS precluded further development.

Termination reason – Formulation: The properties of the NAS (e.g. solubility, stability, absorption, palatability, odour, irritancy, bulk density, flow and compressive properties), or the chemical manufacture of the NAS, preclude pharmaceutical formulation.

Termination reason – Patent or commercial legal: Patent issues, commercial legal reasons e.g. merger divestments preclude the further development of the NAS.

Termination reason – Portfolio considerations: Development of the NAS is no longer justifiable as multiple scientific issues preclude its development (e.g. the characteristics of competitor NASs will not be matched or bettered) or the development is terminated for business purposes such as the rationalisation of the company portfolio or budget or resource constraints.

Termination reason – Preclinical efficacy: Evidence that the ability of the NAS to have a beneficial disease modifying effect or diagnostic value in non-clinical studies, was weak/less than expected as measured by objective or subjective parameters and was directly due to the pharmacology of the NAS.

Termination reason – Preclinical pharmacokinetics/bio-availability: The absorption, distribution, metabolism and elimination (ADME) characteristics in non-clinical studies, from which extrapolation of potential pharmacokinetic/bioavailability profile in humans precludes further development.

Termination reason – Regulatory: Issues which stem directly from regulatory authority decisions (e.g. restricted labelling) or a change in the regulatory requirement(s) for this NAS i.e. "a shift in the regulatory hurdle" mean further development would not be feasible.

Termination reason – Toxicology: Identification of potential hazards (e.g. biochemistry, clinical chemistry, pathology) in non-clinical studies (in vitro and in vivo), conducted at any time during the development of the NAS which, when extrapolated to the potential risk to humans, precluded further development.

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CHAPTER ONE

GENERAL INTRODUCTION

BACKGROUND

Throughout the last two decades the global pharmaceutical industry, by any measure, has been one of the most successful and profitable industries, trading at a premium to the rest of the market (Kola and Landis, 2004). However, a decline in the number of new product launches concurrent with the exponential growth in research and development (R&D) investment observed in the late 1990s has led to questions about the sustainability of the industry. The key to the sustainability of the industry is the continuous development of new products with a combined value, in terms of sales generated, that is sufficient to satisfy stakeholders in terms of profitability and at the same time is able to support the R&D of future products. MacFarlane (1998) studied the industry's investment in R&D during the 1990s and concluded that although the industry had decreased R&D pipeline size in an attempt to increase R&D efficiency, there was still a sufficient number of active substances in development to result in an increase in the number of new molecular entities (NMEs) reaching the market.

However, since then many have voiced concerns about the increasing disparity between the investment made in pharmaceutical R&D and the output of this process in terms of the number of new products reaching the market. Table 1.1 provides an overview of various publications addressing the question of what output might be needed in order for the industry to live up to analyst and shareholder expectations in both the short and the long term. Opinions vary as to the size of the problem, partially due to the range of parameters used to address what has been labelled as the industry's 'productivity crisis'. Doogan (2003) concluded that a productivity gap existed since the mid 1990s, based solely on the number of new drug application (NDA) filings to the US Food and Drug Administration (FDA) relative to the number of investigational new drug (IND) filings received by the same organisation. Although the observed trend is a cause for concern, the approach taken unfortunately does not support any conclusions about productivity since no measure of output has been taken into account. Drews and Ryser (1996) studied the number of new chemical entity (NCE) launches achievable with the then current R&D processes, taking into account success rates, cycle times and cost. In the same study, an assessment

Table 1.1 Overview of studies assessing the difference between required and delivered industry output

Reference	Study focus	Observation	Assumptions/criteria
Drews and Ryser (1996) Drews (1998)	Number of NCEs achievable vs. number of NCEs required per year to sustain growth	Existing innovation base could not sustain current size of the industry, since the level of investment was insufficient to produce 1 NCE per company per year	Average annual sales per product: US$ 400Mn
Arlington (1999)	Number of NCEs required per year to sustain growth	To achieve 7% annual growth, companies would have to produce four to six times more new medicines between 1999 and 2005 than the number produced at the time	Based on new products earning between US$ 1bn and US$ 1.45bn during this seven-year period
Horrobin (2000)	Number of new product launches required per year to sustain growth	To sustain average growth, companies would have to introduce one new product each year for every 1-1.5% of the company's share of the world pharmaceutical market; e.g. a company the size of GSK would require an annual output of three to seven products of average sales value	Based on new products generating on average US$ 300Mn sales per year. The average expected growth incorporated in the calculation was not quantified in this article
Banerjee *et al.* (2001)	Number of NCEs required per year to sustain growth	Medium sized companies (annual pharmaceutical sales ~US$ 8bn) would have to produce at least one NCE per year to sustain 4% annual growth. Larger companies (annual pharmaceutical sales ~US$ 15bn) must average three significant launches per year to sustain similar growth levels	Significant launch is defined as the launch of a product generating revenue in excess of US$300Mn
Ansell (2003)	Number of new product launches required per year to sustain growth rate	To maintain their market share, companies would need to achieve one new product launch per two years for every percentage point of the global market	Based on 'average product size'; according to the author, the exact size was irrelevant for the applied method
Doogan (2003)	Industry yield: number of NDA filings relative to number of IND filings	Declining industry yield, expressed as the annual number of NDA filings compared to the annual number of IND filings to the US FDA	-

was made of the annual number of average-sized NCEs required to sustain several scenarios for growth (Table 1.1), ranging from -15% to +20% growth in pharmaceutical sales. They concluded that with the existing R&D investment and processes even a situation of no growth could not be maintained. In more recent studies, similar approaches have been applied (Arlington, 1999; Horrobin, 2000), demonstrating that the industry would have to achieve more new product launches yearly than it did at the time of the study. In 2001, Accenture assessed whether companies were able to achieve their target growth rates. Even though these were below the double-digit growth rates that the financial market had come to expect from previous performance, the requirement of three significant launches (i.e. generating revenue exceeding US$ 300Mn each) per company per year for the big pharma companies exceeds current industry performance (Banerjee *et al.*, 2001).

Causes for concern

Despite the varying opinions on the exact size of the problem, the consistent outcome of the studies (Table 1.1) is that in the near future it is unlikely that the industry will be able to produce sufficient output, both in terms of numbers and value, to deliver the growth that stakeholders have come to expect. A complex matrix of factors underpins the combination of increased R&D expenditure with the reduced number of new products reaching the market observed in the late 1990s (Booth and Zemmel, 2004). In broad terms, these factors can be grouped into three categories (Table 1.2):

1. Requirements imposed on the pharmaceutical industry (external factors);
2. Factors originating from the industry's ongoing quest for meeting unmet medical needs (innovation-driven factors);
3. Factors originating from the strategic direction pharmaceutical companies have taken (strategy-driven factors).

External factors

Governments around the world are faced with the challenge of dealing with ever growing healthcare expenditure within limited budgets. Every major European country has now introduced some sort of cost-containment measures, ranging from reference pricing to complex and lengthy reimbursement procedures, price

controls and profit controls (Lacetera and Orsenigo, 2001; Middleton, 2004). The consequences for the pharmaceutical industry of ongoing cost containment measures are two-fold. First of all, it increases the focus on developing cost-effective drug therapies, requiring the addition of pharmaco-economic aspects to the clinical studies (MacFarlane, 1998), resulting in longer development times and increased attrition. Secondly, it increases the competition in an already highly competitive market leading not only to a rise in marketing costs (Gilbert *et al.*, 2003), but also necessitating the expansion of clinical trials to demonstrate differential safety or efficacy of new medicines (Engel, 2000).

Table 1.2 Factors contributing to decline in industry output

External factors
□ Ongoing cost containment measures requiring demonstration of cost-effectiveness of drug treatments
□ Increased caution in regulatory environment
□ Increasing entrance barriers in certain therapeutic areas
□ Increasing difficulty in locating and recruiting patients
Innovation-driven factors
□ Greater emphasis on developing medicines for chronic and complex diseases
□ Implementation of new technologies
□ Pursuit of new, yet to be validated, targets
Strategy-driven factors
□ Ongoing industry consolidation
□ Focus on high value, i.e. economically viable products
□ Marketing strategy necessitating the expansion of clinical trials.

It has been speculated that following a number of high profile product withdrawals for safety reasons, such as Bayer's cholesterol lowering Baycol (cerivastatin) in 2001 and more recently Merck's arthritis treatment Vioxx (rofecoxib), regulatory authorities have become more cautious and are now demanding more extensive safety data (Shimmings, 2002; Anon, 2004a; Schulz, 2004; Walker, 2004). Although this has not been explicitly confirmed by the authorities, the fact that the FDA requested additional data for more than twenty products in 2001 does seem to support this theory (Shimmings, 2002). At the same time it has become harder to recruit and retain patients in studies (Bowden, 2001; Anon, 2004a), as demonstrated by the increasing proportion of patients recruited in countries other than the major pharmaceutical markets; in 2002 over 25% of patients were recruited in countries other than USA, UK,

Germany, France, Spain, Italy, Canada, Australia and Japan, compared to less than 5% in 1999 (Van den Haak *et al.*, 2003a).

Innovation-driven factors

To ensure that innovative products continue to be discovered and developed, the pharmaceutical industry must make use of technological advances such as computer aided drug design, molecular biology, high throughput systems and bioinformatics as well as explore new medical opportunities such as gene therapy and proteomics (MacFarlane, 1998; Tranter, 1999; Schmid and Smith, 2004). Utilisation of new technologies, such as molecular biology and combinatorial chemistry, has enabled blanket screening against single drug targets outside a cellular or organ system. Early signs of success of this approach have become evident in products like Novartis' Gleevec, which was found via subset screening of kinase inhibitors (Capdeville *et al.*, 2002; Schmid and Smith, 2004). However, the implementation of new technologies does not only require capital investment, it will also slow down R&D in the short term as experience is being gained (Firn, 2002; Powell, 2004; Schmid and Smith, 2004). The increasing focus of development on new, less validated targets is illustrated by data from Booth and Zemmel (2004), who reported that for targets in development in 1999 the average number of academic literature citations per target was only eight, compared with 100 for targets in development in 1990. Also, concerns have been expressed that development of applied sciences has lagged behind the rapid developments seen in basic and exploratory research, thus limiting the potential benefits of advancements made in discovery (Banerjee *et al.*, 2004; Charles River Associates, 2004).

For every new product that is launched onto the market, the barrier for subsequent market entry increases; the new product will need to be an improvement in terms of safety, efficacy or convenience (e.g. leading to improved patient compliance). This problem can be overcome by focusing the R&D effort on diseases for which limited or no treatment exist currently. However, these are often chronic diseases with complex pathophysiology and difficult outcome measures, requiring longer, larger and more costly clinical trials (Anon, 2004a; De Visser, 2003). Additionally, this may require

identification and validation of new targets thus increasing the duration, cost and risk of drug discovery (Doogan, 2003; Walker, 2004).

Strategy-driven factors

Some contend that consolidation in the industry could be partly to blame for the decline in industry output, as companies struggle to focus multi-billion dollar R&D budgets on the most promising compounds (Firn, 2002; Jung, 2002; Charles River Associates, 2004). The reduction in combined pipeline size that is often the result of mergers or acquisitions is another way in which consolidation might negatively affect the number of new product launches (Anon, 2003a; Walker, 2004). For example, when Pfizer merged with Warner-Lambert, it involved the divestment of all Pfizer's assets relating to the epidermal growth factor receptor tyrosine kinase inhibitor, CP-358 774, since Pfizer and Warner-Lambert were both working on these types of oncology treatments, among a relatively small number of companies. The proposed merger was likely to create anti-competitive effects in this market and the divestment of Pfizer's activities was required to satisfy authorities that no monopoly position would be created (FTC, 2000).

The output of the pharmaceutical industry is not only determined by the number of new product launches; the commercial value is as important. The most recent calculations of returns on pharmaceutical R&D from the Department of Economics at Duke University (based on 118 new products introduced onto the US market between 1990 and 1994) indicate that only one in three new drug introductions is likely to recoup its investments (Grabowski *et al.*, 2002). It is therefore not surprising that the predicted commercial value plays an important role in the decision-making process, to such extent that some companies have a policy of not investing in the development of any medicine for which market research indicates future annual sales of less than £ 300Mn (Horrobin, 2000). Although these policies are put in place in an attempt to maximise the value of the industry's output, it could have a negative effect on the number of products reaching the market.

Increasing clinical workload?

Many of the afore-mentioned developments have contributed to an increase in the complexity and sophistication of the pharmaceutical R&D process, which is believed to have resulted in the expansion of the workload per clinical candidate (Arlington, 1999; McAuslane and Anderson, 2003). However, the reality of this perception remains to be proven, with conflicting information available on the subject. Giorgianni *et al.* (1997) reported that the number of clinical trials per new drug application had doubled between the late 1970s and the early 1990s and that the number of patients per clinical trial had nearly tripled over this period of time. Engel (1999; 2000) reported that at the end of the 20th century, new medicines underwent an average of 64 trials before being submitted for regulatory review. Each new drug application at that point in time required on average more than 4200 patients compared to over 3500 patients ten years earlier. However, the latest data from CMR International demonstrated a decline in the median number of subjects per dossier between 1995 and 2003 (McAuslane and Anderson, 2003). On the other hand, data compiled by DataEdge (Parexel, 2002) indicate a significant increase in the complexity of clinical trials during the 1990s. Their index of clinical trial complexity for Phases I-III, based on the mean number of medical procedures applied to patients in clinical protocols, increased at an annual rate of 4.8% from 1992 to 2000 (in: DiMasi *et al.*, 2003).

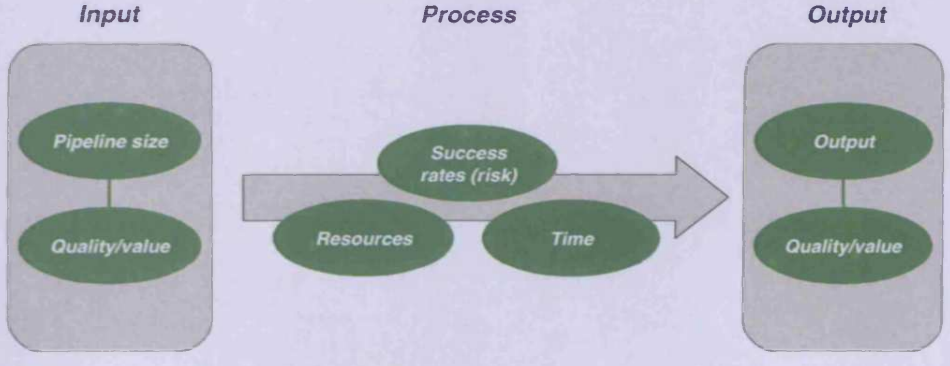
Can the growth continue?

Despite the declining number of new product launches, the pharmaceutical industry has continued to achieve growth in terms of sales generated throughout the 1990s (MacFarlane, 1998; Walton, 2000). However, by the end of 1999, the industry faced the expiration of 50 patents between 1999 and the end of 2005 (Engel, 1999; Beynon, 2000), adding to the pressures of delivering new products, to make up for loss of income due to generic competition for those coming off patent. In 2005 alone, 32 medicines are due to loose patent protection with a combined estimated revenue loss of US$ 38bn (Flemming and Ma, 2002). So what can companies do to improve the productivity of their R&D programmes?

DEFINING PRODUCTIVITY

Productivity has generally been defined as a ratio to measure how well an organisation (or individual, industry, country) converts input resources (labour, materials, machines, etc.) into goods and services. This is usually expressed in ratios of inputs to outputs: cost (input) per unit of goods or service (output). Productivity is not on its own a measure of the efficiency of the conversion process. However, more efficient processes will contribute to a greater productivity. The measure of output should take into account both quantity and quality of the products delivered. In more general terms, in order for a process to be productive it needs to efficiently produce goods or services of high value (Figure 1.1). Therefore, productivity contains both measures of operational efficiency (e.g. number of studies conducted per resources consumed) as well as measures of value generation (CMR International, 2002a; Anon, 2003b; Accell Team, 2004). As such, increasing productivity of pharmaceutical R&D requires improvements to be made in both the efficiency of the R&D process as well as the value of its output (Figure 1.2).

Figure 1.1 Pharmaceutical R&D productivity

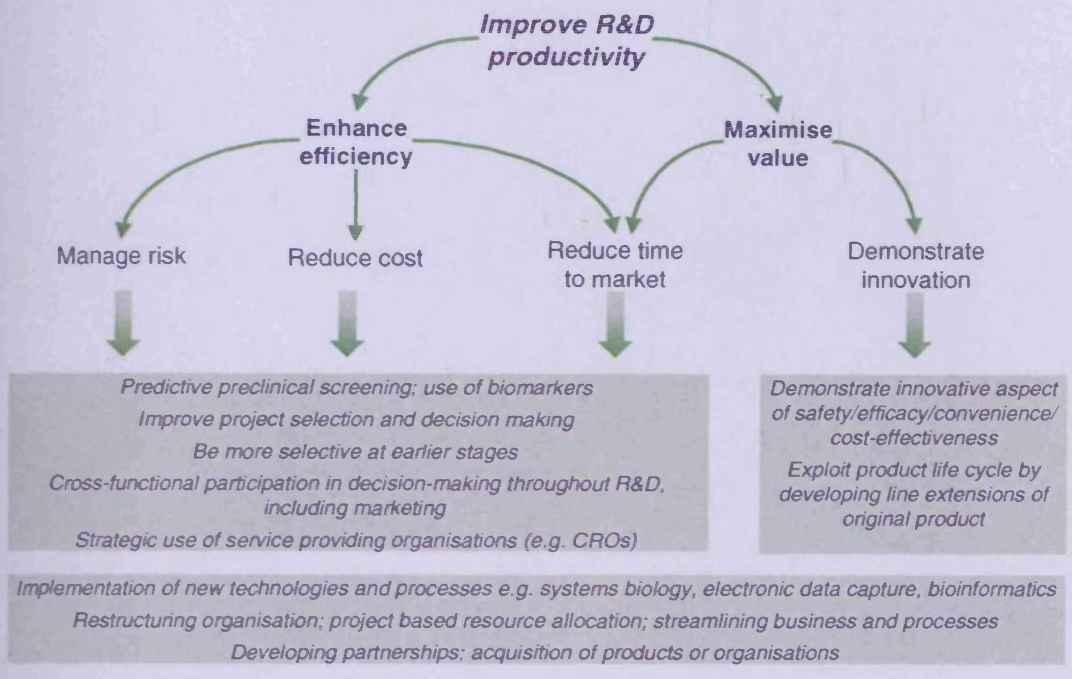


Measuring efficiency

Operational efficiency is a measure of how much output (number of new product launches) can be generated per unit input (e.g. $) and differs from productivity by not taking into account any quality aspect of input or output. Factors contributing to efficiency are speed, attrition and process quality. Success rates and cycle times, both for individual phases as well as for the overall R&D process, are relatively easy to measure for the assessment of speed and attrition. Additional measures could include the number of clinical

candidates and resources used. Process quality is more complex and therefore less straightforward to assess. Potential measures could include the number of, and reasons for, late-stage terminations, focusing on the question whether any of these failures could have been identified earlier.

Figure 1.2 Approaches to productivity improvement



Various components of efficiency

Speed, i.e. the time to market, can be optimised by accelerating individual activities such as clinical trials as well as by limiting the time between activities ("white space"; DiMasi, 2002). This might be achieved by increased internal collaboration and communication between functions as well as portfolio management which incorporates both research and discovery activities. At any point in time, the speed with which R&D is undertaken needs to be balanced against the quality of the work undertaken. Having to redo activities due to mistakes made earlier will not only delay the time to market, it will also have consequences for the cost. Therefore, speed needs to be optimised, not maximised, and should never be the sole driver of the R&D programme. Another metric that is of influence on efficiency is attrition. Fast advancement of an active substance to the next R&D phase might appear to be efficient, but with the relatively higher costs of later phases (US$ 86Mn for Phase III vs. US$ 15Mn for Phase I; DiMasi *et al.*, 2003) the accumulated cost of a product

failing during late-stage development would dramatically decrease overall efficiency, and thereby productivity. DiMasi (2002) estimated that shifting 5% of all clinical failures from Phase III/regulatory review to earlier phases could lower clinical costs by as much as US$ 29Mn. Even more cost-savings could be achieved through increasing overall clinical success rates. Increasing success rates from one in five (DiMasi, 2001a) to one in three clinical candidates receiving marketing authorisation could reduce total costs by US$ 221 – 242 Mn (DiMasi, 2002).

Improving R&D efficiency

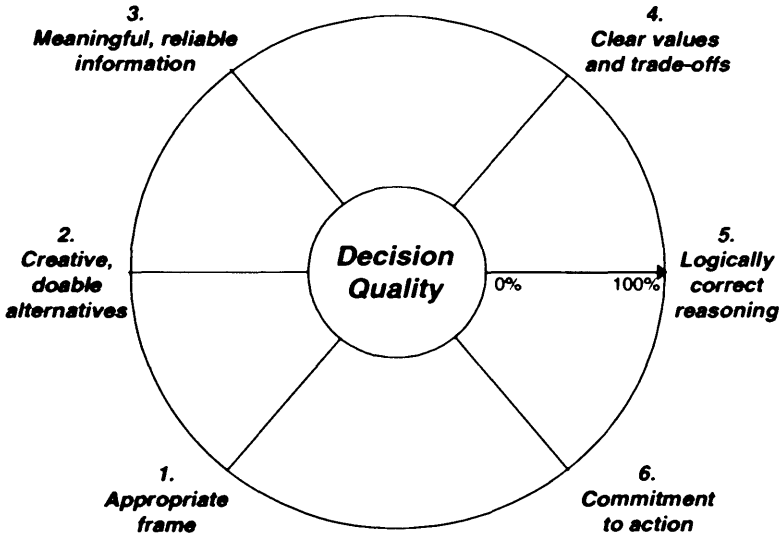
R&D efficiency can be improved by expanding the quantity of output produced per unit of input, which can be achieved by decreasing input (e.g. reducing cost) and/or increasing output. The many factors involved in pharmaceutical R&D as well as technological advances made over the last decades offer companies a variety of opportunities to improve the efficiency of their processes. For example the internet offers ample opportunities, not just in the application of new technologies such as electronic data management in both discovery and development, but it also offers organisations a completely new way of doing business (Fletcher, 2000). For example, electronic data capture has the capability of accelerating data processing as well as making this more cost-effective since it lifts geographical restrictions enabling off-shoring of activities such as clinical trial data management (Arlington, 1999; Anon, 2004; Baker and Gill, 2005).

Risk management

The pharmaceutical industry is characterised by long development times and high attrition compared to other industries. Effective risk management, through improved project selection and decision making, could increase efficiency considerably (Bilyard and Hennessy, 1994). The focus point for this should be the timely identification of unpromising projects, requiring early indicators of the potential efficacy, safety and commercial value of the development projects (Arlington, 1999; Tufts CSDD, 2003; King and Engel, 2004). The development of preclinical studies with better predictive value and the use of biomarkers will help in this (DiMasi, 2001a; Lindon, 2003; Schmid and Smith, 2004). Similarly

important is the involvement of all functions, including marketing, in decision-making throughout the R&D life cycle to ensure that all efforts are geared towards the research and discovery of high quality and economically viable drug targets and active substances (Lam, 2004a; Schmid and Smith, 2004). Lam (2004a) also suggested that an efficient decision-making process could be obtained through formalisation, using decision tools that force the application of formal reasoning, impose order and make assumptions explicit, such as the decision-quality spider diagram as described by Matheson and Matheson (1998). The spider diagram helps to rate a decision on each of the six dimensions defined, which together summarise the quality of a decision (Figure 1.3).

Figure 1.3 Decision quality spider diagram



Source: Matheson and Matheson, 1998

Partnerships and alliances

One of the possibilities available to pharmaceutical companies to improve all aspects of R&D efficiency, i.e. limit cost, manage risk and reduce the time to market, is through partnerships with other organisations. These partnerships can take many forms, for example research collaborations with academic centres, joint ventures with other pharmaceutical firms or biotech companies, the strategic use of service providing organisations such as contract research organisations and licensing agreements. Through these partnerships, companies are able to share both risk and cost as well as make use of external

expertise not available within the organisation itself (Arlington, 1999; Engel, 2001; Fumero, 2002; Anon, 2004a; Lam, 2004a).

Organisational structure

More extreme suggestions to improve R&D efficiency, and thereby productivity, include restructuring the organisation into competing smaller units, project-based resource allocation and streamlining processes, such as support functions. Additional suggestions include streamlining the whole organisation by spinning off complete business units (e.g. veterinary health or over-the-counter (OTC) products) and reducing the number of therapeutic areas in which the organisation is active. This would allow the company to focus on a smaller number of activities, building expertise and knowledge in these areas (Arlington, 1999; Liu, 2000; Truelove, 2003); Hunter, 2004). Bristol-Myers Squibb is one of the companies who have indicated a desire to concentrate its product development efforts; it has agreed to sell its oncology therapeutics network unit to One Equity Partners and is currently in talks with several interested parties over the sale of certain OTC products (Anon, 2005). Similarly, Roche has indicated that it has dispensed with its OTC unit in a bid to focus on ethical pharmaceuticals (Anon, 2004c; Anon, 2004d).

Measuring value

The ultimate measure of value is the level of annual sales and profit generated. However, this information will not be known until a product has reached peak sales. Traditionally, this was taken to be around six years after first product launch (Ansell, 2003); an underestimate of real longevity according to Ansell (2000). Based on the Top 50 global pharmaceutical products in 1998, he estimated that peak sales are achieved on average 14 years after a product reaches the market (Ansell, 2000). However, it is likely that this has changed in the last few years, with more intensive marketing in an attempt to achieve peak sales earlier. When adding the time to reach peak sales to the average development time from first synthesis to first launch (12 years; DiMasi *et al.*, 2003) it becomes apparent that the real productivity of current R&D processes and strategies will not be known until 20-25 years from now. Moreover, this parameter is not determined by R&D effort alone since it is also influenced by

characteristics such as price, size of the market, competition and the marketing effort and expertise of the individual company.

Interim value measures

Interim measures of value would therefore be desirable. Many companies estimate peak sale values of products currently in development as a marker of future commercial value. However, it is generally recognised that these values are more speculation than fact, especially for projects in early development since they are based on an assessment of the market in which the future product is to be launched and on information on its potential safety and efficacy profile. In early development, information on the latter is not yet available and the long development times mean there are many uncertainties about the future market place. Due to the high speculation factor, companies treat these estimates merely as indicative in these early stages rather than truly representative of the potential value (CMR International, 2002b). In today's climate of increasing cost containment measures it is becoming more and more apparent that only products offering advantages over and above existing treatments can command premium prices, and thereby generate high revenues. Drews and Ryser (1996) indicated that these advantages should be looked at as new therapeutic possibilities that can prolong life, save lives or increase the quality of life in an objective measurable way or provide therapy equivalent to what is currently available at substantial lower costs and/or with a better safety profile. In short, for new products innovation needs to be demonstrated in one or more of the four areas of safety, efficacy, convenience and cost-effectiveness (Schmid and Smith, 2004). With the level of innovation critical to commercial success, examining the innovative capacity of the pharmaceutical industry could provide an early indicator as to the value aspect of R&D productivity.

Assessing innovation

There are different levels at which innovation can be assessed, e.g. for individual companies, products or countries. In order to be able to use innovation as an early indicator of value and thereby of productivity, an assessment of innovation at the product level is required. The different measures of product innovation can be split into two categories (Table 1.3).

Determinants of innovation form the first category, referring to novelty of characteristics inherent to the product such as chemical structure or route of administration. However, although innovative, these characteristics do not justify an increased value as such. In order to do so, the observed determinant(s) will need to result in a demonstration of innovation (second category), i.e. improved safety, efficacy, convenience or cost-effectiveness (adapted from MacFarlane, 1998).

Table 1.3 Factors used in assessing innovation

Determinants of innovation *(inherent characteristic)*	Demonstration of innovation *(action of product)*
Chemical structure	Improved efficacy profile
Dosing	Improved safety profile
Duration & offset of action	Improved convenience profile
Formulation	Socio-economic impact
Pharmacological action	
Route of administration	
Therapeutic profile	

Adapted from MacFarlane (1998)

Innovation can be achieved in many ways. As chemical structure is only one of the determinants, innovation is not limited to new active substances; line extensions of existing products should not necessarily be regarded as non-innovative. Similarly, a new class of drugs can only be considered innovative if the differential pharmacological mode of action results in an improvement in one or more of the four demonstrators of innovation (Fumero, 2002). The value aspect of R&D productivity can therefore be improved by the development of products, including line extensions, with one or more innovative characteristics resulting in the demonstration of innovation through an improved safety, efficacy and/or convenience profile or through increased cost-effectiveness compared to available treatments. The power of exploiting the life cycle of an active substance is evidenced by the fact that despite the concomitant decline in the number of new product launches, the growth rate for the Top 50 medicines in every single year between 1994 and 2000 exceeded that of the total market (McCarthy, 2001). However, a continuous output of new active substances will be required to feed life cycle management processes.

Approaches that companies can apply to increase product innovation include

the use of new technologies in the identification of drug targets and (pre)clinical candidates in their in-house discovery function. However, although beneficial in the long-term, this could be a very costly and time-consuming process in more immediate years as time is needed to build internal expertise. Making use of external expertise and knowledge by entering into collaborative partnerships with academic and other research organisations is a more cost-effective way of extending a company's research capability (Fumero, 2002; Tufts CSDD, 2003).

Relationship between efficiency and value

Value and efficiency cannot be assessed in isolation. Indirectly, efficiency can contribute to the value of the product. A reduction of a month in the time to market translates directly into a month's extra effective patent life (MacFarlane, 1998). Furthermore, lengthening development times could also increase risk by allowing more time for external factors, such as the launch of a competitor product or to change the commercial outlook of the product under development. In addition to improving productivity, an increase in industry output could in theory be achieved by increasing input, e.g. taking more candidates into clinical development. Traditionally, this has been described as increasing productivity, but since this does not aim to improve the ratio of output over input, technically it can not be classified as a productivity improvement. However, it is an opportunity to increase output although the high investment levels required to cope with the capacity extension involved might make this a less desirable alternative.

Due to lengthy development times the current deficit in the number of new product launches is derived from strategies set 10-20 years ago, the science base and the investments made at that time (Schmid and Smith, 2004; Gilbert *et al.*, 2003), suggesting that the output of the industry today is an indication of the productivity of the R&D process as it was over a decade ago. As such, the effectiveness of the actions taken by the industry today to improve pharmaceutical R&D productivity and thereby increase the quantity and quality of its output will not be known until many years from now. However, having established that the output of the pharmaceutical R&D process is a product of capacity (i.e. the number of drug targets and candidates in development), cycle

times, risk, investment and value, studying these parameters will provide insight into the potential of today's pharmaceutical R&D programmes. Furthermore, examining R&D expenditure patterns could reveal to what extent the suggested approaches for improving output have already been implemented.

AIMS OF STUDY

The aim of this study is to investigate the efficiency of the pharmaceutical industry in meeting the innovation and marketing challenges of the 21st century. The following objectives have been identified in order to achieve this:

- To determine whether the trends of declining output and increasing R&D investment observed for the 1990s have continued into the 21st century and to investigate the reasons underlying these trends.

- To assess and validate the potential of current R&D practices to produce new ethical pharmaceuticals and to simulate the effect of improvements in success rates, cycle times and development capacity, in order to identify where companies can best focus their efforts to increase R&D productivity.

- To identify which measures have been implemented by the industry to improve its R&D productivity through the study of the current development pipeline and R&D expenditure patterns.

- To ascertain patterns in the reasons for, and timing of, drug development failures in order to review their impact on R&D and to make suggestions as to how future risk management can be improved.

- To investigate the impact of company strategy with regards to attrition on the efficiency and productivity of their development function and to discuss whether a one-size-fits-all strategy exists and what this might look like.

CHAPTER TWO

STUDY RATIONALE AND METHODOLOGICAL FRAMEWORK

STUDY RATIONALE

Chapter one described how success of the pharmaceutical industry both directly and indirectly depends on the continuous output of novel products. Directly, new product launches contribute to the sales generated and thereby to profit and viability of a company. Indirectly, a new product can form the basis for further development activities, e.g. for new indications or for incorporation in novel drug delivery systems or combination products. It was established that the output of the pharmaceutical research and development (R&D) process is a product of:

- Pipeline volume, in terms of the number of new active substances (NASs) in development;
- Development times;
- Risk, quantifiable as the probability of success to market;
- Investment in research and development, both in monetary terms as well as in terms of people;
- Commercial value.

It has been found that there is a lack of comparable published information at the international level on these parameters. Therefore, it is proposed that information be collected from the international pharmaceutical industry to:

- Provide insight into recent developments for the above five parameters;
- Assess whether the current R&D effort is sufficient to sustain a profitable industry;
- Ascertain patterns in the reason and timing of drug development failures in order to improve future decision-making and risk management;
- Assess the impact of companies' approach to attrition on the efficiency of their development function.

The aim of this thesis is to evaluate the sustainability and efficiency of the international pharmaceutical industry in its current state in the 21st century.

METHODOLOGICAL FRAMEWORK

Study design

When considering the sample from which information will be collected, namely global pharmaceutical companies and regulatory authorities located world-wide, together with the confidential nature of data that will be gathered, it was decided that the most appropriate technique for the research of this thesis would be the use of surveys.

Surveys offer the opportunity to make inferences about a population in as objective a way as possible (Anon, 2000a). Several different survey types exist depending on the approach used and the overall objective: snap-shot, baseline, longitudinal and comparative surveys. Snap-shot surveys constitute a point-in-time to give a representative picture of the status quo. They can also be used as a baseline survey to provide a "before" picture that can be later compared to an "after" picture to assess impact or change. If the same population is used to provide the "after" picture, this is known as a longitudinal survey and may be repeated over a lengthy period. Surveys that compare two similar subgroups are referred to as comparative surveys (Anon, 2000a). In order to achieve the objectives of this study, examination of trends over time within the pharmaceutical industry is required. Therefore longitudinal surveys will be used in this study.

There are a number of strengths and weaknesses of surveys (Walonick, 1997; McNamara, 1999; Anon, 2000a; Trochim, 2002a and 2002b). Advantages include the:

- Opportunity for anonymous or confidential participation;
- Comparatively low administration cost;
- Ability to administer to multiple participants;
- Ease with which information can be compared and analysed;
- Quantity and breadth of data that can be generated;
- Reduction of bias due to structured format of questions.

Some of the challenges of surveys include ensuring:

- Informative feedback;
- Questions that do not bias response;
- Ideas of the outputs and deliverables are predetermined and agreed.

Data collection

Data collection techniques

Having decided to use a survey approach, there are two possible techniques that may be used to collect data: questionnaires or interviews. A key difference between these two is that the respondent completes questionnaires directly whereas interview surveys are completed by the interviewer based on the respondent's verbal answers. Given the logistics of these two options and considering the time, cost and purpose of the survey; the questionnaire technique is preferable as it is useful in determining the *status quo*. Questionnaires are also more appropriate when collecting a high volume of data. A further complication to bear in mind is that some of the information required may be located across multiple geographical sites from several personnel. It is unlikely that all information needed for this research will be found in a central system that would enable simple data extraction for this study. There are a number of advantages in using questionnaires (McNamara, 1999; Trochim, 2002a): they are easy to distribute; are a good method for identifying what and where the problems are; and enable suggestions to be offered. The population sample selected for this study is familiar with questionnaire techniques and this will facilitate the ease with which the research will be conducted. Some of the disadvantages of using questionnaires include the knowledge, time and effort involved. They can be deceptively difficult to develop as they must be written to avoid ambiguity and often require a piloting stage to test applicability, practicality and content validity prior to the actual field study.

Data collection methods

There are a number of methods available for collecting data using the survey questionnaire technique. Several factors should be borne in mind when selecting the most appropriate method including the type and size of population

being studied, timelines, budget, resources and purpose of the study (Diem, 2002a).

Paper or electronic mail-delivered

This method uses a printed questionnaire that is mailed to the participant and allows them to respond at their convenience before returning the survey via mail or fax. Alternatively e-mail can be used to deliver a questionnaire that may be either completed electronically and returned via e-mail or may be printed and returned by mail or fax. *Strengths* - The strengths of this method are that it requires minimum resource to prepare; enables privacy of responses and is relatively inexpensive, particularly if using e-mail. *Limitations* - Some of its limitations are that it does take time and requires follow-up to obtain responses. It can also be difficult to judge the quality of responses and to obtain accurate mailing lists or e-mail addresses and may risk being buried among unwanted "junk" mail (Walonick, 1997; McNamara, 1999; Diem, 2002a; Trochim, 2002b).

Group-administered

A group-administered approach involves gathering a group of respondents together, administering the questionnaires and asking the group to complete them individually. *Strengths* - The strengths of this method are that it ensures a high response rate from those administered with the questionnaire and it enables a full explanation of the study to be given with the opportunity for questions and discussions after completion. It also improves the quality of responses (i.e. if respondents are unclear about the meaning of a question then the researcher can clarify issues). *Limitations* - Some of the limitations of this method are that time is limited for respondents to formulate their answers and the total turnaround time can be slow (Trochim, 2002b).

Telephone-administered

Data can be collected by conducting interviews by telephone, typically spontaneously (as perceived by the respondent), although it can be done through scheduling an appointment. It may also be possible to use an automated system where users reply via touch-tone telephone to a computer-based interview system. *Strengths* - Some of the strengths of this method are its rapid response and that it can be inexpensive if calling locally. *Limitations* -

Some of the limitations of this method include access limitations from answer machines, reliance on correct numbers, the difficulty of locating and contacting people and instantaneous credibility of the caller being established in order to complete the call. Time zones and language can also be a barrier (Walonick, 1997; Diem, 2002a; Trochim, 2002b)

Web-based

Questionnaires can be posted on a web site to be completed by respondents, typically remotely from individual computers. *Strengths* - The strengths of this method are that it enables a quick and easy response and that it can be inexpensive if the correct facilities and tools are available. *Limitations* - One of its limitations is its reliance on respondents having web access (Diem, 2002a).

Information sources

Information will be sought from global pharmaceutical R&D companies. The aim is to solicit a response rate such that the cohort of participating companies is considered representative of the global pharmaceutical industry by representing the majority of the international pharmaceutical R&D effort in terms of expenditure (i.e. representing 50% or more of global ethical pharmaceutical R&D expenditure). Table 2.1 provides an overview of all companies that will be approached with data provision requests. Where reliable and comparable data can be obtained from existing data sources, this will be used to decrease the burden of data provision without compromising data quality.

Study data collection procedure

Using mail delivered questionnaires to collect data enables confidentiality and anonymity if required. A name or identifier is used to follow-up between the researcher and responder and may also be used to match and compare data from a pre- or post-study. Anonymous procedures do not enable follow-up or direct comparisons with pre- or post-studies (Diem, 2002b). For this reason confidential procedures will be used for each of the questionnaire surveys included in this research, and data will be aggregated to avoid identification of individual respondents.

Table 2.1 Companies approached with data provision requests

Abbott Laboratories	Human Genome Sciences	Purdue Pharma
Alcon Laboratories	ICOS	QLT Photo Therapeutics Inc
Allergan	Immunex Corporation	Quadrant Healthcare Ltd
Almirall-Prodesfarma	J Uriach & Co Ltd	Recordati SpA
Altana	Japan Tabacco	F Hoffman-La Roche
Amersham Plc	Johnson & Johnson	Sangstat Medical Corporation
Amgen	Kaken Pharmaceutical Co Ltd	Sankyo
AMRAD Corporation	Kissei Pharmaceutical Co Ltd	Sanofi-Synthelabo
AstraZeneca Pharmaceuticals	Kyowa Hakko Kyogo Co. Ltd	Santen Pharmaceutical Co Ltd
Aventis	Leo Pharmaceuticals	Schering AG
Bayer AG	Ligand Pharmaceuticals	Schering Plough
Biogen Inc.	Lundbeck A/S	Schwarz Pharmaceuticals
Boehringer Ingelheim	Mallinckrodt Group Inc	Serono Group
Bristol Meyers Squibb	MedImmune	Servier
Centocor	Meiji Seika Kaisha Ltd	Shionogi
Cephalon	Menarini Pharmaceutical Ind Grp Ltd	Sigma-Tau
Chiron	Merck & Co	Solvay Pharmaceuticals
Chugai	Merck KgaA	Sumitomo Pharmaceuticals Co Ltd
Daiichi Pharmaceutical Co. Ltd	Millennium Pharmaceuticals	Taisho Pharmaceutical Co Ltd
Dainippon Pharmaceutical Co Ltd	Mitsubishi Pharma Corporation	Takeda Chemical Industries Ltd
Degussa	Mochida Pharmaceutical Co Ltd	Tanabe Seiyaku Co Ltd
Eisai Co Ltd	Mylan Laboratories	TAP Pharmaceuticals
Elan Pharma	Nippon Shinyaku Co Ltd	Teijin Ltd
Eli Lilly	Novartis	TEVA Pharmaceutical Industries Ltd
Entremed Inc.	Novo Nordisk A/S	Toray Industries
Esteve	NV Organon	Toyama Chemical Co Ltd
Ferring Pharmaceuticals	Ono Pharmaceutical Co Ltd	Tsumura
Fournier Pharma Inc.	Orion Corporation	UCB Pharma
Fujisawa Pharmaceutical Co Ltd	Otsuka Pharmaceutical Co Ltd	Vernalis
Genentech Inc	Pfizer	Vertex Pharmaceuticals Inc
Genzyme Corporation	Pharmacia	Wyeth
Gilead Sciences Inc	Pierre Fabre	Yamanouchi Pharmaceutical Co Ltd
GlaxoSmithKline	Procter & Gamble	
Guilford Pharmaceuticals		

Company grouping on 31st December 2002

Study instruments

For this study, data will be collected annually by means of three longitudinal surveys. Instead of developing new survey tools, existing questionnaires will be used to collect data directly from the pharmaceutical industry on international R&D expenditure and sales, new molecular entity launches and the global ethical development pipeline. The decision to use existing questionnaires was driven by companies' familiarity with these questionnaires, reducing the burden of data collection, increasing the consistency and thereby quality of the data and allowing comparison with historical data. Furthermore, definitions underlying these questionnaires have been developed in collaboration with the pharmaceutical industry and are well-established, ensuring collection of available and meaningful data and to encourage consistent responses across companies and across years (MacInnes *et al.*, 1992; MacFarlane *et al.*, 1997; Ashton *et al.*, 1998).

The content of each questionnaire will be reviewed annually to ensure up-to-date and relevant information is collected to address the study's objectives. In response to changes in the industry and respondent's feedback questions will be added, amended or deleted. At any time, the need for changes to the questionnaire content will be balanced against the need for continuity of the data collected to enable trend analyses. All three surveys will focus on information relating to ethical pharmaceuticals excluding any additional activities such as veterinary medicines or over-the-counter products.

Survey tool I - International pharmaceutical R&D expenditure and sales

This survey (Appendix I and Appendix II) will be used to annually collect detailed information from pharmaceutical companies on their international pharmaceutical R&D expenditure and sales, including:

- Global R&D expenditure, R&D full-time equivalents (FTEs) and sales;
- A breakdown of global R&D expenditure by function, stage, product type and therapeutic area;
- External expenditure, including expenditure allocated to outsourcing and alliances;
- Proportion of sales derived from recently launched products and the top-three selling products;
- A breakdown of global figures by geographical region.

Information collected through this survey will be used to examine expenditure patterns as early indicators of R&D focus as well as investigating companies' vulnerability to loss of income due to generic competition.

Survey tool II - New active substance activities: submission; authorisation and marketing

This survey (Appendix III and Appendix IV) will be used to annually collect details of new molecular entities (NMEs) introduced onto the world market, such as generic name, the pharmacological mode of action, compound type, indication, date of first synthesis and first world marketing date, country and brand name. The second section of the questionnaire contains questions relating to NAS submission, authorisation and marketing activities in the major pharmaceutical markets (18 European countries, USA, Japan, Canada and

Australia). Intended participants for this survey will be multinational pharmaceutical R&D companies. Information collected in this survey will be used to study trends in the quality and quantity of NMEs reaching the world market, as well as the number of regulatory activities in the major pharmaceutical markets as an indicator of the number of new products reaching the market in the near future.

Survey tool III - The global ethical pharmaceutical development pipeline

This survey (Appendix VI) will be used to annually collect detailed information from pharmaceutical companies on preclinical and clinical NAS development activities, requesting characteristics and milestone information for all NASs in development, including:

- Pharmacological mode of action and intended indication;
- Compound type (e.g. biotech or chemical entity);
- Origin of the active substance;
- Key milestone dates;
- Date and reason for termination.

Data collection will be limited to NASs only and as such will exclude development activities for line extensions. The information collected will be used to examine trends and developments in size and composition of the global development pipeline, success rates and the timing of and reason for clinical development failures.

Psychometric evaluation of the study questionnaires

Validation

Goldstein and Zedeck (1985) define validity as "...the most important consideration in test evaluation. The concept refers to the appropriateness, meaningfulness, and usefulness of the specific inferences from the test scores. Test validation is the process of accumulating evidence to support such inferences." Essentially, the concept of validity is whether or not an indicator/instrument measures what it claims it does and when investigating sensitivity issues this can be complex. There are a variety of methods by which validity can be assessed. The two methods most commonly used for assessing survey tools are content validity and criterion validity.

Content validity - Content validity assesses the extent to which questions (or items) in a survey tool serve to encompass the important facets of the notion the indicator is supposed to represent in a balanced way with the right emphasis. The weighting of the results are also reviewed within the set of indicators (Carmines and Zeller, 1991; Anon, 2001a).

Criterion validity - Criterion validity, also referred to as instrumental validity, assesses how the observed values of the indicator compare with another related measure. The aim is to correlate a new indicator with reference to a measure or procedure which has been demonstrated to be valid ('gold standard') (Anon, 2001a).

Reliability

Reliability refers to the extent to which an experiment, test or any measuring procedure yields the same result on repeated trials. In other words, reliability addresses the question 'is the survey tool measuring consistently?' Understanding the reliability of a questionnaire and, more importantly, its limits will assist the researcher in interpreting the data. Piloting or pre-testing of a questionnaire can help to optimise a survey's reliability. Key types of reliability include equivalence reliability and internal consistency (Palmquist, 2004).

Equivalence reliability - Equivalence reliability, also referred to as 'test/re-test', describes the extent to which two items measure identical concepts at an identical level of difficulty and is determined by relating two sets of test scores to one another to highlight the degree of association. A correlation coefficient, statistically referred to as *r*, is frequently used to show the strength of the correlation. An important consideration is that equivalence reliability is concerned with correlational, not causal, relationships.

Internal consistency - Internal consistency is the extent to which a questionnaire assesses the same characteristic, skill or quality. This type of reliability supports interpretation of the data and prediction of the limits of the relationships among variables.

Study reliability and validity

Content validity will be tested for this study to ensure reliable quality data are collected. The use of existing, piloted questionnaires gives greater confidence that the questions are clear, feasible and unambiguous. Furthermore, respondents' previous experience with the questionnaire and its criteria and definitions will further enhance the reliability of the survey. Criterion validity will be tested by comparing the study outcomes with relevant, related studies (where available) and by assessing the findings within the context of related developments in the pharmaceutical industry.

Study data management

Data will be collected using electronic mail, postal mail and fax methods. Regardless of the delivery method, data will be transferred into Microsoft Access™ databases created and developed specifically for each survey. Data provided by means of a paper questionnaire will be entered into the main database manually, using an electronic form especially designed for this purpose. Every data point entered manually will be quality controlled by a second individual (Anon, 2000a). An electronic data transfer system will be developed and validated in Microsoft Access™ to migrate data from individual Excel™-based and Access™-based questionnaires into the main Access™ database. During data entry and migration, quality controls will be carried out to maintain integrity of the data (Anon, 2000a). Where doubt arises regarding the accuracy of the provided data, the company in question will be approached by e-mail or telephone for clarification.

Data processing and analysis

Data processing and analysis will be carried out using Microsoft Access™, Microsoft Excel™ and SPSS™. Descriptive statistics such as mean, median and ranges will be used where data are quantitative. Where data are qualitative, content analysis will be used to generate major themes.

Hypothesis testing

Hypothesis testing is essential to any part of statistical inference. To perform such a test a theory needs to be presented that is believed to be true or is to be

used as a basis for argument, but has not been proved. An example hypothesis could be the claim that a new drug is better than the current drug for treatment of the same symptoms (Easton and McColl, 2001). In each case, two competing hypotheses are assessed: the null hypothesis, denoted H0, and the alternative hypothesis, denoted H1. These two hypotheses are not treated on an equal basis as special consideration is given to the null hypothesis. This is due to the fact that the null hypothesis relates to the statement being tested, whereas the alternative hypothesis relates to the statement to be accepted if or when the null is rejected (Van Houwelingen *et al.*, 1995; Easton and McColl, 2001). Hypothesis testing will be used to:

- Evaluate international ethical pharmaceutical R&D expenditure and sales;
- Examine new molecular entities reaching the market;
- Evaluate the global ethical pharmaceutical development pipeline.

Evidence will be generated to test a series of hypotheses for each of these studies.

Statistical testing

A statistic is a quantity that is calculated from a sample of data used to give information about unknown values in the corresponding population. Statistical inferences make use of information from a sample to draw conclusions (inferences) about the population from which the sample was taken (Easton and McColl, 2001). Throughout this thesis a variety of statistical inferences will be made depending on the type of data being analysed. For example, much of the data for the evaluation of international ethical pharmaceutical R&D expenditure and sales, the examination of new molecular entities reaching the market and the evaluation of the ethical pharmaceutical development pipeline will be continuous. It will also be possible to categorise the continuous data according to characteristics, e.g. by therapeutic area. Therefore, most of these data will be presented in bar charts to illustrate key features in the distribution of the data. Where trends have been examined, line charts will be used to illustrate developments over time.

The sample mean will be used extensively for estimating the population mean (the "middle" value) as will the median (the value halfway through the ordered

data set, below and above which there lies an equal number of data values). Where applicable, ranges around the median and average will be shown to indicate the spread of the data. Scatter plots will be used to summarise data sets that are bivariate (two variables) to give a good visual picture of the relationship between the two variables. Box and whisker plots will be used on data sets measured on an interval scale to show the shape of the distribution, the central value, and variability. The picture produced consists of the most extreme values in the data set (5^{th} and 95^{th} percentile values), the lower and upper quartiles (25^{th} and 75^{th} percentile values), and the median. Occasionally, pie charts will be used for sets of categorical data where each segment represents a particular category and the area of each segment is proportional to the number of cases in that category (Easton and McColl, 2001). Kaplan-Meier survival plots will be used to investigate the time between two events. The Kaplan-Meier procedure is a method for estimating time-to-event models in the presence of censored cases and allows the calculation of mean and median survival time (Van Houwelingen *et al.*, 1995).

To compare growth over time for parameters with different value ranges, data will be presented as indexed graphs. Data will be indexed by setting the first value of a date range to 100 for all parameters included in the comparison. Subsequent values in the date range will then be calculated relative to the first value. Changes over time for individual companies will be presented as scatter plots, with data for year A in the analysis plotted on the X-axis and data for year B plotted on the Y-axis. A line will be plotted on these graphs to indicate the situation of no change. Company data points above this line will represent an increased value in year B compared to year A, whereas data points below this line will represent companies with lower values for year B than that year A.

Statistical tests

Several statistical tests will be used in this study, depending on the research question asked, the distribution of the data and the number and characteristics of the data set. For each analysis, the test used will be specified.

Regression

Regression analyses will be used to express the relationship between two (or more) variables algebraically. The regression equation indicates the nature of the relationship between two (or more) variables. In particular, it indicates the extent to which some variables can be predicted by knowing others, or the extent to which some are associated with others. A linear regression equation is usually written as $Y = a + bX + e$, where Y is the dependent variable, a is the intercept, b is the slope or regression coefficient, X is the independent variable (or covariate) and e is the error term (Easton and McColl, 2001).

Correlation

Correlation analyses can be used to show the strength of a relationship between two variables. A correlation coefficient, statistically referred to as r, is a number between -1 and 1 which measures the degree to which two variables are linearly related. If there is a perfect linear relationship with a positive slope between the two variables, the correlation coefficient equals +1. There is a positive correlation whenever one variable has a high value and so does the other, or vice versa. If there is a perfect linear relationship with negative slope between the two variables, the correlation coefficient equals -1. There is negative correlation, whenever one variable has a high value and the other has a low value, or vice versa. A correlation coefficient of 0 indicates that there is no linear relationship between the variables (Easton and McColl, 2001).

Chi-square test

The Chi-square test is performed on a two-way frequency table to test whether two variables can be considered statistically independent. This test does not make any assumptions about the distribution of the data and can therefore be used for both normally distributed data and data were no normal distribution can be demonstrated (Anon, 1997).

Mantel-Haenszel Chi-square test

The Mantel-Haenszel Chi-square test for trends, also known as linear-by-linear association, is a measure of linear association between the row and column variables in a cross-tabulation where both measures are at least ordinal (Becker, 2004).

Independent two-sample t-test

An independent two-sample t-test is used to determine whether there is a significant difference in the mean of data collected from two random samples of independent observations. This test assumes normal distribution of the data (Easton and McColl, 2001).

Paired two-sample t-test

A paired t-test is used to determine whether there is a significant difference between the average values of the same measurement made under two different conditions. Both measurements are made on each unit in a sample, and the test is based on the paired differences between these two values. The usual null hypothesis is that the difference in the mean values is zero. This test assumes normal distribution of the data (Easton and McColl, 2001).

Mann-Whitney U-test

The Mann-Whitney U-test is a non-parametric test used to test the difference between the medians of two independent samples (Crichton, 2000a; Easton and McColl, 2001).

Wilcoxon Signed Rank test

The Wilcoxon Signed Rank test is a non-parametric test used to test the median difference in paired data. This test is the non-parametric equivalent of the paired t-test (Crichton, 2000b; Easton and McColl, 2001)

Kruskal-Wallis test

The Kruskal-Wallis test is a nonparametric test used to compare three or more samples. It is used to test the null hypothesis that all populations have identical distribution functions against the alternative hypothesis that at least two of the samples differ only with respect to location (median), if at all. The outcome of this test will not be conclusive as to which of the samples differ. The Kruskal-Wallis test is a logical extension of the Mann-Whitney U-Test (Easton and McColl, 2001).

Log rank test

The log rank test will be used to test for differences between Kaplan-Meier

survival curves. This test tests the null hypothesis that the survival curves in two groups are the same. This method, based on the Chi-square test, should specifically be used in situations where censoring occurs (i.e. situations where survival time will not be achieved for all subjects, e.g. where patients drop out of clinical studies) (Van Houwelingen *et al.*, 1995); Anon, 2004e).

Repeated measures ANOVA

The repeated measures one-way analysis of variance (ANOVA) is used to compare three or more matched groups, based on the assumption that the differences between matched values are normally distributed. This test can be used to compare measurements of one population over time and is of particular use in analysing data from longitudinal surveys, such as those used in this study (Karpinski, 2004).

Friedman's test

The Friedman test is a nonparametric test that compares three or more groups. This test is an alternative for the repeated measures ANOVA when normal distribution can not be demonstrated (Anon, 1999a).

Methodologies for the assessment of success rates

In this study, success rates of the pharmaceutical development process will be assessed as a measure for risk in pharmaceutical R&D. In general, success rates are expressed as the number of successful NASs as a proportion of the number of successful and failed NASs. In order to calculate meaningful success rates, the selection of NASs to be included in the analysis as well as the definition of success and failure is critical (Spilker, 1994). There are three methodologies for calculating success rates for the pharmaceutical development process: (1) the 'entry' methodology, (2) the 'longitudinal' methodology and (3) the 'progression-decision' methodology.

Success rate methodologies

For the *'entry' methodology* the cohort of NASs included in the calculation are selected based on their date of entry into a phase. The fate of this cohort is then tracked to progression to the next phase, or to termination within phase. Using this methodology, success rates can be calculated for each phase of the

development process, which can subsequently be used to estimate the probability of success from the start of each phase to market.

For the *'longitudinal' methodology* the cohort of NASs to be included in the calculation are selected based on their date of entry into clinical development. The fate of this cohort of NASs is then tracked to market or to termination, thus calculating the actual success rates to market rather than the probability of success.

The *'progression-decision' methodology* is similar to the 'entry' methodology in the calculation of success rates for individual phases. The difference between the two methodologies can be found in the inclusion criteria. For the 'progression-decision' methodology the cohort of NASs included in the calculation are selected based on the date that they exited the phase (i.e. when the decision to progress or to terminate the NAS was made). An overview of the advantages and disadvantages of each of the three methodologies is provided in Table 2.2.

In this study, the 'entry' methodology will be used for the majority of analyses since this provides more current success rates than the 'longitudinal' methodology and takes into account NASs still in phase at the end of the tracking period (unlike the 'progression-decision' methodology). The 'longitudinal' methodology, resulting in actual success rates from 'first human dose' to market, will be used to validate the probabilities of success estimated with the 'entry' methodology. The 'progression-decision' methodology will not be used in this study, since success rates calculated using this methodology support similar conclusions and findings as success rates calculated using the 'entry' methodology (Van den Haak *et al.* (2004), indicating that unless limited data are available there is no need for both methodologies to be used.

Success rate calculation

The cohort of NASs to be included in a success rates calculation using the 'entry' methodology is determined by the date of entry into a phase. For example, to calculate success rates from 'first human dose' to 'first patient dose'

Table 2.2 Comparison of the advantages and disadvantages of three success rates methodologies

'Entry' methodology *Advantages* - Overcomes timing and tracking issues encountered when using the 'longitudinal' methodology - Because the probability of success to market is based on between-phase success rates that reflect recent industry practices, this provides a good indicator of current probabilities of success to market. - The active substances still in phase at the end of the tracking period are taken into account, thus providing the maximum and minimum boundaries to the calculated probabilities of success, which can be utilised for modelling future output. *Disadvantages* - This approach cannot always be used with smaller data sets, e.g. by individual companies, to calculate robust success rates
'Longitudinal' methodology *Advantages* - Provides the actual success rate to market based on the absolute outcome of all the active substances in the cohort. *Disadvantages* - Due to the length of development, it requires following a historical cohort of active substances that entered the clinic 10 to 15 years ago. The resulting success rates are unlikely to be relevant to current development practices. - This method requires good tracking systems to have been in place for a prolonged period of time to ensure all relevant active substances and decisions are captured.
'Progression-decision' methodology *Advantages* - Overcomes timing and tracking issues encountered when using the 'longitudinal' methodology - Success rates can be calculated based on smaller data sets (e.g. individual companies can use this method to calculate recent internal decision outcomes). *Disadvantages* - The decisions relate to active substances that entered development at any time point in the past (and may therefore relate to historical development practices). - No account is taken of active substances still in development in each phase.

a cohort of NASs will be selected that passed the milestone 'first human dose' within the time frame specified. The progress of this cohort of NASs will subsequently be tracked for the duration of three years, allowing sufficient time for the majority of NASs to either complete the phase or be terminated. At the end of the three years, the number of progressed NASs (P), the number of terminated NASs (T) and the number of NASs still in phase (I) will be assessed. Based on this, the current, minimum and maximum success rates can be calculated for each phase. Current success rates are based on NASs with known fate only (P and T), minimum success rates are based on the assumption that all NASs still in phase (I) will be terminated and maximum

success rates are based on the assumption that all NASs still in phase (I) will be progressed (Figure 2.1).

Calculation of probability of success to market

Having calculated the between-phase success rates for all development phases, the current probability of success to market will be assessed using the equations shown in Figure 2.2. The minimum and maximum probability of success to market will be calculated using the same approach.

Figure 2.1 Equations for the calculation of between-phase success rates; 'entry' methodology

$$CurrentSR_{Phase} = \frac{P_{Phase}}{P_{Phase} + T_{Phase}} \times 100\%$$

$$MinSR_{Phase} = \frac{P_{Phase}}{P_{Phase} + T_{Phase} + I_{Phase}} \times 100\%$$

$$MaxSR_{Phase} = \frac{P_{Phase} + I_{Phase}}{P_{Phase} + T_{Phase} + I_{Phase}} \times 100\%$$

Where CurrentSR = current success rate; MinSR = minimum success rate; MaxSR = maximum success rate; P = number of progressed NASs; t = number of terminated NASs and I = number of NASs still in phase at end of tracking period.

Figure 2.2 Equations for the calculation of probability of success to market; 'entry' methodology

$$CurrentPROB_{I} = CurrentSR_{I} \times CurrentSR_{II} \times CurrentSR_{III} \times CurrentSR_{Submission}$$

$$CurrentPROB_{II} = CurrentSR_{II} \times CurrentSR_{III} \times CurrentSR_{Submission}$$

$$CurrentPROB_{III} = CurrentSR_{III} \times CurrentSR_{Submission}$$

$$CurrentPROB_{Submission} = CurrentSR_{Submission}$$

Where $CurrentProb_X$ is the current probability of success from the start of Phase X to market

DEFINITION OF PRODUCTIVITY AND EFFICIENCY

For the purpose of this study, productivity will be defined as the quality and quantity of output per unit of input and efficiency will be defined as the quantity of output per unit of input. In other words, productivity is a measure of both the number and the value of goods produced whereas efficiency is a measure of the number of goods only.

SUMMARY

Three longitudinal surveys will be used to collect data from multinational pharmaceutical companies for the five year period 1998-2002 on the topics:

- International pharmaceutical R&D expenditure and sales;
- New active substance activities: submission, authorisation and marketing;
- The global ethical pharmaceutical development pipeline.

Existing questionnaires will be used to collect data for each survey directly from the pharmaceutical industry. The use of existing questionnaires was driven by companies' familiarity with these questionnaires as well as the well-established definitions. Descriptive statistics as well as statistical tests and graphs and tables will be used to analyse the data.

CHAPTER THREE

EVALUATION OF PHARMACEUTICAL R&D EXPENDITURE AND SALES – A LONGITUDINAL STUDY

INTRODUCTION

Throughout the last twenty years the global pharmaceutical industry, by almost any measure, has been one of the most successful and profitable industries, trading at a premium to the rest of the market (Kola and Landis, 2004). However, in recent years many challenges have emerged, raising questions about the sustainability of the current business model. Changing population demographics, technological advances and the movement of health economics to the forefront of the political agenda of more and more countries are all acting to force the evolution of the operating environment for the industry. The latest estimate from the Tufts Center for the Study of Drug Development (CSDD) puts the cost of bringing a new chemical entity to market at $802 Mn (DiMasi *et al.*, 2003), a figure confirmed by calculations from the Centre for Medicine Research (CMR) International (Sculthorpe and Ogg, 2003). When including average launch costs of $250 million Gilbert *et al.* (2003) estimates this cost to be even higher – closer to $1.7bn per successful launch. Combined with declining research and development (R&D) success rates and the falling number of new products reaching the market, a clear signal is being given. The industry needs to focus now more than ever on identifying successful business models (Gilbert *et al.*, 2003).

The traditional business model of a fully integrated pharmaceutical company, undertaking all activities from early research to late development itself, has been challenged by many in recent years with an increased focus on alternatives such as joint ventures, licence agreements, outsourcing and partnerships (Engel, 2001; Dyer, 2002; Gilbert *et al.*, 2003; Tufts CSDD, 2004). None of the suggested alternatives are new to the pharmaceutical industry but until now the opportunities seem to have been used mainly to address temporary operational problems such as resource shortage, rather than as long-term business strategies. However, companies could benefit from implementing one or more of the suggested approaches. Partnerships could lower risk and volatility, while at the same time bringing in experience and knowledge not available internally (Grabowski, 2000). Outsourcing could provide ways to decrease the rigidity of operating costs by reducing the fixed costs in the form of

internal full-time equivalents (FTEs). Additionally, one of the benefits of outsourcing over internal development is the ability to employ specific resources at no extra costs by recruiting appropriate service providers.

In the long term, launching novel products seems to be the key to securing income, leading to products that can stand the increased pressure from governments around the world on pharmaco-economic benefits. In the short term, value can be generated through maximising the market potential of current medicines by extending the life cycle of a drug substance. Life cycle management of the original product is one of the strategies that companies can employ to both diminish the loss of income due to patent expiration as well as to provide patients with improved treatment opportunities.

Information on overall research and development expenditure is available at a certain level from sources in the public domain such as company annual reports, financial consultants and publishing houses. However, these figures do not always relate to ethical pharmaceutical activities only (e.g. these could include development of veterinary medicines, or the sales derived from over-the counter (OTC) medicines). A study has been developed to collect financial data relating to the R&D and sales of ethical pharmaceuticals directly from the pharmaceutical companies, ensuring comparability of the data. Companies participating in the study are asked to provide data at a more detailed level than available in the public domain, allowing more focused analyses of R&D practices in the pharmaceutical industry.

OBJECTIVES

Data collected in this study were used to evaluate international ethical pharmaceutical R&D expenditure and sales over the years 1998-2002 in order to generate evidence to test the following hypotheses:

1. The proportion of sales re-invested in the research and development of ethical pharmaceuticals has remained constant over the duration of this study.

In the light of shareholders expectations of the industry's profit margins, it is not unreasonable to expect that R&D expenditure is budgeted as a fixed percentage of sales and that this has remained constant over time since increasing this percentage may lead to lower profit margins.

2. Companies are increasingly entering into partnerships with other organisations for the research and development of new medicines, which is reflected in an increased proportion of R&D expenditure being allocated to alliances.

3. Companies are increasingly outsourcing both their discovery and development activities, which is reflected in an increased proportion of R&D expenditure allocated to these type of activities.
   More and more companies are making use of co-development, licensing-in and outsourcing as alternatives to the traditional business model of an integrated pharmaceutical company, undertaking all activities by itself, from the earliest discovery stages through to marketing (Arlington, 1999; Engel, 1999; Dyer, 2002). It is therefore logical to expect that the percentage of R&D expenditure allocated to alliances and outsourcing has increased.

4. Companies have invested an increasing percentage of their R&D expenditure in life cycle management.
   Extending the life cycle of a drug substance by developing line extensions of the original product is one of the strategies that companies can employ to both diminish the loss of income due to patent expiration as well as to provide patients with improved treatment opportunities. In the light of the high number of top-selling products either having lost patent or about to loose patent (Beynon, 2000), it is not unrealistic to expect an increase in the proportion of R&D expenditure allocated to these type of activities.

5. The vulnerability to loss of income from patent expiration due to generic competition varies across the industry.

By the end of 1999, the industry faced the expiration of 50 patents between 1999 and the end of 2005 (Engel, 1999, Beynon, 2000). Although the impact on the industry in its entirety is undisputable, it is logical to expect that its impact on individual companies will vary, depending on each company's portfolio of marketed products.

METHODS

The study of global sales and R&D expenditure of international pharmaceutical companies was conducted by means of an annual questionnaire-based approach, which was initiated with a pilot study in 1996 (MacFarlane *et al.*, 1997; MacFarlane, 1998). Subsequent rounds of data collection encompassed the top pharmaceutical companies by R&D expenditure, as well as the leading biotechnology companies. Invitations to participate were sent to at least the Top 20 pharmaceutical companies and the Top five biotechnology companies, based on pharmaceutical R&D expenditure in the year over which data were to be collected. References for annual pharmaceutical R&D expenditure were obtained from the September issue of MedAdNews Magazine (Anon, 1999b; 2000b; 2001b; 2002; 2003c). This list of Top 20 pharmaceutical companies and Top 5 biotechnology companies was complemented with any other company undertaking ethical pharmaceutical R&D that had expressed an interest in this type of study in the past and within which a suitable contact could be identified. Companies invited to participate in one or more years are listed by name in Table 2.1, with an overview of the number of companies invited year on year provided in Table 3.4. For this chapter, data collected for the five years 1998-2002 are analysed in detail.

Data collection

The study focused on ethical (prescription only) pharmaceuticals, excluding any additional activities such as veterinary medicines or OTC products. The content of the questionnaire was assessed annually to ensure that up-to-date and relevant information was collected. Definitions were provided along with the questions to encourage consistent responses between companies and across years. An overview of how the questionnaire evolved for the years 1998-2002 is provided in Table 3.1. The questionnaires used for data collection for 2001 and

2002 are provided in Appendix I and Appendix II respectively.

In each round of data collection, companies were asked to provide actual data for the year over which data were collected, as well as estimates for the current year for a subset of the questions. For example, in 2003 actual data were collected for 2002 and estimates were collected for 2003.

Data collection was carried out in the first half of the year following the calendar year in which activities took place, e.g. the questionnaire used for collecting data on activities in 1999 was made available to all companies invited to participate between January 2000 and June 2000. Each company was contacted prior to sending out the questionnaire to ascertain the most appropriate person to receive it. Recipients of the questionnaires were subsequently contacted by phone and/or e-mail to ascertain the likelihood of their participation in the study. An electronic reminder of the data collection deadline was sent one week before the end of data collection. Those companies not returning a completed questionnaire by the data collection deadline without a formal notice of decline were subsequently contacted to either discuss the possibility of late data provision or to confirm that the company had chosen subsequently not to participate.

The level of completeness of the questionnaires returned by the participants varied by company each year, depending on both the internal availability of the information as well as the willingness to share externally such detailed and confidential data. Some companies were in the position to supply detailed breakdowns of both R&D expenditure and sales, whereas others had indicated that their internal systems did not support a further breakdown of top-level data in line with the definitions given.

Use of historical data

For this study, data were collected from 1998 onwards. To allow assessment of trends and developments prior to 1998, data collected in historic CMR International studies were used. This information was available from CMR International's Global R&D Expenditure Database (GLOBEX). GLOBEX holds

Table 3.1 Aspects of global R&D expenditure and sales addressed in the annual study, 1998-2002

Global R&D expenditure	✓	✓	✓	✓	✓
Global sales	✓	✓	✓	✓	✓
Global R&D staff (FTEs)		✓	✓	✓	✓
Global capital investment				✓	✓
Geographical breakdown					
• R&D expenditure				✓	✓
• Sales				✓	✓
• R&D staff				✓	✓
• Capital investment				✓	✓
Outsourcing					
• Expenditure allocated to research contracts with external *commercial* organisations	✓	✓	✓	✓	
- Discovery/non-clinical research	✓	✓	✓	✓	
- Clinical/ regulatory activities	✓	✓	✓	✓	
• Expenditure allocated to research contracts with external *academic* organisations	✓	✓	✓	✓	
- Discovery/non-clinical research	✓	✓	✓	✓	
- Clinical/regulatory activities	✓	✓	✓	✓	
R&D expenditure by activity (%)					
• Discovery research	✓	✓	✓	✓	
• Non-clinical research	✓	✓	✓	✓	
• Total Clinical research			✓	✓	
- Pre-marketing clinical evaluation (Phase I-III)	✓	✓			
- Phase I activities			✓	✓	
- Phase II & III activities			✓	✓	
- Post-marketing clinical evaluation	✓	✓	✓	✓	
• Regulatory	✓	✓	✓	✓	
• Other research	✓	✓	✓	✓	
External expenditure and FTEs by function					
• Discovery research					✓
• Chemistry, Manufacturing and Controls (CMC)					✓
• Clinical research					✓
• Non clinical safety evaluations					✓
• Regulatory					✓
• Miscellaneous					✓
External expenditure and FTEs by stage of development					
• Discovery stage of development					✓
• Early development					✓
• Late development					✓
• Submission and launch programme					✓
• Further activities					✓
R&D expenditure by product type (%)					
• NASs	✓	✓	✓	✓	
• Biotech NASs					✓
• Non-biotech NASs					✓
• Line extensions	✓	✓	✓	✓	✓
• Other products	✓	✓	✓	✓	✓
R&D Expenditure allocated to new technologies (%)					
• Combinatorial chemistry		✓			
• High-throughput screening		✓			
• Bioinformatics		✓			
• Pharmacogenomics		✓			
Capital expenditure allocated to new technologies (%)					
• Combinatorial chemistry		✓			
• High-throughput screening		✓			
• Bioinformatics		✓			
• Pharmacogenomics		✓			
R&D expenditure by therapeutic area (%)					
• Alimentary and metabolism/ Blood/ Cardiovascular/ Dermatologicals/ GU/Sex hormones/ Hormones/ Anitinfectives/ Cancer/ Musculoskeletal/ Nervous system/ Respiratory/ Sensory/ Various (ATC)			✓	✓	✓
• Miscellaneous				✓	✓
Sales derived from top three selling products (%)	✓	✓	✓	✓	✓
Sales derived from products launched in previous five years (%)	✓	✓	✓	✓	✓

detailed information on annual ethical pharmaceutical R&D expenditure, capital expenditure, R&D FTEs and sales for over 80 companies. Since its inception in 1982, the database has been updated with confidential data obtained directly from pharmaceutical companies, supplemented with company confirmed data from the public domain.

External data sources

Information on overall global pharmaceutical sales was obtained annually from IMS Health. Pharmaceutical sales figures include all prescription and certain OTC data and represent manufacturer prices. Exchange rates to convert data provided in local currency into US$ were taken from the monthly publication Main Economic Indicators from the Organisation for Economic Co-operation and Development (OECD).

Data processing and analyses

Companies were given the opportunity to submit their data electronically using a Microsoft Excel™-based questionnaire, or by use of a paper form. Participants were encouraged to provide data electronically rather than on a paper questionnaire that was returned by post or fax, to eliminate the need for additional data handling steps such as interpreting handwriting.

Data were processed using Microsoft Access™. Both Microsoft Access ™ and Microsoft Excel™ were used to obtain descriptive statistics of the data. SPSS™ for Windows™ was used to run statistical analyses on the data:

- *Linear regression* was used to test whether global ethical pharmaceutical R&D expenditure as a percentage of global ethical pharmaceutical sales declined over time
- Differences in R&D to sales ratios for a consistent cohort of companies between 1998 and 2002 were tested with the *Wilcoxon Signed Rank test* since the data was not normally distributed.
- *Repeated measures one-way analysis of variance (ANOVA)* was used to test the statistical significance of changes over time in the proportion of R&D expenditure allocated to alliances for a consistent cohort of companies.

- The proportion of R&D expenditure allocated to line extensions was compared for company cohorts with the *Mann-Whitney U-test* since this did not require normal distribution of the data.
- A *Friedman test* was used to test whether the distribution between discovery and clinical alliance expenditure had changed over time.

Observation of confidentiality agreement

Data collected in this study were covered by a confidentiality agreement with respondent companies, thus preventing the presentation of identifiable individual company data. To assess whether any of the trends or developments observed differed between larger and smaller companies, respondent companies were characterised according to their level of global R&D expenditure in ethical pharmaceuticals in 2002. Companies for which 2002 ethical pharmaceutical R&D expenditure equalled or exceeded US$ 1bn were classified as "major" companies, whereas those companies for which this expenditure was less than US$ 1bn were classified as "other" companies. Where historical data are presented, the activities of companies that now form part of a larger company, due to merger and acquisition activities, have been attributed to the company grouping as it was in 2002. Company nationality was based on the geographical location of corporate headquarters.

Monetary currency and its calculation

Expenditure and sales information was requested in national currency (defined as the local currency used in the country where the corporate headquarters for the company were located) without adjustment for inflation. Conversion to US dollars was achieved using the mean exchange rates for the year the activities took place, based on data from the OECD as quoted in their monthly publication Main Economic Indicators (Table 3.2).

Calculations of global R&D expenditure and sales

Global R&D expenditure estimates are based on the 1996 global R&D expenditure that was calculated by Hynes *et al.* (1997). For each year, global R&D expenditure was estimated by applying the mean growth rate for a consistent cohort of companies to the global R&D expenditure for a base year. The cohort of companies was selected as those companies for which individual

R&D expenditure data were available for all years between the base year and the year for which the parameter was calculated. For example, global R&D expenditure for 1998 was estimated by applying the mean growth rate for a cohort of 22 companies to 1996 global R&D expenditure. Table 3.3 provides an overview of the number of companies and the source years on which the annual estimates were based. Future projections of global R&D expenditure and sales for the years 2003-2007 were estimated assuming that growth in R&D expenditure and sales for those years will match the average growth rate per

Table 3.2 Exchange rates used for conversion of local currency to US dollars, 1998-2002

Country	1998	1999	2000	2001	2002	2003e**
Australia	1.592	1.550	1.726	1.935	1.841	1.686
Belgium	36.30	37.86	43.77	*Euro zone**		
Denmark	6.696	6.980	8.090	8.321	7.884	6.920
Euro zone	-	0.938	1.085	1.117	1.061	0.932
Finland	5.345	5.580	6.452	*Euro zone**		
France	5.899	6.156	7.118	*Euro zone**		
Germany	1.759	1.835	2.122	*Euro zone**		
Italy	1736	1817	2101	*Euro zone**		
Japan	130.9	113.9	107.8	121.5	125.3	119.0
Netherlands	1.985	2.068	2.391	*Euro zone**		
Spain	149.4	156.1	180.5	*Euro zone**		
Sweden	7.947	8.262	9.149	10.338	9.271	8.554
Switzerland	1.450	1.503	1.688	1.687	1.557	1.366
UK	0.604	0.618	0.661	0.694	0.667	0.624
USA	1.000	1.000	1.000	1.000	1.000	1.000

**In 2000, the Euro became the official currency for any financial transaction on paper and report for all countries in the Euro zone (including Belgium, Finland, France, Germany, Italy, the Netherlands and Spain). The currencies for the individual countries were fixed relatively to the Euro exchange rate (2000 rates). **Exchange rates for 2003 reflect the average exchange rate for the first three months of 2003. Source: OECD, Main Economic Indicators.*

Table 3.3 Information used for estimating global R&D expenditure, 1997-2002

Year	Source / Base year	Number of companies	% of global R&D expenditure base year
1998	1996	22	50%
1999	1996	16	38%
2000	1999	21	36%
2001	2000	18	42%
2002	2001	23	63%

annum observed between 1997 and 2002. By applying this average growth rate to 2002 global R&D expenditure and sales figures, an assessment was made of what the future might hold if current practices continue. Where estimates for 2003 provided by participants are reported in this chapter, the data are referred to as data for the year 2003e. Where calculations were applied to project future values, e.g. for global R&D expenditure and sales, data were referred as 2003p.

Assessment of vulnerability of loss of income

The vulnerability to loss of income from patent expiration due to generic competition is assessed using a combination of two parameters; the percentage of sales derived from top three products and the percentage of sales derived from recently launched products, where recently launched is defined as launched in the four years preceding the year in which data are collected or launched during the year in which data are collected. It is postulated that companies are less vulnerable to potential loss of income when sales are derived from a large portfolio of products, indicated by a relatively low percentage of sales derived from a small number (top three) products. If the percentage of sales derived from the top three products is high, the company is at a risk of loosing a considerable proportion of its income due to generic competition for any of these three products. In the same way, it is postulated that companies that have successfully launched products in recent years, that have produced or have the potential to produce significant income, are under less direct threat than those for which the majority of their current portfolio of marketed products are nearing the end of their patent protection.

Trend analysis

For trend analyses, only data from those companies were included for which the required information for all years in the analysis was available, unless otherwise stated. Where relevant to the interpretation of the data, the cohort of companies included in trend analysis was defined by the proportion of global R&D expenditure and / or sales it represented in 2002. Trends in annual growth rate for R&D expenditure and sales have been presented as three-year moving averages to minimise fluctuations from one year to the next. The mid-point of the three-year interval is used as the year label. In this analysis the data point

for 1999 for example, represents the average of all data corresponding to 1998, 1999 and 2000. To examine the growth rates in R&D expenditure and sales for individual companies, an assessment was made of the number of companies for which growth rates could be calculated for the period 1998-2003p. The largest cohort for R&D expenditure growth rates (in terms of the proportion of global R&D expenditure) was obtained when including companies for which growth rates could be calculated for three, four or five years of the five years included in this analysis. To ascertain comparability of the R&D expenditure data and the sales data, the same inclusion criteria was applied for the analysis of individual company sales growth rates.

RESULTS

Response rate

A total of 52 companies participated in the study for one or more years (1998-2002) based on the company grouping as it was in 2002. In any given year over this period, a minimum of 23 companies participated in the study, with a maximum of 41 companies participating in 1999 (Table 3.4). On average, respondent companies represented a minimum of 66% of global R&D expenditure year on year. Non-respondent companies chose not to participate for one or more of the following reasons: (1) the requested data in line with the definitions provided were not readily available within the company, (2) the requested data could not be made available within the given time frame for data collection, or (3) the company was not willing to provide the requested data.

Table 3.4 Number and description of study respondents (1998-2002)

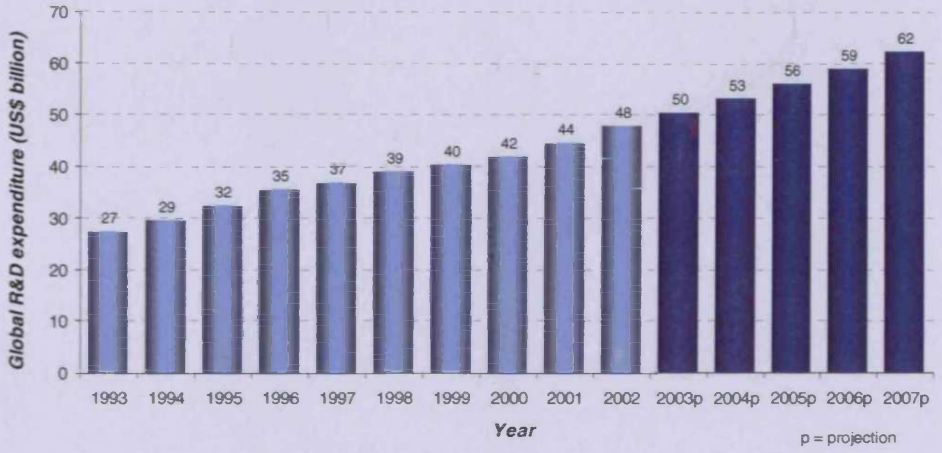
Year(s)	Number of companies approached	Number of respondent companies	% of Global R&D expenditure	Number of respondent "major" companies[a]
1998	67	37	64%	9
1999	80	41	71%	11[b]
2000	100	37	71%	12[c]
2001	63	27	63%	11
2002	42	23	67%	12

[a]The total number of "major companies" per year varied between 14 and 15. [b]Three "major" companies confirmed publicly available figures for their global sales and R&D expenditure. [c]One "major" company confirmed publicly available figures for their global sales and R&D expenditure

Global R&D Expenditure and sales

In 2002, global ethical pharmaceutical R&D expenditure was estimated to have reached a total of US$ 47.8bn, representing an increase of 75% in ten years time compared to US$ 27.3 in 1993. Global R&D expenditure has grown by an average of 5.4% per year over the last five years leading up to 2002; if growth continues at this rate, it was estimated to reach US$ 62bn by 2007 (Figure 3.1).

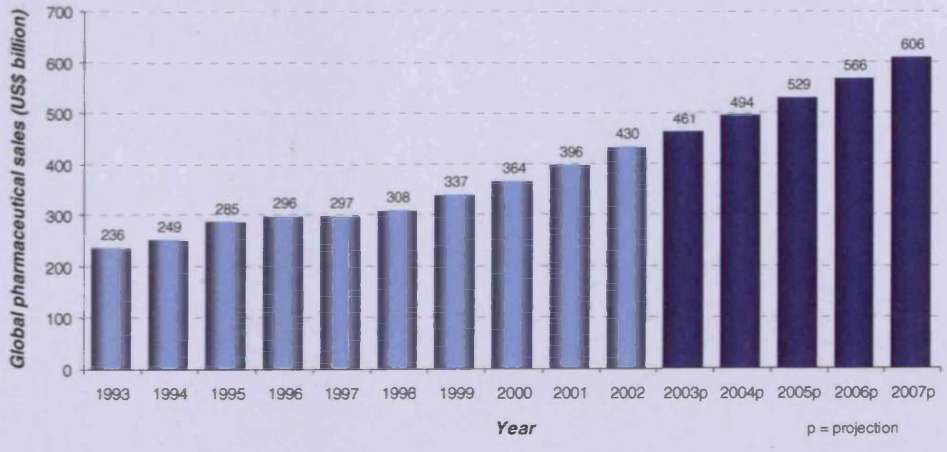
Figure 3.1 Global pharmaceutical R&D expenditure (1993-2007p)



Global pharmaceutical sales were estimated to total US$ 430bn in 2002, an increase of over 80% compared to US$ 236bn in 1993. If future growth matches the average annual growth in sales over the last five years (7.7%), global sales were estimated to exceed US$600 by 2007 (Figure 3.2).

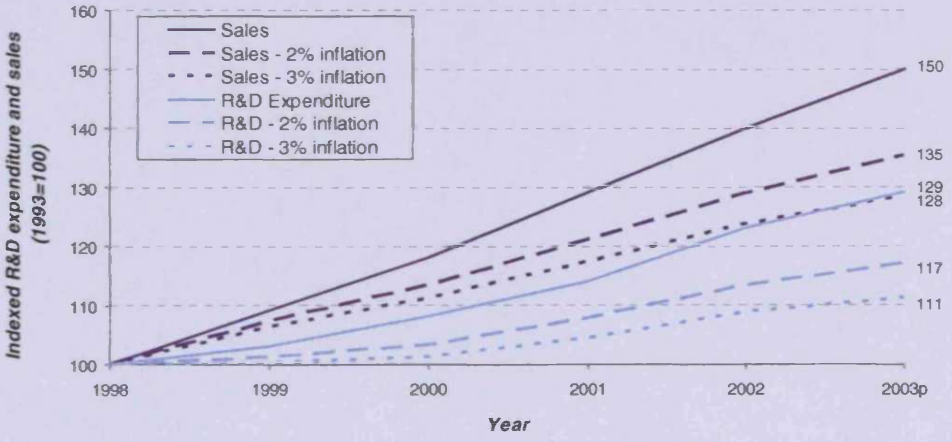
Overall, global sales increased by 40% between 1998 and 2002. Despite a considerable increase in investment in R&D activities, this was not matched by

Figure 3.2 Global pharmaceutical sales (1993-2007p)



the overall growth in R&D expenditure, which increased by 23% over the same time period (Figure 3.3). It should be noted that no correction for inflation was applied to either calculation. Inflation has influenced the collected data in a complex manner. Inflation rates vary by country and as such country specific data would be required to assess the exact inflation correction. In this study, data was collected at a company level, with many companies operating at an international level. Although a breakdown by geographical region was provided, this was not detailed enough to establish inflation accurately. As an alternative, the potential influence of inflation is simulated by applying artificial year-on-year inflation rates of 2% and 3% (Figure 3.3), based on the average annual Consumer Price Index for the USA over 1993-2002 (~2.5%), as well as recent Harmonized Indices of Consumer Prices for the EU member states (~2.2%) (Bautier, 2004; GPEC, 2004).

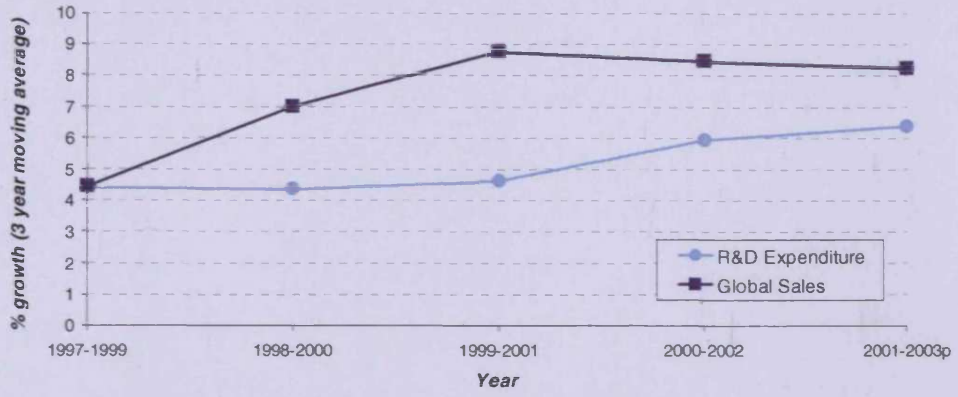
Figure 3.3 Indexed global R&D expenditure and sales (1998-2003p)



Underlying this trend of growth in sales outpacing growth in R&D expenditure was the continuous increase in annual average growth rate for global sales in the late 90s. Although a decline was observed in this growth rate for global sales from 2000 onwards, coinciding with a rise in the growth rate for R&D expenditure, sales growth rates were estimated to continue to exceed R&D expenditure growth rates in 2003 (Figure 3.4).

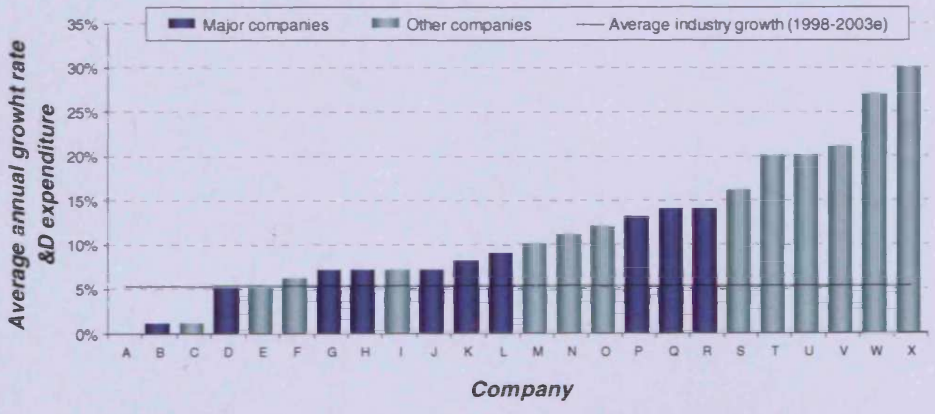
For 24 companies, representing 55% of global R&D expenditure in 2002, the annual R&D expenditure growth rate could be calculated for three or more years of the years 1998-2003p. The average growth rate per annum for these

Figure 3.4 Rates of growth in global R&D expenditure and global sales (1997-2003p)



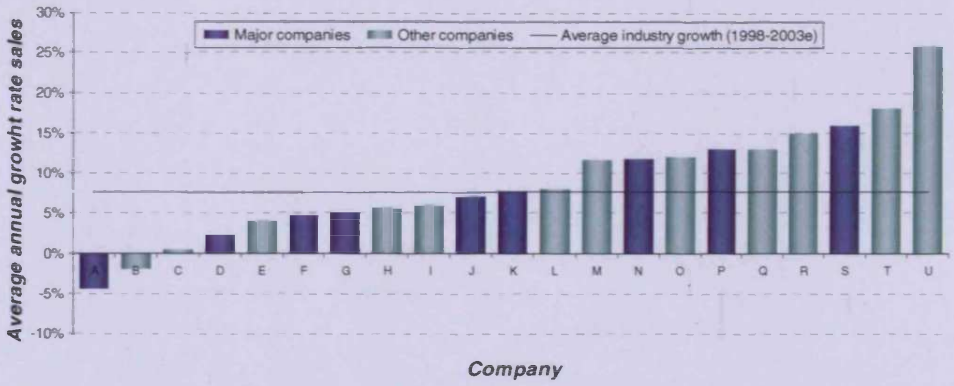
companies for the five-year period 1998-2002 is presented in Figure 3.5. Against the industry background of an average annual growth rate of 5.4%, average annual growth rates for individual companies ranged from 0% to 30%, exceeding four times the industry average. Only five of the 24 companies could not match the industry growth rate, two of which were "major" companies. The reasons for the skewed distribution between companies achieving less growth than the industry average and those achieving higher growth is most likely due to the fact that the industry growth rate is driven by the performance of larger companies, whereas the majority of the companies demonstrating growth rates over and above the industry average are "other" companies. For the 21 companies where the annual sales growth rate could be calculated for three or more of the five years 1998-2003e, the average growth rate per annum for this

Figure 3.5 Average R&D expenditure growth rate for 24 individual companies (1998-2003e)



Representing companies where annual growth rates could be calculated for 3 or more of the 5 years included in this analysis.

Figure 3.6 Average sales growth rate for 21 individual companies (1998-2003e)



Representing companies where annual growth rates could be calculated for 3 or more of the 5 years included in this analysis.

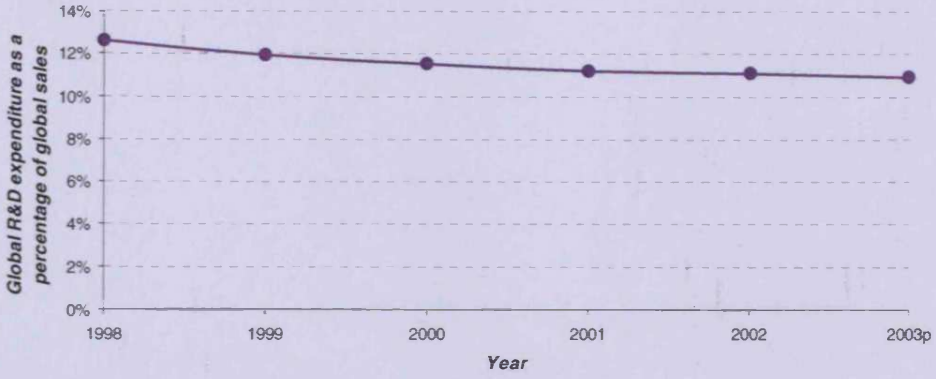
five-year period is presented in Figure 3.6. Against the industry background of an average annual growth rate of 7.7%, growth rates for individual companies ranged from a decrease of 4.4% to an increase of over 25%. In total, 11 of the 21 companies demonstrated an average annual growth rate equal to or exceeding that of the industry. Four of those companies were classified as "major" companies (companies with R&D expenditure equal to or over US$ 1bn in 2002), whereas five of the ten companies where sales growth did not reach the level of the industry growth were "major" companies. With the activities of companies that now form part of a larger company being attributed to the company grouping as it was in 2002, it is suggested that the trends described in Figure 3.5 and Figure 3.6 have primarily been achieved through organic growth and not through merger or acquisition activities.

R&D expenditure to sales ratio

Figure 3.7 shows global ethical pharmaceutical R&D expenditure (see Figure 3.1) as a percentage of global pharmaceutical sales (see Figure 3.2). For 2002, this percentage was calculated to be 11.1% - a decline from 1998 when global R&D expenditure represented 12.6% of global sales. Statistical analysis showed this decline to be significant ($p<0.01$).

To allow a more detailed analysis of trends over time, R&D expenditure to sales ratios were calculated for individual companies, the aggregated results of which

Figure 3.7 Global R&D expenditure as a percentage of global sales (1998-2003p)



Statistical analysis of these data using a linear regression model showed that there was a negative correlation between global R&D expenditure as a percentage of global sales and time ($p<0.0.1$)

are shown in Table 3.5. The R&D expenditure to sales ratio per company per year demonstrated little change over the years 1998-2002. Based on data from all companies for which the relevant data were available for at least one of the years included in the analysis, R&D expenditure on average accounted for around 17% of sales for all five years 1998-2002, ranging from just under 10% to around 26% per company (5^{th} - 95^{th} percentile). The different trends observed in Figure 3.1 and Table 3.5 are likely to be due to the influence of company size in the calculations. Larger companies will have more influence on the outcome the analysis presented in Figure 3.1, since every company contributed relative to its company size, whereas in the data in Table 3.5 each company's contribution is equal. At least two factors will have contributed to the distinct difference observed between R&D expenditure as a percentage of global sales (Figure 3.1, 11-12%) and the R&D expenditure to sales ratio based on

Table 3.5 R&D expenditure to sales ratio based on individual company data (1998-2003e)

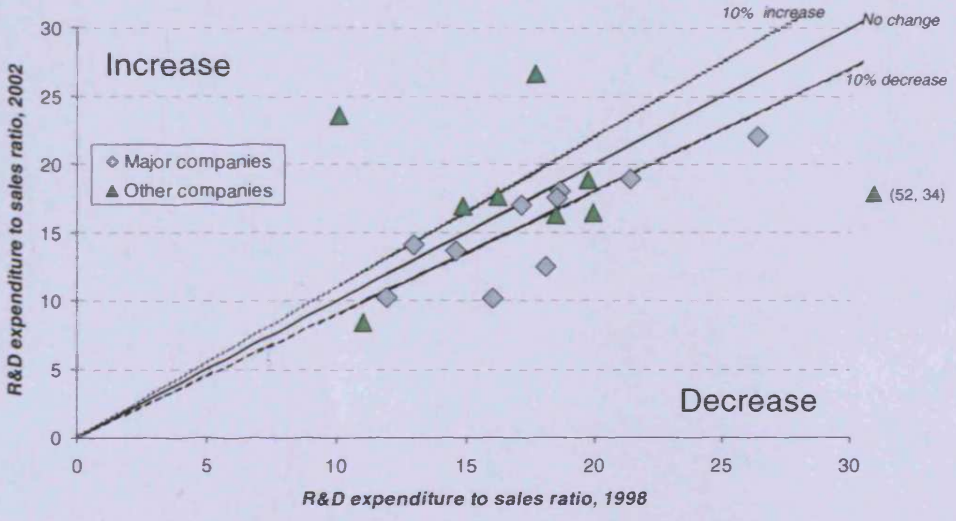
	1998	1999	2000	2001	2002
Mean	0.177	0.170	0.174	0.161	0.167
Median	0.171	0.170	0.158	0.156	0.169
5^{th} percentile	0.099	0.083	0.097	0.073	0.084
95^{th} percentile	0.256	0.269	0.262	0.250	0.266
Number of companies	27	31	24	29	21
Percentage of global R&D expenditure represented by company cohort	57%	54%	53%	72%	57%

Two companies with average ratios in access of 0.40 have been excluded from the analysis.

individual company data (Table 3.5, 16-17%). Firstly, there is a slight difference in the inclusion criteria for global sales and for sales figures for individual companies. Global sales data were obtained from IMS Health and included a limited amount of OTC data, whereas for individual companies data included sales derived from ethical pharmaceuticals only. Secondly, although the cohort of companies participating in this study is responsible for around two-thirds of global R&D expenditure in 2002, it only represents a small proportion of the total number of companies active in pharmaceutical R&D. The latest estimates suggest that more than 1,400 companies are developing drug candidates (Lloyd, 2003).

Ten "major" companies and nine "other" companies provided all relevant data points to calculate the R&D expenditure to sales ratio for both years 1998 and 2002 (Figure 3.8). For this cohort of companies, the R&D expenditure to sales ratio ranged from around 10% to companies spending the equivalent of more than 25% of their sales income on R&D activities. The solid line in Figure 3.8 shows the situation of no change between an individual company's ratio in 1998 and that in 2002, with the dotted lines indicating the range of less than 10% change between the two years. Only three of the 19 companies, all being

Figure 3.8 R&D expenditure to sales ratio for individual companies (1998 vs. 2002)



Statistical analysis of these data using a Wilcoxon Signed Rank test indicated that there was significant difference between the two years investigated for "major" companies ($p<0.05$), but not for "other companies.

classified as spending less than US$ 1bn in pharmaceutical R&D in 2002, had increased their R&D expenditure as a percentage of sales. Five of the ten "major" companies included in this analysis reported to have decreased their R&D expenditure to sales ratio within the give time frame. For the remaining five "major" companies the 2002 ratio was within 10% of the 1998 value and was therefore classified as a situation of no change (Table 3.6). Statistical analysis using the Wilcoxon Signed Rank test (since no normal distribution of the data could be demonstrated) showed that the difference between the two years investigated was significant for "major" companies, but not for "other" companies. The combined data from Figure 3.7 and Figure 3.8 indicate that R&D expenditure as a percentage of sales for "major" companies has declined since 1998, driving an overall industry decline.

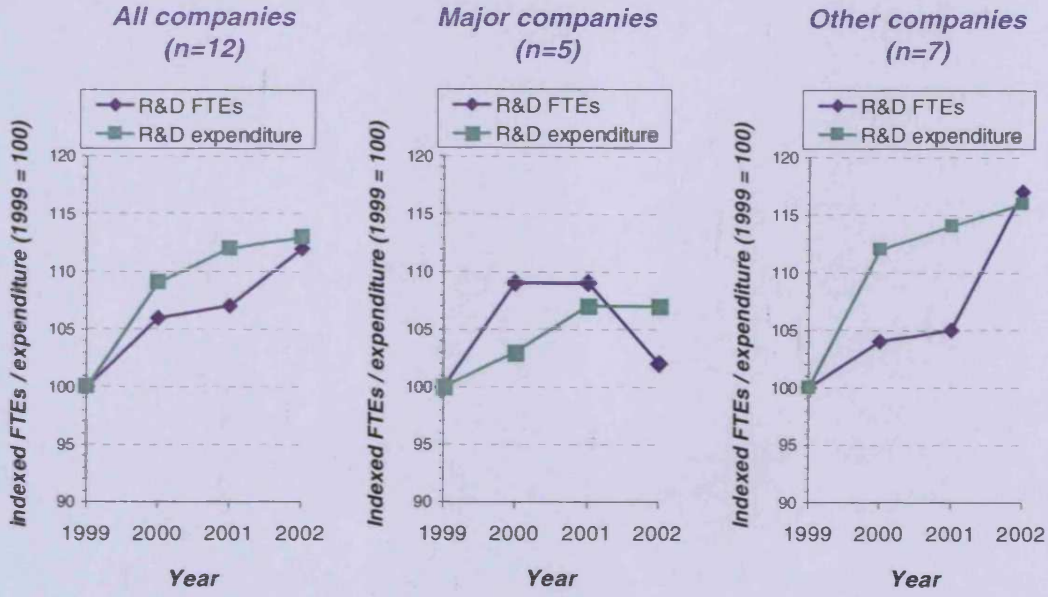
Table 3.6 Change in R&D expenditure to sales ratio (1998 vs. 2002)

		All companies	"major" companies	"other" companies
Total number of companies included in analysis		19	10	9
Increase	*2002 ratio increased by 10% or more compared to 1998 ratio*	3	0	3
No change	*2002 ratio within 10% of 1998 ratio*	7	5	2
Decrease	*2002 ratio decreased by 10% or more compared to 1998 ratio*	9	5	4

R&D FTEs

In 1999 a new question was added to the study, asking companies to provide the total number of R&D staff. In this first year, 36 companies reported to employ an average of 2,334 FTEs in R&D, ranging from less than 100 to almost 10,000 for individual companies. For five "major" companies and seven "other" companies, information about the number of R&D staff employed was available for all four years 1999-2002. For these companies, growth in aggregated R&D staff numbers and in R&D expenditure is depicted as indexed data in Figure 3.9. For this cohort of 12 companies, the rate with which R&D staff numbers (in FTEs) increased from 1999-2001 was less than the rate with which R&D expenditure increased. However, the considerable increase observed in the number of FTEs in 2002, resulted in a similar overall growth for this four-year period of 12-13% for both metrics. Within this cohort, the data for the seven

Figure 3.9 Indexed growth in R&D expenditure and FTEs (1999-2002)

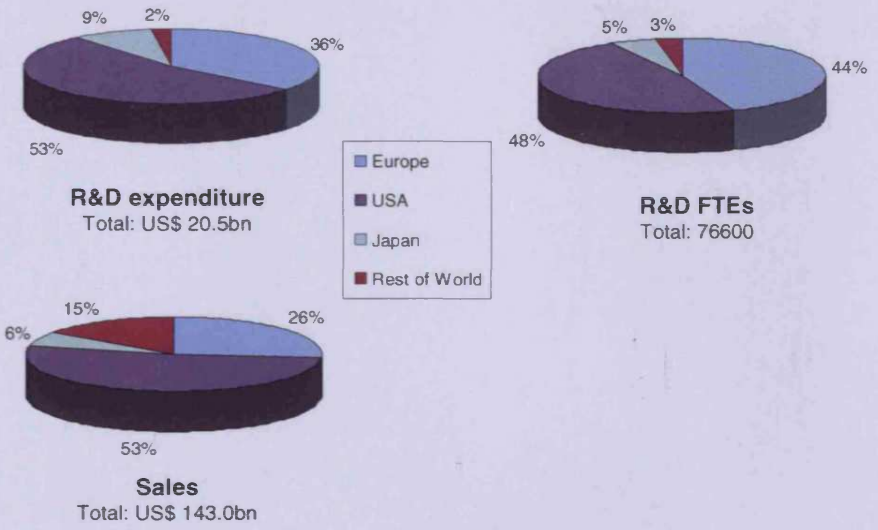


"other" companies displayed the same trend with a growth time lag between FTEs and expenditure for 1999-2001, while still resulting in a similar overall increase over the full four-year period (16-17%). Data for the five "major" companies identified a different pattern. This cohort increased their total number of R&D FTEs by nine percent from 1999 to 2000, followed by a year with no growth. In 2002, it fell steeply, resulting in a net increase of only 2% between 1999 and 2002. Over the same period of time, the R&D expenditure for this cohort of companies increased with 7% from 1999 to 2001, with a situation of no change observed in 2002. The different patterns observed between R&D expenditure and FTEs suggest that FTEs is not the sole driver for R&D expenditure and that other factors, for example outsourcing, make a major contribution to the cost of drug development.

Geographical breakdown of R&D expenditure, R&D FTEs and sales

Five USA companies, 11 European companies and one Japanese company provided a geographical breakdown of R&D expenditure, sales and R&D FTEs for 2002 (Figure 3.10). Company nationality was determined by the location of corporate headquarters. It should be noted that the majority of the companies operate on a global level. This cohort of 17 companies accounted for a total R&D expenditure of US$ 20.5bn, 53% of which was allocated to R&D activities

Figure 3.10 Geographical breakdown of headline figures (2002)



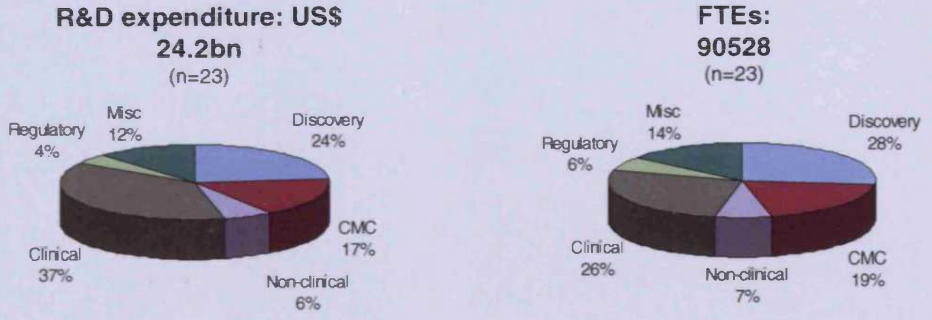
Data presented as the percentage of aggregated totals

in the USA. The USA was also the main source of R&D FTEs, accounting for 48% of the 76,600 FTEs employed in the R&D functions of these 17 companies. Not surprisingly, it is also the USA that was the major pharmaceutical market in terms of sales (53%). More remarkable however, is that although Europe accounted for only a quarter of ethical pharmaceutical sales, it attracted 36% of R&D expenditure and 44% of FTEs.

Functional breakdown of R&D expenditure

In 2002, the clinical function accounted for over a third of R&D expenditure, yet it represented only 26% of all R&D FTEs (Figure 3.11). The discovery function accounted for 24% of expenditure and 28% of FTEs. A comparable proportion of R&D expenditure and FTEs was allocated to chemistry, manufacturing and controls (CMC) activities (both around 18%) and to the regulatory function (both

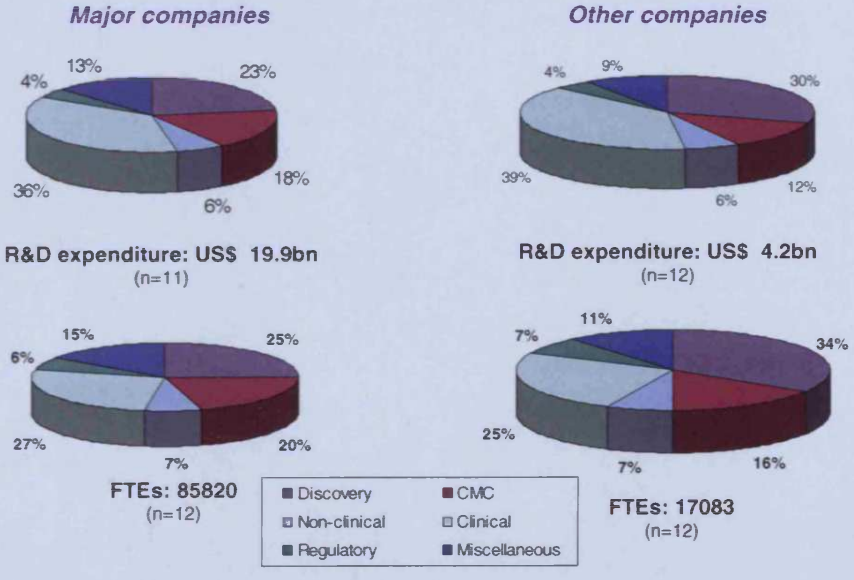
Figure 3.11 Percentage of R&D expenditure and FTEs by function (2002)



around 5%). The different distributions between R&D expenditure and FTEs again indicate that salary is not the only major driver of R&D cost. Outsourcing of clinical trials might, for example, be contributing to a higher proportion of clinical expenditure than the relative number of FTEs allocated to this function. "Major" companies allocated a smaller percentage of both R&D expenditure and FTEs to the discovery function (23% and 25%, respectively) than "other" companies (30% and 34%, respectively, Figure 3.12). Interestingly, for both company cohorts the clinical function accounted for a higher percentage of R&D expenditure (36% and 29%, respectively) than of FTEs (27% and 25%, respectively) in 2002.

In the 2002 questionnaire, the definitions and inclusion criteria underlying the breakdown of R&D expenditure by activity were changed to better reflect current industry practices. As a consequence, data collected in 2002 were not comparable with data collected for 1998-2001. Unfortunately, insufficient data were available to perform trend analyses of R&D expenditure by activity for a consistent cohort of companies for the years 1998-2001.

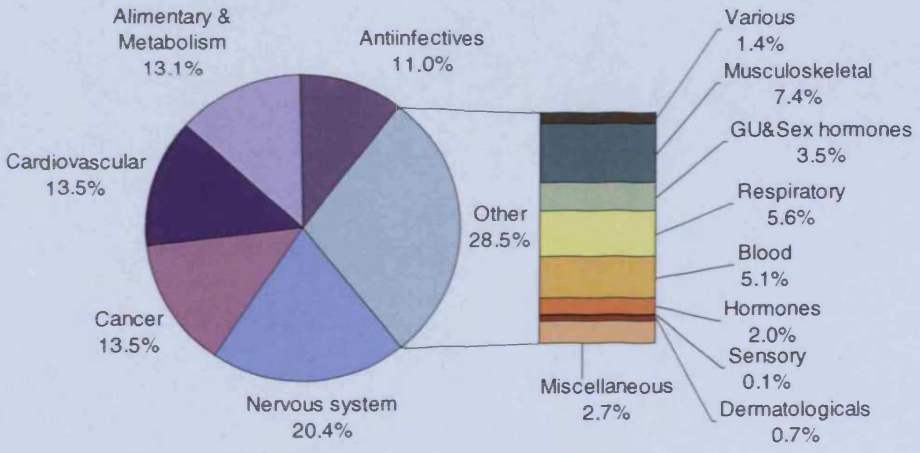
Figure 3.12 Percentage of R&D expenditure and FTEs by function by company cohort (2002)



R&D expenditure by therapeutic area

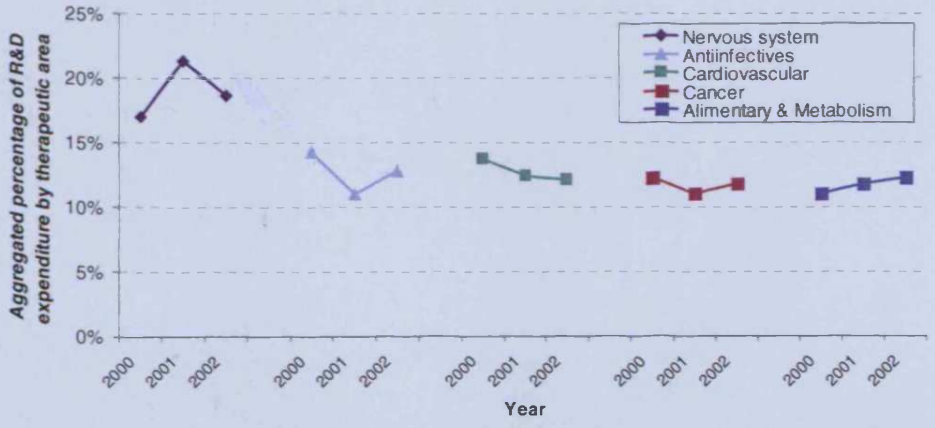
A cohort of 19 companies, including nine "major" companies and ten "other" companies, provided information relating to the distribution of R&D expenditure by therapeutic area in 2002. For this cohort, over two-thirds of 2002 R&D expenditure was allocated to activities relating to products in development in one of five therapeutic areas: nervous system (20.4% of R&D expenditure), cancer (13.5%), cardiovascular (13.5%), alimentary & metabolism (13.1%) and anti-infectives (11.0%, Figure 3.13). For 12 of these companies, this information was available for all three years 2000-2002 (Figure 3.14). Expenditure on the therapeutic areas nervous system and anti-infectives demonstrated the most variability, with nervous system expenditure fluctuating between 17% and 21%

Figure 3.13 Aggregated R&D expenditure by therapeutic area (2002)



An overview of therapeutic areas is provided in Appendix VII.

Figure 3.14 R&D expenditure for five therapeutic areas (2000-2002)



Information on the breakdown of aggregated R&D expenditure by therapeutic area was available for 4 Major companies and 8 Other companies for all three years 2000-2002.

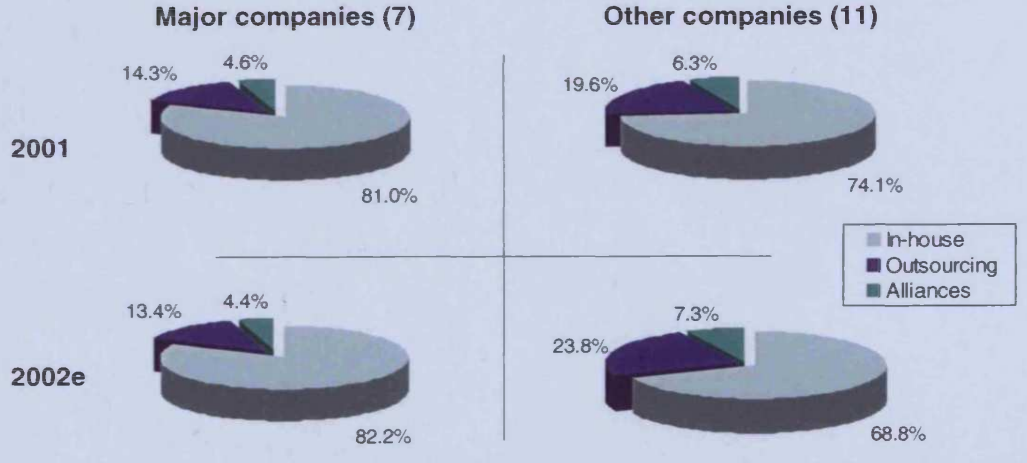
of total R&D expenditure in this three-year period. Anti-infectives expenditure fluctuated between 11% and 14% for this cohort of companies, while the other three main therapeutic areas all remained stable around 12% of R&D expenditure (Figure 3.14).

Outsourcing and alliances expenditure

In response to suggestions from study participants, questions relating to outsourcing expenditure were modified in the 2002 questionnaire to better reflect current industry practices. As a by-product of this update, the 2002 data set did not support analyses on outsourcing expenditure as a separate entity within total R&D expenditure. However, participants did provide estimates for 2002 outsourcing expenditure as part of the 2001 study.

In 2001, just over 80% of total R&D expenditure for seven "major" companies was accounted for by in-house activities, with the remaining expenditure split between alliances (4.6%) and outsourcing activities (14.3%; Figure 3.15). Estimates provided for the next year suggested that no noteworthy change was expected in this expenditure pattern for 2002. Eleven smaller companies allocated a considerably higher percentage of R&D expenditure to outsourcing activities and alliances. For 2001, 19.6% of R&D expenditure was allocated to

Figure 3.15 Percentage of R&D expenditure allocated to Outsourcing and Alliances by company cohort (2001-2002e)

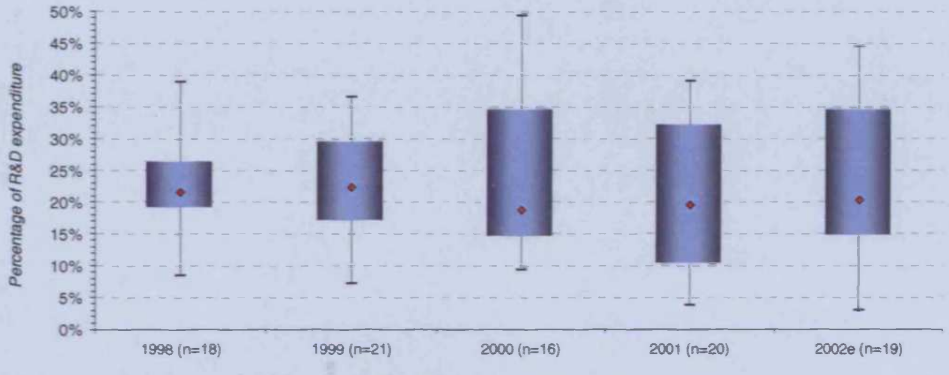


Presented as the percentage breakdown of aggregated R&D expenditure. Expenditure on both outsourcing and alliances in 2001 and 2002e was provided by 18 companies (7 Major and 11 Other companies).

outsourcing and this was estimated to increase to 23.8% for 2002. Alliances accounted for 6.3% of expenditure in 2001 and this was estimated to increase by one percentage point to 7.3% in 2002 for those 11 "other" companies.

The percentage of R&D expenditure allocated to external outsourcing contracts for the years 1998-2002e is presented in Figure 3.16. The median percentage demonstrates minor year on year fluctuations reaching a high of 22% in 1999 and a low of 19% in 2000. Most remarkable however, is the increasing range of individual company data. For 1998, half of the companies for which 1998 data

Figure 3.16 Percentage of R&D expenditure allocated to outsourcing (1998-2002e)

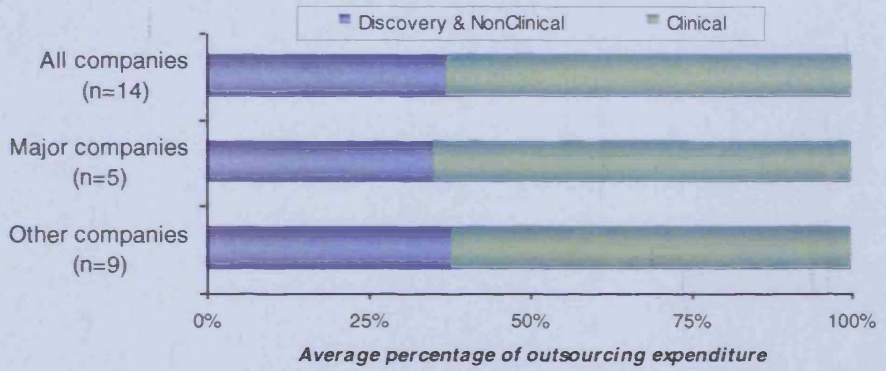


(n) is the number of companies. Data is presented as 5th -95th percentile range (whiskers), 25th – 75th percentile range (box) and median (diamond).

were available indicated to have allocated between 19% and 26% of their R&D expenditure to outsourcing activities (25^{th}-75^{th} percentile range, box), a spread of seven percentage points. A continuous rise in this range was observed over the four-year period, reaching a spread of 22 percentage points in 2001 (from 10% to 32%). For the 19 companies that provided estimates for 2002, this range was predicted to decrease slightly to 20 percentage points, still a considerably wider range than the seven percentage points observed in 1998.

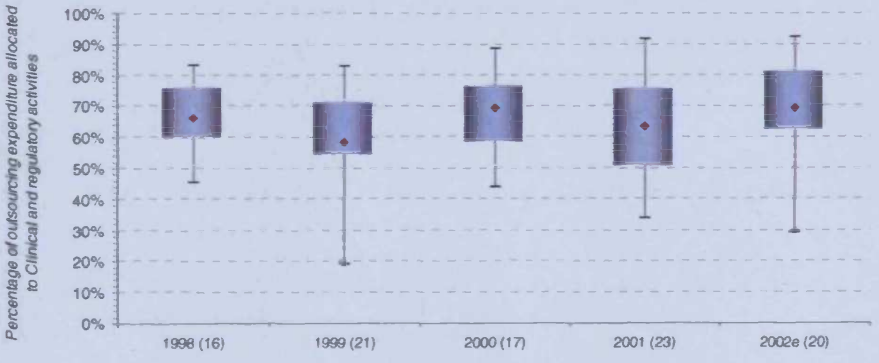
The majority of outsourcing expenditure occurred in the later phases of the R&D process (Figure 3.17). Five "major" companies and nine "other" companies indicated that around 60% of their outsourcing expenditure in 2001 related to clinical and regulatory activities and only a third of outsourcing expenditure was allocated to discovery and non-clinical activities.

Figure 3.17 Outsourcing expenditure by stage of R&D by company cohort (2001)



A slight variation was demonstrated in this distribution over the four-year period 1998-2001. The percentage of outsourcing expenditure (median value) allocated to clinical activities fluctuated between 58% and 69%, with the range around the median remaining relatively stable between 1998 and 2000 (around 17 percentage points), increasing slightly in 2001 to 25 percentage points (Figure 3.18). Estimates for 2002, however, suggested that this increase was likely to be due to year on year variation rather than be interpreted as a change in companies' outsourcing policy.

Figure 3.18 Percentage of outsourcing expenditure allocated to clinical and regulatory activities (1998-2001)

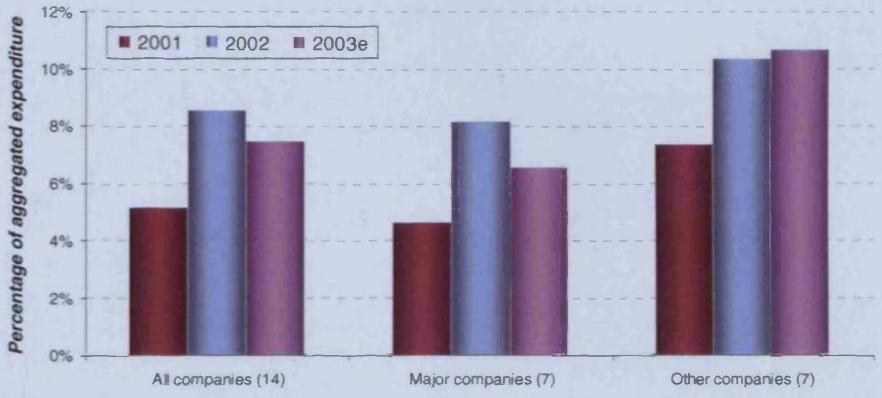


(n) is the number of companies. Data is presented as 5th -95th percentile range (whiskers), 25th – 75th percentile range (box) and median (diamond).

Data relating to alliance expenditure were first collected in the 2001 study. A cohort of seven "major" and seven "other" companies provided this type of information for both years 2001 and 2002, as well as providing estimates for 2003 (Figure 3.19). The percentage of expenditure allocated to alliances increased considerably from 2001 to 2002, for both "major" and "other"

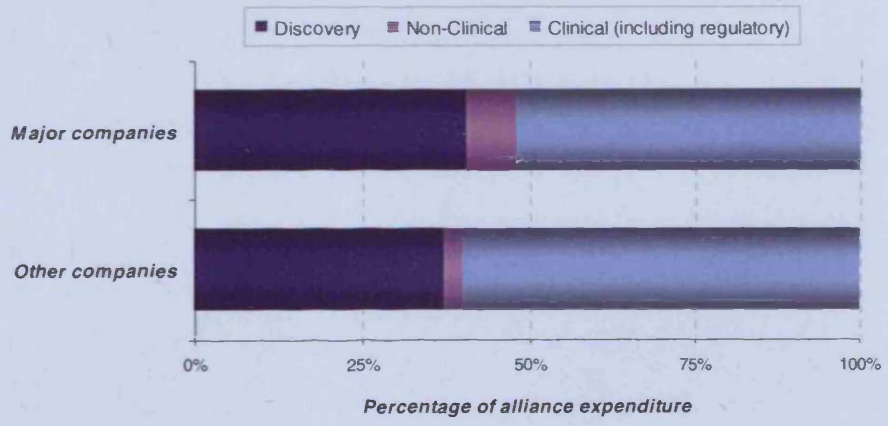
companies in this cohort. "Major" companies almost doubled this percentage from 4.6% in 2001 to 8.1% in 2002. For 2003, they predicted a slight decrease for the percentage of R&D expenditure allocated to alliances to just over 6%. "Other" companies, on the other hand, indicated that they would continue to allocate around 10% of their R&D expenditure to alliances in 2003.

Figure 3.19 Aggregated percentage of R&D expenditure allocated to alliances by company cohort (2001-2003e)



The distribution of alliance expenditure by stage of R&D showed a slightly higher emphasis on activities early in the R&D process than the distribution of outsourcing expenditure for "major" companies. Nine "major" companies indicated that almost half of their alliances expenditure was focused on discovery (41%) and non-clinical activities (7%), compared to one-third of that of the outsourcing expenditure (Figure 3.17 and Figure 3.20). "Other" companies demonstrated a slight difference in their alliance expenditure with a bigger

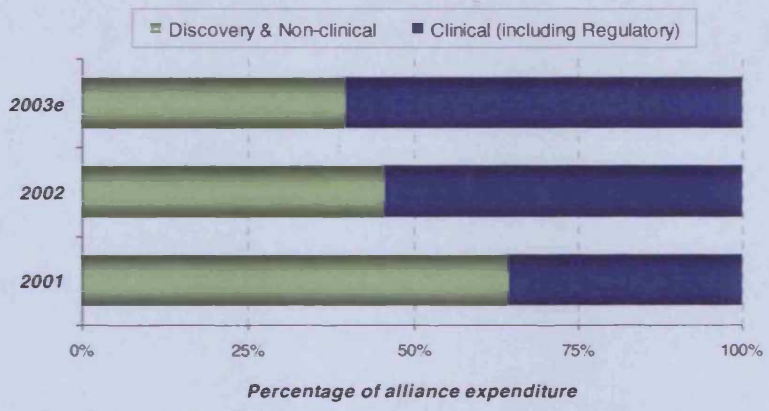
Figure 3.20 Percentage of alliance expenditure by stage of R&D by company cohort (2002)



emphasis on clinical activities, accounting for 60% of the total amount spent on alliances in 2002.

Relevant data available from two "major" companies and eight "other" companies suggested a shift in the balance between alliance expenditure on clinical activities and alliance expenditure on discovery and non-clinical activities over the three-year period 2001-2003e (Figure 3.21). In 2001, around

Figure 3.21 Percentage of alliance expenditure by stage of R&D (2001-2003p)



Statistical analysis of these data using a Friedman test shows that there was no significant change over the period 2001-2003e for the companies included in the analysis (two "major" and eight "other" companies, p>0.05)

two-thirds of alliance expenditure was allocated to discovery and non-clinical activities. In 2002, alliance expenditure was almost equally distributed between the two types of activities. For 2003 however, this cohort of companies estimated that around two-thirds of alliance expenditure would be allocated to clinical activities. The visual shift of focus from Discovery & Non-clinical to Clinical activities was not significant.

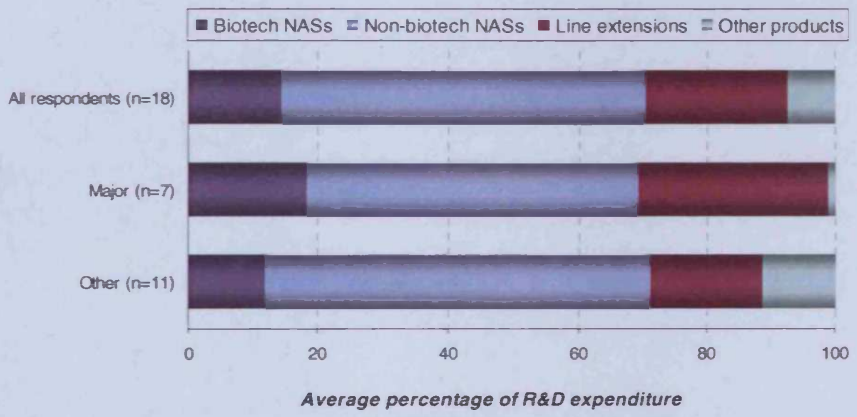
R&D expenditure for NASs vs. line extension products.

On average, new active substances (NASs) accounted for over two-thirds of R&D expenditure in 2002, for both "major" and "other" companies. Within this, "major" companies allocated a higher percentage of R&D expenditure to the R&D of biotech compounds than "other" companies (18.2% and 11.8% of total R&D expenditure, respectively). "Major" companies also allocated a higher percentage of their R&D expenditure to the development of line extensions (29.5%), whereas "other" companies demonstrated a focus on "other" products,

such as contraceptives and hormonal preparations, in comparison to "major" companies (7.4% and 1.1%, respectively) (Figure 3.22).

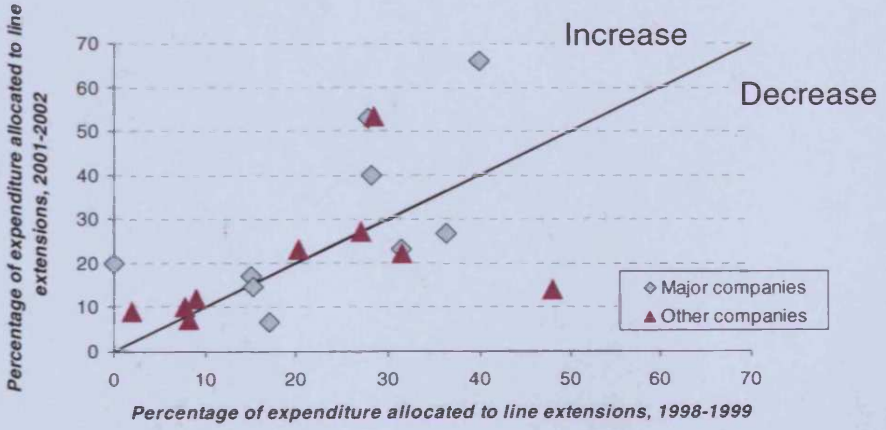
When comparing the percentage of R&D expenditure allocated to the R&D of line extensions for the years 1998/1999 with the same metric for 2001/2002 (Figure 3.23), companies could be split into three categories: (1) those that continued to allocate the same percentage of R&D expenditure to line extension

Figure 3.22 Percentage of R&D expenditure by product type by company cohort (2002)



Statistical analysis of the proportion of expenditure allocated to line extensions for "major" and "other" companies using a Mann-Whitney U-test showed no significant difference between the two company cohorts (p>0.05).

Figure 3.23 Percentage of R&D expenditure allocated to line extensions (1998-1999 vs. 2001-2002)



Representing companies where the percentage of R&D expenditure allocated to line extensions was available for at least one year of the years 1998 and 1999 and for at least one year of the year 2001 and 2002. Where data was available for both years, the average of the two years was calculated.

activities (data points located on the line in Figure 3.23), (2) those that increased this percentage (data points located above the line in Figure 3.23), and (3) those that decreased the percentage of line extension expenditure in favour of the R&D of NASs (data points located below the line in Figure 3.23). No differences were observed between "major" companies and "other" companies, with any of the three categories including companies from both cohorts.

Sales vulnerability

The likelihood of loss of income from patent expiration due to generic competition is assessed using a combination of two parameters; the percentage of sales derived from top three products and the percentage of sales derived from recently launched products, where recently launched is defined as launched in the four years preceding the year on which data were collected or launched during that year. Nineteen companies indicated that in 2002, on average, they derived half of their sales from top three products. This percentage is slightly lower for "major" companies than for "other" companies (45.8% and 55.1%, respectively). Sixteen companies provided information relating to the percentage of 2002 sales derived from recently launched products. Only a minor difference was found between six "major" and ten "other" companies, with the first cohort having derived on average 18.5% of their sales from recently launched products and the second cohort having derived an average of 17.3% of their sales from recently launched products (Table 3.7).

Table 3.7 Percentage of sales attributable to top three products and derived from products first marketed in the previous five years (2002)

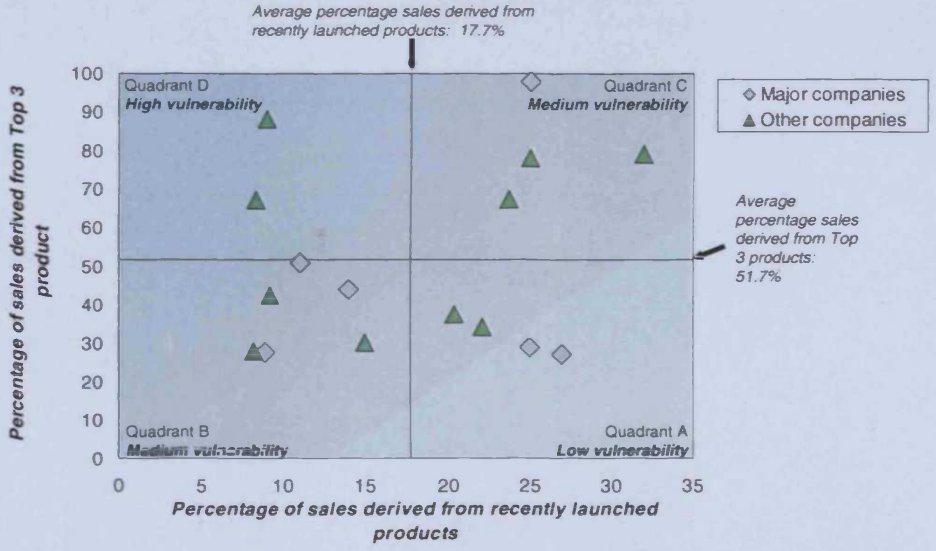
	% sales of top three products		% sales for the previous five years	
	%	Number of companies	%	Number of companies
All respondents	50.7	19	17.7	16
"major" respondents	45.8	9	18.5	6
"other" respondents	55.1	10	17.3	10

Although little difference was found between the two company cohorts, individual company data for 16 companies for which all relevant data were available revealed a wide spread for both metrics in 2002 (Figure 3.24), ranging

from 27% to nearly 100% of annual sales being derived from top three products. The percentage of sales derived from recently launched products ranged from 8% to over 30%.

The graph shown in Figure 3.24 can be divided into four quadrants. Companies in quadrant A reported an above average percentage of sales being derived from recently launched products, and a below average percentage of sales being derived from the top three products. The likelihood of loss of income from patent expiration due to generic competition is lowest for the companies in this quadrant. The relatively high number of recent product launches and the relatively low dependence on the three Top products are signs that even if a

Figure 3.24 Vulnerability to loss of income from patent expiration due to generic competition, 2002



product is nearing the end of its patent protection the remaining portfolio has sufficient substance to support ongoing income. At the other end of the scale are those companies falling into quadrant D. With limited sales derived from recently launched products and a high dependency on the top three selling products the likelihood of loss of income from patent expiration is highest for the companies in this quadrant. Companies in quadrant B indicated that a relatively high percentage of sales was derived from products that have been marketed more than 5 years ago, and that are therefore nearer to patent expiration than recently launched products. However, their income is derived from a number of products indicating that if a product does go off patent, the proportion of income

that could be lost to generic competition will be limited. For companies in quadrant C, the situation is reversed. Although a relatively high proportion of sales was derived from recently launched products, the companies in this quadrant reported a high dependence on a limited number of products. If one or more of the top three products become subject to generic competition, the proportion of income that could potentially be lost is substantial. In short, the vulnerability to loss of income from patent expiration due to generic competition was highest for companies grouped in quadrant D and lowest for companies in quadrant A. Companies in quadrant C and B were classified as "medium vulnerability" to loss of income.

Data on both metrics relating to 2002 sales data were available for six "major" companies and ten "other" companies (Figure 3.24). None of the "major" companies was placed in quadrant D (highest vulnerability to loss of income), with two "major" companies being placed in quadrant A (lowest vulnerability to loss of income). Of the remaining four "major" companies, one company reported to have derived >90% of its sales in 2002 from three products. The ten "other" companies were evenly distributed over the four quadrants, with two companies located in quadrant D (highest vulnerability to loss of income) and two companies located in quadrant A (lowest vulnerability to loss of income).

DISCUSSION

MacFarlane (1998) demonstrated that the investment of the international pharmaceutical industry in the research and development of ethical pharmaceuticals had doubled during the five-year period 1990-1994. The results of the study described in this chapter indicated that global R&D expenditure continued to increase since then, with the pharmaceutical industry investing an estimated US$ 39bn in R&D in 1998. In 2002, global R&D expenditure was estimated to have reached US$ 48bn, representing an overall increase of 75% over the ten-year period 1993-2002. The average annual growth rate from 1998-2002 was observed to be 5.4%. If growth continues at this rate, it is predicted to reach US$ 62bn by 2007. In 2003, global sales was estimated to have reached US$ 50bn, confirming continued growth in the level

or R&D investment (CMR International, 2004a). Increasing clinical development costs are quoted as at least partially driving this upward trend. Increasing regulatory complexity and the expansion of clinical trials to comply with marketing requirements could be underlying the increased clinical workload. Since 1980, the average number of clinical trials conducted before filing a NDA has more than doubled and the number of patients in clinical trials per new drug application has increased three-fold (Engel, 2000). Other suggested explanations for the continuous increase in R&D expenditure were sought in the different indications for which medicines are being developed. Many of the diseases that fuelled the growth in profit and turnover in the pharmaceutical industry in the 1980s and 1990s (e.g. asthma and gastric ulcers) are now well controlled, reducing the potential added-value of any new treatment in these areas. Many of the diseases for which treatment is still inadequate (such as neuropsychiatric diseases or cancer) are chronic, with complex pathophysiology and difficult outcome measures (De Visser, 2003). Arlington (1999) suggested that the increased R&D investment could also partially be attributed to a growing number of products in the pipeline. This hypothesis will be examined in the study reported in Chapter five, in which the global ethical pharmaceutical development pipeline is studied in more detail.

Global sales figures have more than matched the observed growth in R&D expenditure. Global pharmaceutical sales increased by more than 80% over the last decade, reaching US$ 430bn in 2002. If the annual growth rates observed for the period 1998-2002 continue (7.7%), global sales figures are estimated to cross the US$ 600bn mark in 2007. Recent figures from IMS Health puts global sales for 2003 at almost US$ 500bn, confirming continued growth (Anon, 2004).

Hypothesis 1: The proportion of sales re-invested in the research and development of ethical pharmaceuticals has remained constant over the duration of this study.

In the light of shareholders expectations of the industry's profit margins, it is not unreasonable to expect that R&D expenditure is budgeted as a fixed percentage of sales and that this has remained constant over time since increasing this percentage may lead to lower profit margins. On a global level,

growth in pharmaceutical sales has outpaced growth in pharmaceutical R&D expenditure over the duration of this study (1998-2002). As a result, the proportion of sales that was re-invested in the research and development of ethical pharmaceuticals by the industry as a whole has significantly declined from 12.6% in 1998 to 11.1% in 2002 ($p<0.05$). An insufficient number of companies provided this type of information consistently for all five years 1998-2002 to support meaningful conclusions to be drawn from the aggregated company R&D to sales ratios for all five consecutive years. However, 19 companies provided this information for 1998 as well as 2002. Almost half of these companies reported a ratio for 2002 that was over ten percent lower than that reported for 1998. Only three companies reported an increase by more than ten percent over this period of time. A distinct difference was observed between R&D expenditure as a percentage of global sales (11%-12%) and the average R&D to sales ratio based on individual companies' data (16-17%). This was most likely due to the slight difference in inclusion criteria for global sales and for sales figures for individual companies. Global sales data were obtained from IMS Health and included a limited amount of OTC data whereas the individual company data were limited to sales derived from ethical pharmaceuticals only. The R&D components of both calculations were based on the same definitions and related to ethical pharmaceuticals only. A second factor potentially underlying the observed difference is the fact that although participating companies were responsible for the majority of global pharmaceutical R&D expenditure, they represent only a small proportion of the more than 1400 companies active in pharmaceutical R&D (Lloyd, 2003). The companies represented in this survey are mainly large to medium-size companies, with expenditure patterns that can differ substantially from the really small companies.

The above data did not support the hypothesis that the proportion of sales re-invested in pharmaceutical R&D has remained constant over time. Rather, a statistically significant decrease was shown for the "major" companies included in the analysis. One potential driver for this could be that companies, in order to satisfy continuous demand from shareholders for growth, are cutting expenditure to make up for lower sales figures. Recent announcements made

by pharmaceutical companies seem to support this theory. Eli Lilly, GlaxoSmithKline, Bristol-Myers Squibb, Schering Plough and Merck & Co all reported decreasing revenues due to generic competition following loss of patent protections for one or more of their key products (Anon, 2004g; 2004h; 2004i; 2004j; 2004k). To increase profits, despite disappointing revenues, some companies are resorting to workforce reductions. In 2003, Abbott cut 2000 jobs, while Merck & Co announced the elimination of 4400 positions (Arndt, 2004). Similarly, Schering AG announced that it is on track to reducing its workforce with 2000 jobs by 2006 (Anon, 2004l). However, decreasing R&D expenditure, although a seemingly effective short-term remedy, could backfire on the industry in the long run. If the R&D budget is merely set as a percentage of sales, and is not supported by a thorough assessment of what resources are required to develop the current pipeline and support ongoing discovery activities, it is highly unlikely that the industry can improve its performance. Only if a diminished R&D budget coincides with company-wide efforts to improve the efficiency of its R&D function, might the industry be able to address the current productivity crisis in terms of the declining number of new medicines reaching the market.

More and more companies are making use of co-development, licensing-in and outsourcing as alternatives to the traditional business model of an integrated pharmaceutical company, undertaking all activities by itself, from the earliest discovery stages through to marketing (Arlington, 1999; Dyer, 2002; Engel, 1999). Doing everything within one company carries a higher risk with increasingly significant investment. Partnerships, licensing and outsourcing can lower risk and volatility and at the same time provides access to skills and expertise not available within the organisation itself (Gilbert *et al.*, 2003; Lam, 2004a; Grabowski, 2000). Signs of these developments could potentially be found in surrogate markers such as the proportion of the development pipeline that does not originate from a company's own discovery function and the percentage of R&D expenditure allocated to these type of activities. In this study the allocation of R&D expenditure was investigated in detail, whereas the effects on the global ethical development pipeline were investigated in the study reported in Chapter five.

Hypothesis 2: Companies are increasingly entering into partnerships with other organisations for the research and development of new medicines, which is reflected in an increased proportion of their R&D expenditure being allocated to alliances.

The percentage of expenditure allocated to alliances was collected from 2001 onwards. For the 14 companies providing the information for both years, this percentage almost doubled from five percent in 2001 to nine percent in 2002. This increase was observed for both "major" and "other" companies, although "other" companies predicted that this increase would continue in 2003, whereas "major" companies predicted a minor decrease in 2003. Based on expenditure allocated to alliances, partnerships were present in both the early and later stages of the R&D process. The percentage of alliance expenditure allocated to clinical and regulatory activities demonstrated an increase from around 30% in 2001 to an estimated 60% for 2003. Although data were only available from 2001 onwards, the observed increase in the proportion of R&D expenditure allocated to alliances suggests that companies are indeed increasingly entering into partnerships. Furthermore, the data seem to suggest that this increase is mainly driven by an increased use of partnerships in the clinical and regulatory stage of the R&D process. Partnerships and collaborations in both early and late stages of the R&D process will allow companies to share both cost as well as make use of external expertise not available within the organisation itself (Arlington, 1999; Fumero, 2002; Anon, 2004a). The academic world can be explored for innovative research, molecules and technologies, providing access to a much wider knowledge base than could be built internally, at much lower cost (Fumero, 2002). Similarly, collaborations at later stages, either with specialist companies or with peers, could provide access to expertise or budgets not available internally. For example, a small company with less of an international presence could engage with a larger company, thereby gaining access to clinical trial facilities not within reach of its own budget and at the same time offering its partner access to a proportion of potential revenue. A strategic approach to partnerships and collaborations is required to ensure that it is not seen as the less desirable way of acquiring new technologies or products ('not-invented-here' syndrome) or that the organisation becomes entirely dependent on external parties (DeLamarter and Fumero, 2001). The

latter is of special importance in discovery. Although a wealth of knowledge, technologies and potential new products can be obtained from academia or specialist discovery organisations, this is available to all whereas a company's internal discovery function contributes greatly to its competitive position.

Hypothesis 3: Companies are increasingly outsourcing both their discovery and development activities, which is reflected in an increased proportion of R&D expenditure allocated to these type of activities.

In 2001, "major" companies (i.e. those spending US$ 1bn or more on ethical pharmaceutical R&D) allocated around 14% of R&D expenditure to activities contracted out to external organisations. Smaller companies appeared to make slightly more use of services offered by contract research organisations (CROs) and other companies, with 19% of expenditure allocated to outsourced activities. In general, around two-thirds of contracted-out activities related to clinical and regulatory stages of the R&D process.

The spread of the individual company data around the median increased considerably from 1998 to 2001. Over this time period, the range from the 25th to the 75th percentile increased from seven percentage points to 22 percentage points. This suggests that, although no apparent increase or decrease in the use of outsourcing was observed for the industry as a whole, the approach of individual companies appears to differentiate over this period of time. Some companies had decreased the proportion of expenditure allocated to outsourcing, suggesting that they were focusing on in-house development, whereas other companies appeared to have increased their reliability on external contract organisations. No change was observed in the distribution of expenditure allocated to outsourcing between discovery/non-clinical activities and clinical/regulatory activities, suggesting that any increase or decrease that might have taken place would be reflected in both early and late R&D activities.

The outcome of this study indicates that the industry as a whole does appear to recognise the potential of strategic options such as outsourcing and co-development. A widespread variation was observed, however, in the extent to which individual companies use these "building blocks", suggesting that there

might not be a one-size-fits-all solution in facing the current pressures to which the industry is subjected. Instead companies are developing individual strategies, making use of those options that are most suitable for their specific situation.

Hypothesis 4: Companies have invested an increasing percentage of their R&D expenditure in life cycle management.

Extending the life cycle of a drug substance by developing line extensions of the original product is one of the strategies that companies can employ to both diminish the loss of income due to patent expiration as well as to provide patients with improved treatment opportunities. In the light of the high number of top-selling products either having lost patent or about to loose patent (Beynon, 2000), it is logical to expect an increased effort by companies to maximise the value of their drug substances by developing line extensions, resulting in an increased proportion of R&D expenditure being allocated to these type of activities.

For a cohort of seven "major" and 11 "other" companies, it was observed that in 2002 around 22% of R&D expenditure was allocated to the development of line extensions, with "major" companies spending proportionally more than "other" companies (30% vs. 18% respectively), although this difference was not significant. Within each cohort, no clear pattern could be identified as to changes over time. In the comparison of the proportion allocated to line extensions in 1998/1999 with the 2001/2002 proportion, both cohorts included companies that reported increased proportional line extension expenditure as well as companies that reported a decrease. The outcome of the study does not support an overall increase in the percentage of R&D expenditure allocated to the development of line extensions. However, it does suggest that individual companies have started to recognise its value and have increased their investment in this area.

However, a similar comparison of relative line extension expenditure between 1997 and 2001 for a cohort of six "major" and eight "other" companies showed a different picture. Ten of the 14 companies reported an increased proportion of

R&D expenditure in 2001 compared to 1997, and data for only three companies showed a decrease (van den Haak, 2002), suggesting that the alleged increased focus on line extensions had already occurred prior to the time period reported in this study.

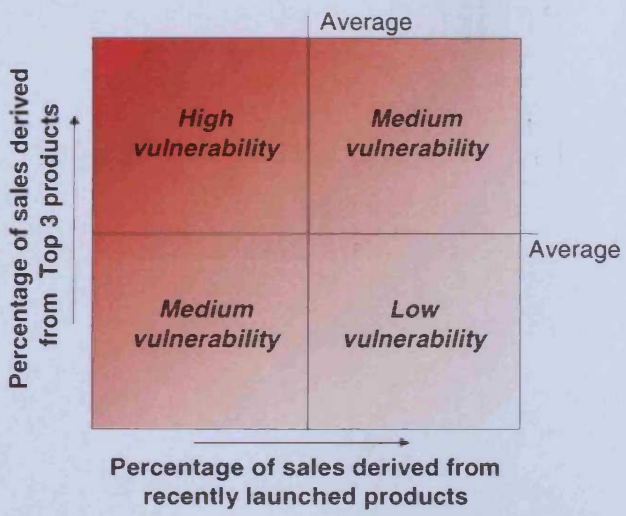
The overall level of R&D investment in life cycle management as observed in this study were corroborated by findings from Engel (2000), who reported that about 18% of R&D expenditure in the USA was devoted to significant improvements or modifications of existing products. How successful life cycle management can be is proven by products such as Adalat, which was launched in 1975 for the treatment of angina. The patent for this Bayer product expired in 1985, but in 2000 the product was still generating more than a billion US dollars in sales. Recognition of emerging indications (hypertension), dosage flexibility and geographic expansion were quoted as factors that had contributed to the product's success (McCarthy, 2001).

Hypothesis 5: The vulnerability to loss of income from patent expiration due to generic competition varies across the industry.

By the end of 1999, the industry faced the expiration of 50 patents between 1999 and the end of 2005 (Engel, 1999; Beynon, 2000). Although the impact on the industry in its entirety is undisputable, it is logical to expect that its impact on individual companies will vary, depending on each company's portfolio of marketed products.

In this study, the vulnerability to loss of income from patent expiration due to generic competition was assessed using a combination of two parameters: the percentage of sales derived from top three products and the percentage of sales derived from recently launched products. Companies were grouped into four cohorts based on these two parameters. Companies were considered to be at high risk to loss of income from patent expiration when the percentage of sales derived from their Top 3 products was above average and the percentage derived from recently launched products was below average, suggesting that a relative high proportion of their income was derived from products that have been on the market for some time, which are therefore more likely to undergo

patent expiry. Similarly, companies reporting a below average proportion of sales derived from top three products and an above average proportion of sales derived from recently launched products were considered to be least vulnerable.



Ten of the 16 companies for which both metrics could be calculated were classified as having medium vulnerability to loss of income from patent expiration due to generic competition. Two companies were classified as highly vulnerable, with one company deriving 90% of its sales from three products, with recently launched products accounting for less than 10 percent. It should be noted that this analysis is an assessment of the vulnerability and not of the likely of individual companies loosing income from patent expiration due to generic competition, which is illustrated by the fact that one of the three companies observed to be at low risk is currently facing generic competition of multiple top selling products. However, due to this company's balanced portfolio of marketed products the impact will be relatively low compared to the impact generic competition might have on companies observed to be highly vulnerable.

An interesting observation was made for one "major" company (i.e. with R&D expenditure exceeding US$ 1bn in 2002). Although the vulnerability of this company was classified as medium, 98% of its sales were derived from the top three products. Because 25% of sales were derived from recently launched products, the relative vulnerability, compared to the other 15 companies included in the analysis was considered medium, however if one of the top three products would come off patent the impact could be significant.

SUMMARY

- In 2002, global pharmaceutical R&D expenditure was estimated at US$ 48bn, an overall increase of 75% over the ten-year period 1993-2002. The average annual growth rate from 1998-2002 was 5.4%. If growth continues at this rate, global R&D expenditure is predicted to reach US$ 62bn by 2007.

- Global pharmaceutical sales increased by more than 80% over the last decade, reaching US$ 430bn in 2002. If the annual growth rates for 1998-2002 continue (7.7%), global sales figures are estimated to cross the US$ 600bn mark in 2007.

- The outcome of this study showed that R&D expenditure to sales ratios for "major" companies and the industry as a whole declined from 1998 to 2002.

- The outcome of this study indicated that the industry as a whole does appear to recognise the potential of outsourcing and co-development, although a variation was observed in the extent to which individual companies use these strategic options.

- The postulated variety regarding vulnerability to loss of income from generic competition due to patent expiration was supported by the outcome of this study. Furthermore, it was demonstrated that companies could be vulnerable because of high dependency on a small number of products and/or limited income derived from newly launched medicines.

- The outcome of this study does not support an overall increase in the percentage of R&D expenditure allocated to the development of line extensions. It does suggest that individual companies have recognised its value and increased investment in this area.

CHAPTER FOUR

STUDYING TRENDS IN THE NUMBER OF NEW MOLECULAR ENTITIES LAUNCHED ONTO THE WORLD MARKET – A LONGITUDINAL STUDY

INTRODUCTION

The number of new medicines reaching the world-market on a yearly basis is a widely accepted metric for measuring the success of research and development (R&D) in the pharmaceutical industry. Reflecting the cyclical character of the pharmaceutical industry and many other industries, this measure could also be viewed as an indicator of the future sustainability of a company. R&D activities are funded mainly from income derived through product sales and in the competitive environment of the pharmaceutical industry; the life cycle of a product can be limited by challenges from generic competition. For a company to secure future income it is therefore vital to ensure that the portfolio of marketed products is regularly extended with new medicines. The contribution of these new medicines to income generation is two-fold. Firstly, as a direct input, sales of the product itself will contribute to the overall income of the company. Secondly, in a more indirect manner, newly developed drug substances will provide a company with ample opportunities to develop subsequent products. Sales from these line extension products will also increase the company's income.

Over the last decade, a steady increase in global R&D expenditure has been observed (Chapter three). However, it is questionable whether or not this translates into the development of an increased number of new medicines. The cost of bringing a new drug substance to market has increased considerably over the last two decades. The average cost for products approved during the 1980s was estimated by DiMasi (2003) to amount to a total of US$ 318Mn (in 2000$). Having updated the calculation in recent years for products approved during the 1990s, it was estimated that the current cost to develop a new drug from discovery to approval has now reached a value in excess of US$ 800Mn (in 2000$, DiMasi *et al.*, 2003). Not taking into account inflation, the pharmaceutical industry increased their combined R&D expenditure by US$ 20bn in the ten years leading up to 2002. However, the main question remains whether or not this has been sufficient to support the development of an increased number of medicines reaching the market.

A study was developed investigating details of new molecular entities (NMEs) launched onto the world market between 1993 and 2002. Additionally, participating companies were asked to provide details on all regulatory and marketing activities in the major pharmaceutical markets for the years 1998-2001 to support assessment of pending approvals as an indication of future output.

OBJECTIVES

Data collected in this study have been used to evaluate new molecular entities reaching the market between 1993 and 2002 in order to generate evidence to test the following hypotheses:

1. The annual number of NMEs reaching the market has remained constant over the duration of this study.
   It is postulated that the 80% increase in R&D expenditure from 1993 to 2002 (Chapter three) was sufficient to sustain a constant output in terms of the annual number of NMEs reaching market over this period of time.

2. The overall level of innovation, in terms of the number of new medicines that are first or second in class, has increased over the duration of this study.
   Increasing pressures from governments and regulatory authorities to demonstrate efficacy and safety over and above that of existing treatments as well as pharmaco-economic benefits means that product innovation is key to maximising the economic value of a product. It therefore seems logical to expect an increasing proportion of new product launches to be first or second in class based on the pharmacological mode of action.

3. Biotechnology has made a considerable contribution to the pharmaceutical industry's new medicine output and this has increased over the duration of the study.
   Considering the growing biotechnology industry and the continuing quest

from pharmaceutical companies for innovative medicines, it seems logical to expect an increasing proportion of new medicine launches derived through biotechnological processes.

4. "Major" companies are responsible for the majority of new medicines reaching the market.
   "Major" companies (i.e. those spending US$ 1bn or more on ethical pharmaceutical R&D) accounted for over 62% of global R&D expenditure in 2002. It therefore seems logical to expect that this cohort of companies is responsible for the development and marketing of the majority of new medicines reaching the market.

5. The overall development time for new medicines, from first synthesis to first launch, has decreased over the duration of this study.
   The impetus in the mid and late 1990s was on cutting both development times and regulatory review times. It therefore seems reasonable to expect a downward trend in development times.

METHODS

The data in this chapter have been derived by means of an annual questionnaire-based study entitled 'New Active Substance Activities: Submission, Authorisation and Marketing'. This study has two sections:

Section I

The first section of the study focused on NMEs reaching the world market between 1993 and 2002. The objective of this section was to obtain a complete list of new medicine launches each year and great efforts were made to ensure all NMEs launched onto the world-wide market were identified. These efforts included:

- Contacting all companies who had participated for one year or more in Section II of the survey;
- Literature research;
- Interrogation of pipeline data collected for the study reported in Chapter five;
- Interrogation of PJB Publications' PharmaProjects database (PJB, 2005).

Section II

The focus of the second section was on submission, authorisation and marketing activities for new active substances (NASs) in the major pharmaceutical markets (18 European countries, USA, Japan, Canada and Australia) in the period 1998-2001. This part of the study was initiated with a pilot study in 1996 (MacFarlane *et al.*, 1997; MacFarlane, 1998). Subsequent studies encompassed the top pharmaceutical companies by R&D expenditure, as well as the leading biotechnology companies. Invitations to participate were sent to at least the Top 20 pharmaceutical companies and the Top five biotechnology companies, based on pharmaceutical R&D expenditure in the year over which data were to be collected. References for annual pharmaceutical R&D expenditure were obtained from the September issue of MedAdNews Magazine (Anon, 1999b; 2000b; 2001b; 2002; 003c). This list of Top 20 pharmaceutical companies and Top 5 biotechnology companies was complemented with any other company undertaking ethical pharmaceutical R&D that had expressed an interest in this type of study in the past and within which a suitable contact could be identified. Companies invited to participate in one or more years are listed by name in Table 2.1 (page 25) with an overview of the number of companies invited year on year provided in Table 4.4.

Data collection

The study focused on new ethical (prescription only) pharmaceuticals, excluding any additional activities such as veterinary medicines or over-the-counter products. In section one of the study, companies were asked to provide information on all NMEs that were launched in their first market during a given year. In the second section, they were asked to provide details of all submissions, authorisations and marketing activities in the world's 22 major markets (18 European countries, USA, Canada, Japan and Australia) in a given year. In the study on activities during 2001, companies were asked to provide information on the number of line extension products launched in addition to details on NASs launched in their first world market. For all other years, data collection was limited to NAS activities. For the calendar year 2002, data were collected for section one of the survey only.

The content of the questionnaire was assessed annually to ensure that up-to-date and relevant information was collected. Definitions were provided along with the questions to encourage consistent responses from companies. An overview of how the questionnaire evolved over the years 1998-2002 is provided in Table 4.1 (Section I) and Figure 4.2 (Section II).

The questionnaire used for data collection for 2001 is provided in Appendix III. Companies that had participated in the study in previous years were supplied with data provided in these years in Section II and asked to confirm and update the information. Additionally, to minimise the workload of providing the requested information, where public domain information was available on submission, authorisation or marketing activities, this was provided to participants for validation.

A thorough search of public domain information was undertaken annually to extend the list of NASs first launched by study participants with NMEs launched by companies not participating in the study. Any information obtained from the public domain was confirmed with the relevant marketing company. By doing so, a complete list of all NMEs reaching the market was composed annually, with details of the brand name, the generic name, the date and country of first world launch, the marketing company and a description of the therapeutic benefits of the product.

Data collection for the first section of the study took place in the three months of the year following the calendar year in which activities took place, i.e. the questionnaire for data collection on activities in 1998 was made available between January 1999 and March 1999. The objective of this round of data collection was to create a complete list of all NASs that first reached the market in the year for which data were collected. Each company likely to have launched a new medicine onto the world market, based on data from the public domain and on data collected in previous years on submission and authorisation activities, was contacted either by letter, e-mail or phone. If no response was received from the original contact within a company, other departments (e.g.

Table 4.1 Characteristics of NMEs requested in Section I, 1993-2002

Question	1993-1999	2000	2001	2002
NMEs reaching the world market in theyear				
• Generic name	✓	✓	✓	✓
• Pharmacological class	✓	✓	✓	✓
• First indication	✓	✓	✓	✓
• Biotech compound yes/no	✓	✓	✓	✓
• Originating company	✓	✓	✓	
• First world marketing date & country	✓	✓	✓	✓
• First phase I initiation date	✓			
• Patent priority filing date & country	✓	✓	✓	
• First synthesis date & country	✓	✓	✓	
• Brand name			✓	✓
• Co-marketing company			✓	✓
NMEs expected to reach the world market in following year				
• Generic name	✓	✓	✓	
• Biotech product yes/no	✓	✓	✓	
• Therapeutic area	✓	✓	✓	

Table 4.2 Aspects of submission, authorisation and marketing activities requested in Section II, 1998-2001

Question	1998	1999	2000	2001
NAS regulatory submissions in 22-country market – for each country				
• Generic name	✓	✓	✓	✓
• Country	✓	✓	✓	✓
• Submission date	✓	✓	✓	✓
• For EU countries only: Approval procedure (National / Mututal recognition / Centralised)	✓	✓	✓	✓
• Co-marketed yes/no		✓	✓	✓
• Submission method (electronic / partially electronic / paper-based)			✓	✓
NAS regulatory marketing authorisations in 22-country market – for each country				
• Generic name	✓	✓	✓	✓
• Country	✓	✓	✓	✓
• Date on which marketing authorisation was granted	✓	✓	✓	✓
• For EU countries only: Approval procedure (National / Mututal recognition / Centralised)	✓	✓	✓	✓
• Co-marketed yes/no		✓	✓	✓
NAS marketing activity in 22-country market – for each country				
• Generic name	✓	✓	✓	✓
• Brand name	✓	✓	✓	✓
• Country	✓	✓	✓	✓
• Marketing date	✓	✓	✓	✓
• Co-marketed yes/no		✓	✓	✓
Line extension activities (1) in the year:				
• Number of line extension submissions			✓	
• Number of active substances for which line extension submissions were made			✓	
• Number of line extension approvals			✓	
• Number of active substances for which line extension approvals were received			✓	
• Number of line extension product launches			✓	
• Number of active substances for which line extension products were launched			✓	
Line extension activities (2) – for each line extension product launched				
• Product description				✓
• Active substance (generic name)				✓
• Line extension type				✓

marketing or public relations) were contacted to obtain the required information. A simple one-page form was designed to assist in this data collection (see Appendix IV for an example of the form used to collect data for 2000).

In the second section of the study, information on NAS submission, authorisation and marketing activities in a 22-country market was collected during the second quarter of the year following the calendar year in which activities took place. Each company was contacted prior to sending out the questionnaire to identify the most appropriate person to receive the questionnaire. Recipients of the questionnaire were subsequently contacted to ascertain the likelihood of their participation in the study.

Use of historical data

For this study, data were collected from 1998 onwards. To allow assessment of trends and developments over time, the data collected in this study were added to the Centre for Medicines Research (CMR) International database on internationally marketed medicines (IMMED). This database was established in 1987 and holds comprehensive information on more than 1500 NMEs (including biological compounds and products of biotechnology) introduced onto one or more of the worlds 22 major markets (18 European countries, USA, Canada, Japan and Australia) since 1970. IMMED is continually being updated and data obtained from public domain sources are verified and supplemented with additional confidential information from pharmaceutical companies and regulatory authorities. Where historical data are presented, the activities of companies that now form part of a larger company, due to merger and acquisition activities, have been attributed to the company grouping in 2002.

External data sources

Annual R&D expenditure data were obtained from the study reported in Chapter three, data from which was added to CMR International's Global R&D Expenditure Database (GLOBEX). GLOBEX holds detailed information on annual ethical pharmaceutical R&D expenditure, capital expenditure, R&D full-time equivalents (FTEs) and sales from over 80 individual companies. Since its inception in 1982, the database has been kept up to date with confidential data

obtained directly from pharmaceutical companies through the annual R&D Expenditure and Sales study, supplemented with company confirmed data from the public domain.

Two additional data points were taken from external data sources to increase the number of new product launches for which total development time could be calculated. Information on the date on which the first compound code was assigned to a NAS was taken from CMR International's Global R&D Performance Metrics Programme as the equivalent of the first synthesis date (CMR International, 2003). Information on the patent priority filing, where not provided by the marketing company directly, was taken from PJB Publications' PharmaProjects (PJB, 2005).

Data processes and analyses

Following data provision, thorough checks were carried out to ensure data quality. Any data point provided by companies that was contradicted by data obtained from the public domain or provided by a second company was queried with the original data provider. The questionnaire on 1998 activities was made available in paper format only. In later years, companies were given a choice to submit their data either on paper or by use of an electronic, Microsoft Access™-based, questionnaire. The use of electronic questionnaires greatly improved the quality of the data collected by eliminating the need for additional data handling steps, such as interpreting handwriting and manually entering data into the database. As such participants were encouraged to provide data electronically rather than by returning the Word™ questionnaire.

Data were processed using Microsoft Access™. Both Microsoft Access™ and Microsoft Excel™ were used to obtain descriptive statistics of the data. SPSS™ for Windows™ was used to run statistical analyses on the data:

- *Linear regression* was used to test for significant changes over time in the number of NMEs reaching the market, as well as in the proportion of these NMEs that were biotech-derived and in the proportion of novel NMEs that were first or second in class.
- Differences in development times by company size ("major" vs. "other"

companies), by compound type (biotech vs. non-biotech) and by novelty ($1^{st}/2^{nd}$ in class vs. not $1^{st}/2^{nd}$ in class) were tested using the *Mann-Whitney U-test* since the data were not normally distributed.

- Differences in development times by therapeutic area and region of first launch were tested using the *Kruskal-Wallis test*. If significant differences were found in this test, *Mann-Whitney U-tests* were carried out on pairs of the data to test which categories were significantly different.

Details of NMEs rather than NASs were requested in section I of the study. More than 95% of the NASs in each analysis are also NMEs; exceptions include new salts, pro-drugs and esters of existing products, and certain biological compounds (e.g. antigens). The definitions for NASs and NMEs are provided in Table 4.3. Vaccines were excluded due to the difficulty in differentiating between vaccines containing new active components and those for which all active components are already in use in existing vaccines (Ashton, 2001).

Table 4.3 Definitions of NMEs and NASs

New Molecular Entities (NMEs) A product (including new chemical entities, biological products, vaccines and products of biotechnology) that has not been previously available for therapeutic use in man and is destined to be made available as a "prescription only medicine", to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in man. New salts, pro drugs and esters of existing products and certain biological compounds (e.g. antigens) are excluded. Combination products are also excluded unless one or more of the active constituents has never been previously marketed.
New Active Substances (NASs) A new active substance (NAS) is a chemical, biological or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a '**prescription only medicine**', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans. **The term NAS also includes:** • an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available; • a biological substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process; • a radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.

Observation of confidentiality agreement

Data collected in this study were covered by a confidentiality agreement with respondent companies, preventing the presentation of identifiable individual

company data. To assess whether any of the trends or developments observed differed between larger and smaller companies, respondent companies were characterised according to their level of global R&D expenditure in ethical pharmaceuticals in 2002. Companies for which 2002 ethical pharmaceutical R&D expenditure equalled or exceeded US$ 1bn were classified as "major" companies, whereas those companies for which this expenditure was less than US$ 1bn were classified as "other" companies.

Calculation of development time

Overall development time was calculated as the difference in years between the date of first synthesis of the active substance and the date of first world launch. The date of first synthesis was not readily available for all NMEs, therefore two surrogate starting points have been identified to maximise the number of NMEs for which development time could be calculated. The first surrogate marker was the date on which the first compound code was assigned to the active substance. The second surrogate marker was the date the first patent was filed (patent priority date). For 134 NMEs where both the date of first synthesis and the patent priority date were available, the median time from first synthesis to patent priority was 0.34 years. Therefore, where the patent priority date was used as a starting point, 0.34 year was added to the calculated difference in years to account for the time from first synthesis to patent filing. Those NMEs with development times of more than 25 years were excluded from all development time calculations, since it is unlikely that these compounds will have been in active development for this full duration (Ashton, 2001).

Determination of novelty

In determining whether a new product was an innovative launch, novelty of the mode of action is a key factor. For each NME reaching the world market, an assessment was made of the market entry position within its pharmacological class, e.g. if an NME was the first compound to be launched with a particular mode of action, the NME was assigned market entry position one; the second NME launched with that particular mode of action was assigned market entry position two, and so on. As a measure of novelty of the annual industry output, the percentage of NMEs with market entry position one or two was calculated.

This was based on the assumption that the development of both the first and the second in class will have experienced the complications of developing an NME with a new pharmacological mode of action, i.e. both developing companies will not have had the benefit of previous experience with this mode of action, either from within their organisation or externally.

Therapeutic area classification

Information on therapeutic area and / or indication was obtained by means of an open-ended question, enabling participants to provide as much or as little detail as they were able to identify. This information was then used to consistently classify all NMEs using the World Health Organisation (WHO) anatomical therapeutic and chemical code (ATC coded) system (WHO, 2002). Appendix VII provides an overview of the different therapeutic areas and the associated WHO ATC codes.

RESULTS

Characterisation of data source

For the first section of the study, it was critical that a complete list of new product launches was obtained; the number of participating companies was secondary to this. A full overview of all NMEs launched between 1998 and 2002 is provided in Appendix V. The completeness of the data collection effort was illustrated by the occurrence of only two new product launches being identified at later stages, after data collection for that year was completed. One NME first launched in 1999 was overlooked during data collection over that year. This oversight was identified during the next round of data collection. One product launched in 2002 was originally confirmed by the marketing company to be launched in January 2003. However, during data collection for 2003 (Read and Sculthorpe, 2004), the company indicated that it was launched in December 2002 instead. Both products have since been added to the list of new medicine launches and are included in the analyses presented in this thesis.

Participation in the second section of the study was not compulsory, as meaningful analyses could still be conducted using data taken from a subset of

companies, providing that this cohort represented the majority of the pharmaceutical industry. Table 4.4 provides an overview of the number of companies invited as well as the response rates for each year of data collection for Section II of the study. In any given year between 1998 and 2001, a minimum of 29 companies participated in the study, with a maximum of 50 companies participating in 1999. In 2001, the respondent companies represented 70% of global R&D expenditure.

Table 4.4 Number and characteristics of study respondents for Section II (1998-2001)

Year(s)	Number of companies approached	Number of respondent companies	Number of "major" respondent companies[a]
1998	67	35	10
1999	80	50	11
2000	100	30	10
2001	63	29[b]	11

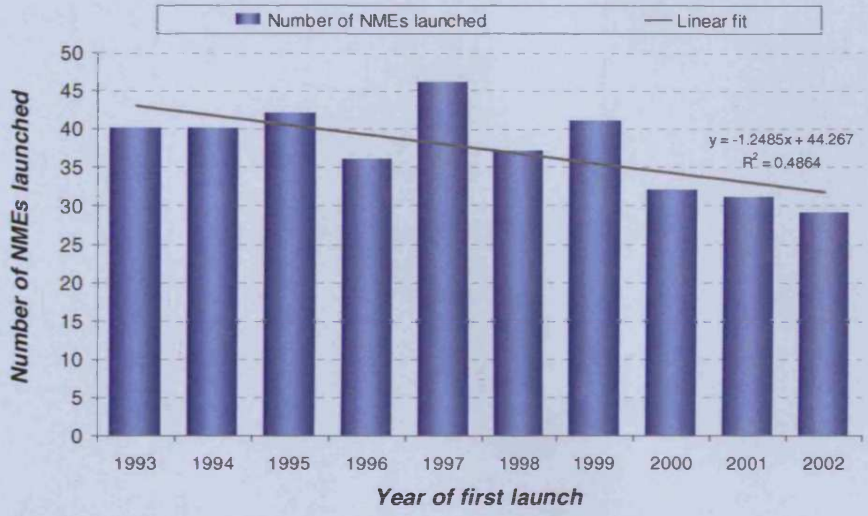
Based on company grouping and cohort as in year over which data were collected. [a]The total number of "major companies" per year varied between 14 and 15. [b]In 2001, respondent companies represented 70% of global R&D expenditure.

New medicine launches

During the 1990s, the output of the pharmaceutical industry in terms of the number of NMEs reaching the market per year remained relatively stable (Figure 4.1). Although year on year fluctuations were observed, an average of around 40 NMEs reached the market annually during the 1990s. However, in the first years of the new millennium this changed into a downward trend. A change in the stable condition of around 40 NMEs reaching the market was first noticeable in 2000 and continued through to 2002 when only 29 NMEs were launched. This significant downturn (regression model, $p<0.05$) in the number of new medicine launches is in sharp contrast with the increase in both R&D expenditure and sales global figures, both of which have nearly doubled over the last decade (Chapter three).

Even more pronounced was the downward trend observed in the number of NASs for which dossiers were submitted in the years 1998-2001 (Figure 4.2). In 2001, the number of submissions was only half of that in 1998 (176 and 352

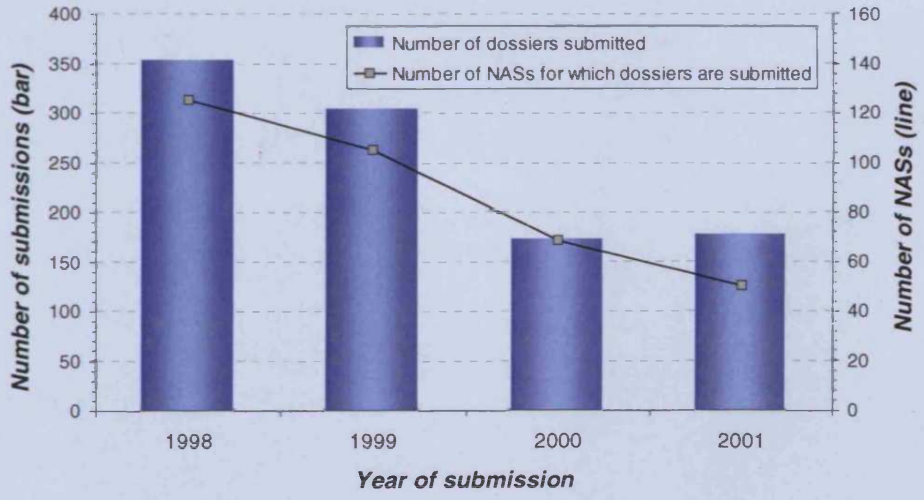
Figure 4.1 NMEs first launched onto the worldwide market (1993-2002)



Statistical analysis of these data using a linear regression model shows that there was a significant decline in the number of NME launches over time ($p<0.05$)

submissions, respectively) and the decrease in the number of NASs this related to was even more considerable; 125 NASs in 1998 vs. only 50 NASs for which submissions were filed in 2001. Similar trends were observed when looking at regulatory activities for a consistent cohort of six "major" and ten "other" companies providing the relevant information for all three years 1997, 1999 and 2001. For this cohort, representing 36% of global R&D expenditure in 2001, the number of NAS submissions dropped from 160 in 1997 to 51 in 2001. Although the data presented in Figure 4.2 were not limited to first marketing activities - instead it also includes activities in subsequent markets - the decreasing

Figure 4.2 Regulatory submission activities in the world's 22 major markets (1998-2001)

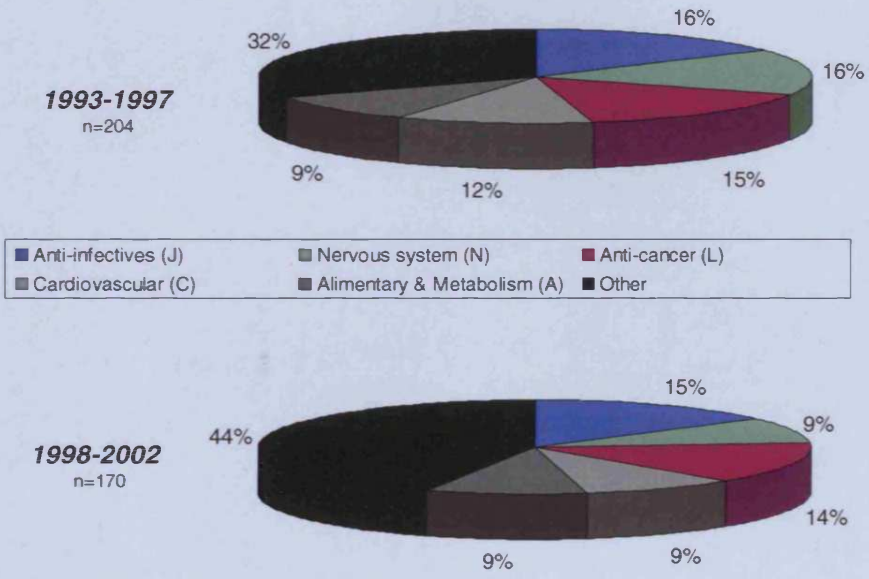


number of NASs for which dossiers were submitted can still be seen as an indication that a recovery of the falling number of new product launches is not likely to happen in the near future.

Therapeutic area

Analysing the NME output by therapeutic class illustrates how the therapeutic area focus of the industry has changed over the last ten years (Figure 4.3). During 1993 to 1997, the therapeutic areas nervous system, cancer, cardiovascular, anti-infectives and alimentary & metabolism accounted for 68% of the aggregated NME output. By 1998 to 2002 the collective contribution of

Figure 4.3 NMEs first launched by therapeutic class (1993-2002)



n is the total number of NMEs included in the analysis

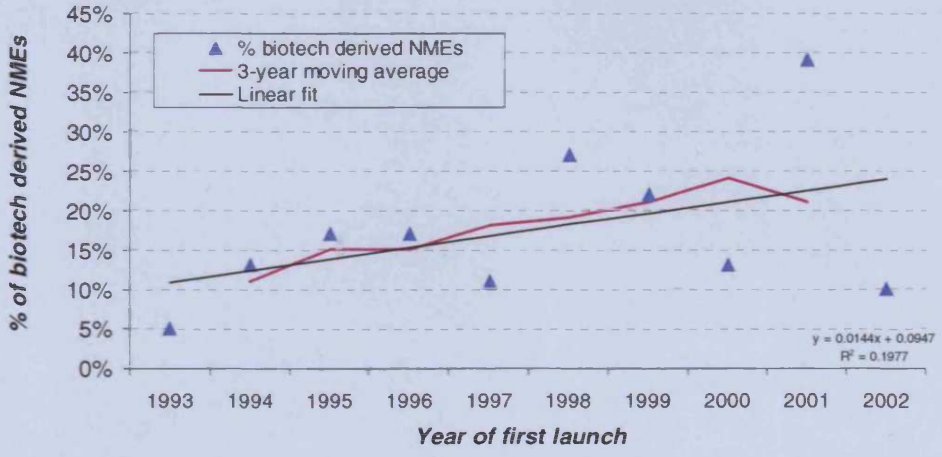
these five therapeutic classes, which are traditional focus points of the pharmaceutical industry, had declined to 56% of all new NMEs launched over this period of time. Nervous system was the area for which the observed decline was the greatest, decreasing from 16% in 1993-1997 to only 9% in 1998-2002. In actual numbers this decline was even more pronounced with only 15 NMEs launched for nervous system indications during 1998-2003, less than half of the 32 NMEs launched in the preceding five years. Musculoskeletal, including indications such as osteoporosis and rheumatoid arthritis, was one of the therapeutic areas for which an increasing frequency was observed: five percent

of new medicines launched in 1993-1997 compared to nine percent for 1998-2002.

Biotechnology

The number of biotechnology-derived NMEs reaching the market fluctuated considerably over the ten years investigated in this study (Figure 4.4). As a proportion of the total number of new product launches, the lowest contributions were made in 1993 and 2002 (5% and 10%, respectively). At the other end of the scale, biotechnology-derived products accounted for 39% (12 NMEs) of all new product launches in 2001. A three-year moving average has been calculated in an attempt to minimise the effect of year-on-year fluctuations. The

Figure 4.4 Percentage of biotechnology-derived NMEs first launched (1993-2002)



Statistical analysis of these data using a linear regression model shows that there was a significant increase in the proportion of biotech-derived NME launches over the period 1993-2001 ($p<0.05$), though not over the total duration of the study 1993-2002.

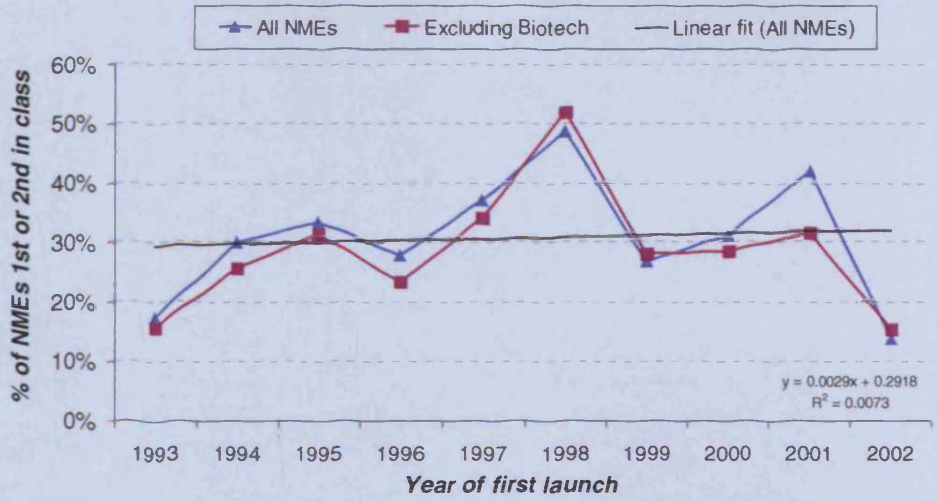
resulting curve demonstrates a steady increase from just over 10% for the period 1993-1995 to almost 25% in the three-year period 1999-2001. A slight decrease in the proportion of biotech NMEs was observed for the last three-year period in the calculation; 21% of all new product launches in 2000-2002 were based on active substances derived through biotechnological processes, which was caused by the fact that only three of the 29 NMEs launched in 2002 were biotech compounds (Figure 4.4). Statistical analysis of the data using a linear regression model showed that the low value for 2002 caused the observed increase to be non-significant for the duration of the study (1993-

2002), although significance was demonstrated for the nine-year period 1993-2001 ($p<0.05$).

Novelty

In determining whether a new product is an innovative launch, novelty of the pharmacological mode of action is a key factor. In 2002, 14% (four NMEs) of first launched NMEs were first or second in class, based on their mode of action, the lowest proportion observed during the ten-year period 1993-2002 (Figure 4.5). This percentage has fluctuated considerably over the period investigated. The second lowest proportion was observed in 1993 (18%, seven NMEs), whereas in 2001 42% (13 NMEs) of all launches was classified as first or second in class. In absolute numbers 1998 was the best year, witnessing 18 NMEs reaching the market as first or second in their class. Statistical analysis of these data using a linear regression model shows that there was no significant change over time in the proportion of NME launches that were first or second in class ($p>0.05$).

Figure 4.5 Percentage of NMEs first launched that are first or second in class based on pharmacological mode of action (1993-2002)



Statistical analysis of these data using a linear regression model shows that there was no significant change over time in the proportion of NME launches that was first or second in class ($p>0.05$).

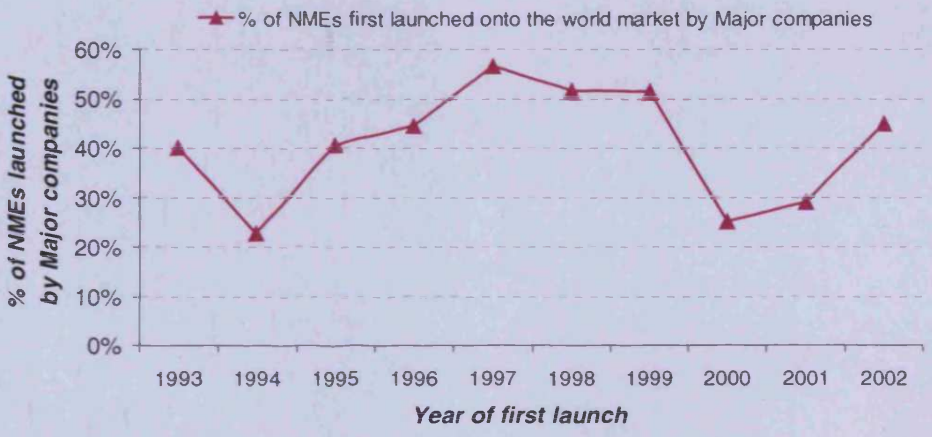
The contribution of biotechnology to product innovation was most noticeable in 2001. When excluding biotechnology derived products from the analysis, the proportion of first launches that were first or second in class was observed to be

lower in this year than when including biotech products, suggesting that the increase seen in the overall novelty in that year was at least partially driven by biotechnology-derived products (Figure 4.5).

"Major" companies

The fourteen "major" companies, defined as those companies with an R&D expenditure on ethical pharmaceuticals in 2002 of US$ 1bn or over, were responsible for 62% of global R&D expenditure in 2002. The involvement of the "major" companies in first launches has fluctuated considerably over the duration of this study, from a minimum of 23% in 1994 to a maximum of 57% in 1997 (Figure 4.6). For only three of the ten years investigated in this study, "major" companies were responsible for just over 50% of new product launches. In all other years, they were responsible for less than half the product launches. In 1994, 2000 and 2001, not even a third of new product launches could be attributed to this cohort of companies.

Figure 4.6 Percentage of NMEs first launched by "major" companies (1993-2002)?

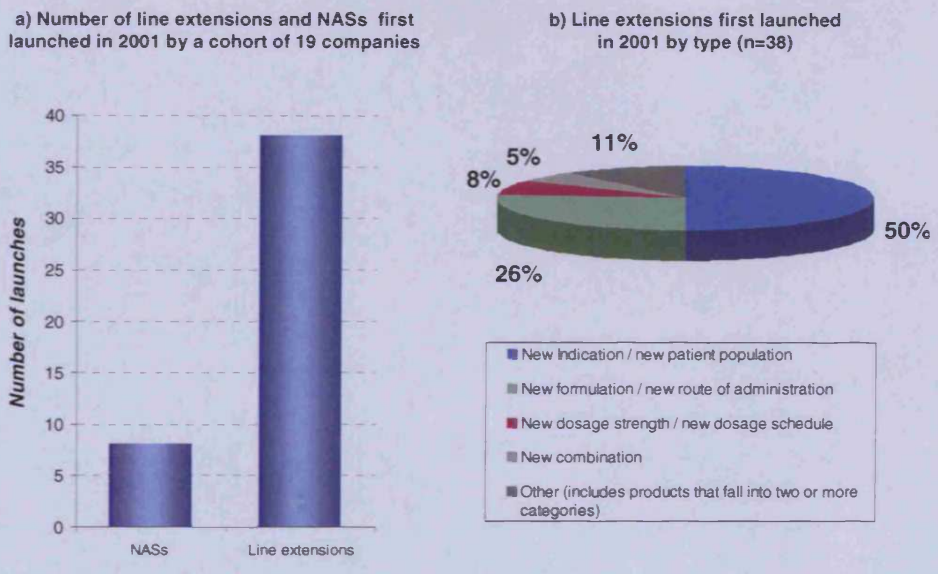


Line extensions

Although a continuous output of NASs is required to sustain the current pharmaceutical industry, a considerable part of the industry's income is derived from line extensions. In order to create an understanding of the relative volume of line extension product launches in comparison to NAS launches, a question was added to the 2001 study asking companies to provide details of the number of line extension products launched (Figure 4.7). In 2001, a cohort of 19

companies (seven "major" and 12 "other" companies) provided the relevant information on both NAS and line extension product launches. Between them, they launched a total of eight NASs. In that same year, they were responsible for the launch of an additional 38 line extension products (Figure 4.7a). Half of these line extension products were developed for a new indication or patient population and around 25% (ten NASs) related to a new formulation or new route of administration (Figure 4.7b).

Figure 4.7 Line extension activity (2001)

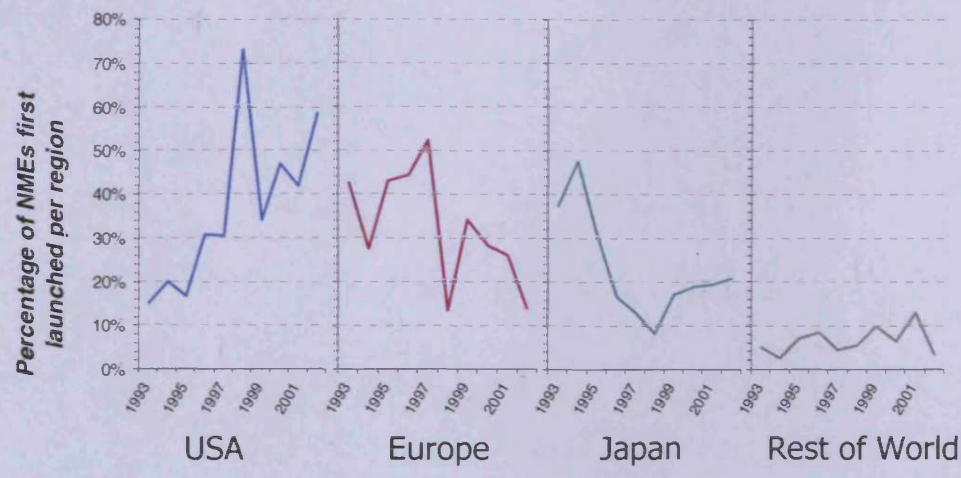


Based on data from a cohort of 19 companies (7 Major and 12 Other companies).

Region of first launch

Launching new medicines in one of the major world markets is high on the agenda of most pharmaceutical companies, but the region for first launch appears to have shifted over time from primarily Europe and Japan in the early 90s to the USA in more recent years (Figure 4.8). Between 1993 and 1995, Europe and Japan were the most popular regions, together representing around three quarters of first launches. At this period in time, the USA (around 20% of first launches) was less attractive as a region of first launch. In the years that followed, this picture changed considerably resulting in a reversed situation for 1998, with over two-thirds of new products being introduced in the USA. In this year, Japan and Europe were the country of choice for only 8% and 14% of all NME launches, respectively.

Figure 4.8 NMEs first launched by region of first launch (1993-2002)



Five NMEs simultaneously launched in more than one region have been excluded from the analysis.

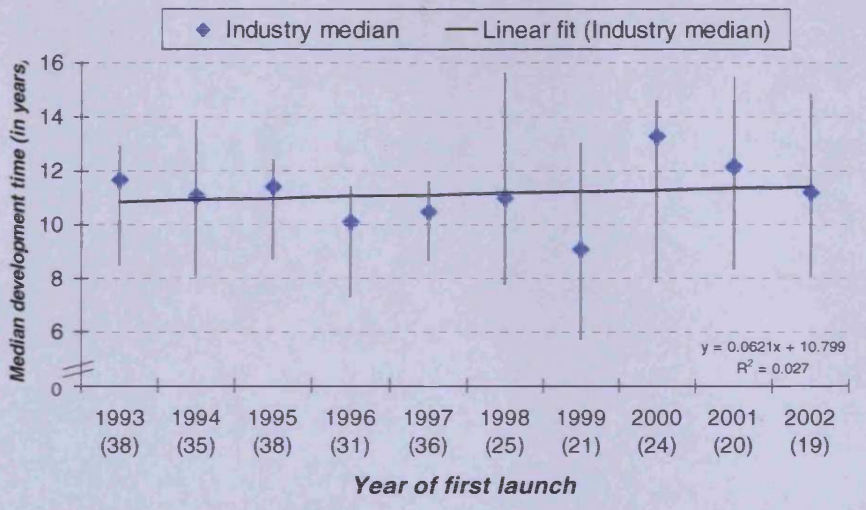
As the picture for the new millennium emerged, the fluctuations seem to have somewhat stabilised, with the split across the three regions USA, Japan and Europe appearing less skewed. As the world's major pharmaceutical market, responsible for around half of global sales in 2002 (Sellers, 2003), it is not surprising that companies continue to look at the USA as the preferred region of first launch (over 40% of first launches in 2000-2001 and even 59% in 2002). Japan has picked up since its low in 1998, stabilising at around 20% of the annual number of new product launches from 2000 onwards. Europe, the second country of choice after the USA for the years 1999-2001, is lagging somewhat, demonstrating a slow but steady decrease from 1999 onwards and representing a lower proportion of new product launches in 2002 than Japan (14% and 21%, respectively).

Development times

Figure 4.9 shows the overall development time (calculated as the time taken from first synthesis to first world launch) for NMEs first launched between 1993 and 2002 by year of first launch, presented as the median and the range from 25th to 75th percentile. Development times could be calculated for 287 (77%) of the 374 NMEs first marketed between 1993 and 2002. Seven NMEs with development times exceeding 25 years have been excluded from all development time analyses. Despite year-on-year fluctuations, the median development time appeared to decrease slightly during the 1990s, from 11.6 years in 1993 to 9.1 years in 1999. However, in 2000 a sharp increase to 13.3

years was observed, the longest median duration for the ten-year period investigated. In 2001 and 2002, the median development time decreased slightly from the high in 2000 (Figure 4.9). No significant changes over time were shown for either the total study duration or the seven-year period 1993-1999 (linear regression model, p>0.05).

Figure 4.9 Development time for NMEs first launched onto the world market 1993-2002



The data are displayed as the range from 25th percentile to 75th percentile around the median (blue diamond) for each year 19993-2002, by year of first launch. (n) represents the number of NMEs. Statistical analysis of these data using a linear regression model shows that there was no significant change over time in overall development time for either the total study duration or the seven-year period 1993-1999 (p>0.05).

Table 4.5 represents an overview of development times by therapeutic area, compound type and novelty. For each characteristic, the median time from first synthesis to first launch was calculated for NMEs launched during 1993 and 2002. Not surprisingly, a wide range was observed for the development times across different therapeutic areas. Out of the ten therapeutic areas investigated, six demonstrated development times similar to the overall industry median of around 11 years. For three therapeutic areas the median development times were shorter: ant-infectives, cancer and blood and blood forming agents (8.8, 9.5 and 10.0 years, respectively). The median development time for NMEs developed for nervous system indications (13.1 years) exceeded the industry median by more than two years. Statistical analyses showed that development times for nervous system indications were significantly longer than development times for other therapeutic areas. Another characteristic that appeared to impact

on development times was compound type. Based on median data, research and development for biotechnology-derived NMEs was reported to be completed a year earlier than for non-biotechnology derived NMEs, including biologicals and chemical entities (10.0 years vs. 11.1 years). Whether a product was first or second in class appeared to be of less influence than therapeutic area and compound type. Only a minor difference of 0.3 years was observed between NMEs that reached the market as first or second in their class, compared to NMEs with a higher market entry position. This limited difference might partially be due to the fact that the market entry position (i.e. whether the NME is first, second or later in class) is not known until the products reach the

Table 4.5 Development times by characteristic, 1993-2002

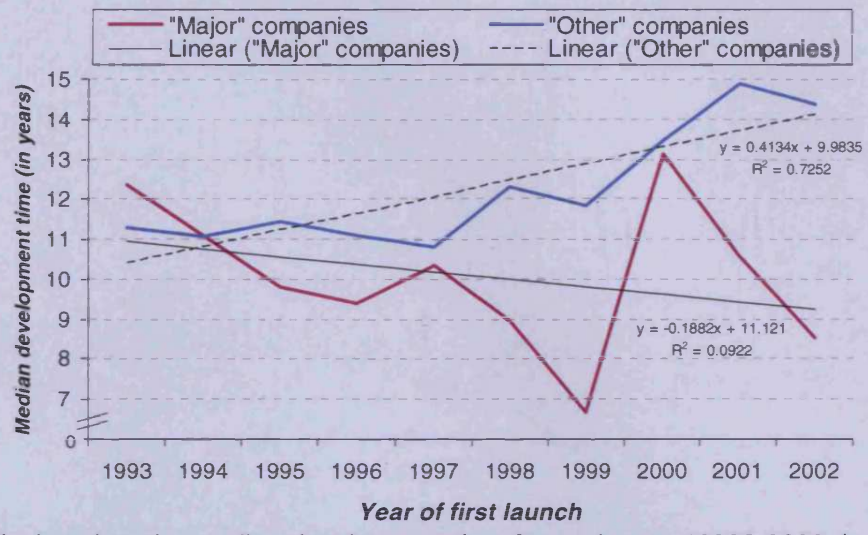
Characteristic	Development time	Number of NMEs included in calculation
All data	11.0 yrs	287
Therapeutic area		
Anti-infectives	8.8 yrs	49
Cancer	9.5 yrs	36
Blood & blood forming agents	10.0 yrs	23
Musculoskeletal	11.3 yrs	18
Respiratory	11.3 yrs	10
GU & Sex hormones	11.4 yrs	14
Dermatological	11.4 yrs	5
Cardiovascular	11.6 yrs	34
Alimentary & Metabolism	11.6 yrs	31
Nervous system	13.1 yrs	40
Compound type		
Biotech NMEs	10.0 yrs	37
Other NMEs	11.1 yrs	250
Novelty		
First or second in class	10.8 yrs	92
Other NMEs	11.1 yrs	195
Region of first launch		
USA	9.3 yrs	85
Europe	10.3 yrs	108
Japan	12.0 yrs	71

Statistical comparison of the data using the Kruskal-Wallis test across all therapeutic areas included in the table showed that there was a significant difference in development times between therapeutic areas ($p<0.01$) and regions ($p<0.01$). Further statistical comparison between pairs of characteristics using Mann-Whitney U-tests showed that development times for the therapeutic area Nervous System were significantly longer than development times for other areas ($p<0.001$) and that development times for NMEs first launched in Japan were significantly longer than for NMEs first launched in the USA or in Europe ($p<0.01$). Statistical comparison of the data using the Mann-Whitney U-test showed that development times for biotech NMEs were significantly shorter than for other NMEs ($p<0.05$) and that there was no significant difference in development times for novel NMEs (first or second in class) and other NMEs.

market. In today's competitive environment it is not unthinkable that several companies are simultaneously developing compounds within one, new, pharmacological class. Each company will strive to minimise development time in order to reach the market first. However, only two NMEs can be classified as first and second ('novel'). As a consequence, development times for 'other' NMES (i.e. not first or second) could still reflect the development strategy of a first in class product. The shortest development times were observed for NMEs first launched in the USA (9.3 years). The median development time for NMEs first launched in Europe was one year longer (10.3 years), whereas for NMEs for which Japan was the country of first choice for launch this was more than 2.5 years longer (12.0 years).

Figure 4.10 shows the median development time by company size, with the number of NMEs included in the analysis depicted in Table 4.6. Opposite trends were observed for the two company cohorts over the duration of the study. The median development times for "major" companies declined from 12.6 years in 1993 to 8.5 years in 2002, with the exception of 2000, when the median development time for this cohort of companies was observed to be 13.1 years. For "other" companies, an increase in the overall development time was observed, from 11.5 years in 1993 to 14.4 years in 2002. Statistical analysis of the data showed that there was a significant difference in development times between "major" and "other" companies (Mann-Whitney U-test, $p<0.05$) and that the observed increase in development times from 1993-2002 for "other" companies was significant (linear regression, $p<0.05$), whereas the observed decrease for "major" companies was not. The decrease in overall development time for NMEs launched by "major" companies coincided with a decreasing proportion of NMEs in this cohort that were marketed for CNS indications, as well as with a decrease in the proportion of NMEs first launched in Europe. Although a decrease in the latter was also observed for "other" companies, the decline was steeper for "major" companies. These observations might provide some insight into the reasons underlying the declining development times for "major" companies, since longer development times were observed for CNS products and median development times for NMEs reaching a European market first were higher than those that were first launched in the USA (Table 4.5).

Figure 4.10 Development time for NMEs first launched onto the world market 1993-2002, by company size



The data are displayed as the median development time for each year 19993-2002, by year of first launch. Table 4.6 shows the number of NMEs included in this analysis. Statistical analysis of these data using a linear regression model shows that there was a significant increase ($p<0.05$) in development time for "other" companies, but no significance could be proven in the development times for "major" companies. Statistical comparison of the data across the two company cohorts using the Mann-Whitney U-test shows that there is a significant difference ($p<0.05$) in the development times between "major" and "other" companies.

Table 4.6 Number of NMEs included in development time calculation by company size

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
"major" companies	12	6	17	14	19	11	14	8	9	10
"other" companies	24	28	21	17	15	9	7	16	11	17

DISCUSSION

In this study, new molecular entities (NMEs) reaching the world market between 1993 and 2002 were examined in detail. Additional information was collected on the regulatory and marketing activities of participating companies in the major pharmaceutical markets between 1998 and 2001, as well as data relating to line extension products reaching the market in 2001. These data were utilised to generate evidence to test five hypotheses.

Hypothesis 1: The annual number of NMEs reaching the market has remained constant over the period 1993-2002

It was postulated that the 80% increase in R&D expenditure over the duration

the period 1993-2002 (Chapter three) was sufficient to sustain a constant output in terms of the annual number of NMEs reaching market over this period of time. Indeed, the outcome of this study seems to support this hypothesis for the 1990s. Annual fluctuations aside, the number of NMEs reaching the market remained relatively stable from 1993 to 1999 at ~40 NMEs per year. However, the observed decrease in the number of new medicines reaching the market during 2000-2002 resulted in a statistically significant overall downward trend in the industry's annual NME output for the ten years investigated in this study, thereby not supporting the hypothesis. The declining annual output in terms of NMEs reaching the market observed in this study is corroborated by studies reported annually in Scrip Magazine. Although the exact number of products differs slightly from the numbers reported in this study, due to different inclusion criteria, the observed trends are similar (Davis, 1994; 1995; 1996; 1997; 1998; Shimmings, 1999, 2000; Southgate, 2001; 2002; Lloyd, 2003). The reason for the declining output is a topic of much debate and it has become clear that it is related to a combination of developments in pharmaceutical R&D, such as the use of new technological advances (e.g. high-throughput screening, combinatorial chemistry and molecular biology), the implementation of which requires both time and investment (Firn, 2002). Other factors suggested to contribute to the observed decline include a shift in focus to the development of medicines for more chronic and complex diseases (Anon, 2004a; De Visser, 2003) as well as increasing pressures on the industry to demonstrate cost-effectiveness as well as differential safety and efficacy, resulting in an increased clinical workload, longer development times and higher attrition (Gilbert *et al.*, 2003).

Due to lengthy development times, the current deficit in the number of new medicines reaching the market is the result of strategies set and investments made over the last 10-20 years (Schmid and Smith, 2004; Gilbert *et al.*, 2003). As such, a delay exists between the actions taken by the industry today and any consequences this might have on its output. The main question therefore is whether the ongoing efforts of the pharmaceutical industry to improve R&D productivity will result in a reversal of this downward trend in the future. Data on the submission activities of all participating companies in the major

pharmaceutical markets between 1998 and 2001 demonstrated a sharp decline in the number of NASs submitted for regulatory review, from 125 NASs in 1998 to only 50 NASs in 2001. A similar analysis for a cohort of 16 companies for which data were available for all four years supported this reduction. Although this analysis included submissions to both first markets and subsequent markets, the decreasing number of NASs does suggest that a recovery of the declining industry NME output is not likely to happen in the near future. The industry's output for 2003 confirmed the continuation of the downward trend suggested by the falling number of submissions (Read and Sculthorpe, 2004; Lloyd, 2004). Read and Sculthorpe (2004) reported the launch of only 26 NMEs in 2003, three NMEs less than reached the market in 2002. In Chapter six current pipeline activities are investigated to estimate future output in more detail.

Although a continuous output of new active substances (NASs) is required to sustain the current pharmaceutical industry, a considerable part of the industry's income is derived from line extensions. In order to better understand the volume of line extension products, a comparison was made between the number of line extension products and NASs launched onto the world market in 2001 by a cohort of 19 companies for which information on both were available. This cohort of companies reported the launch of only eight NASs between them. In the same year, they were responsible for the launch of an additional 38 line extension products. No trend data is available for an assessment of changes over time for the number of additional line extension products per year. However, the breakdown of R&D expenditure by product type, as reported in Chapter three seems to suggest that some companies have increased the proportion of expenditure allocated to line extensions from 1998 to 2002, suggesting an increased number of line extension products in development.

Hypothesis 2: The overall level of innovation, in terms of the number of new medicines that are first or second in class, has increased from 1993 to 2002

Increasing pressures from governments and regulatory authorities to demonstrate efficacy and safety over and above that of existing treatments as

well as pharmaco-economic benefits means that product innovation is key to maximising the economic value of a product. It therefore seems logical to expect an increasing proportion of new product launches to be first or second in class. Based on NMEs launched between 1993 and 2001, this hypothesis appears to be supported by the outcome of this study. Over this period of time, despite year-on-year fluctuations, the proportion of NMEs that were first or second in class, based on pharmacological mode of action, increased from a low of 18% in 1993 to a high of 42% in 2001. In this year, products such as Novartis' Gleevec (imatinab), the first selective tyrosine-kinase inhibitor to be approved for the treatment of cancer (Capdeville *et al.*, 2002), and Merck & Co's Cancidas (caspofungin acetate), the first of a new class of antifungals, the echinocandins (which inhibit cell wall synthesis), reached the market. However, the proportion of novel NMEs in 2002 was observed to be only 14%, resulting in a minimum overall increase over the ten years included in this study. Statistical analysis of the data demonstrated that this increase could not be distinguished from a situation of no change, refuting the hypothesis that the overall level of innovation in terms of the number of new medicines that are first or second in class has increased over the duration of this study.

Although slightly wider inclusion criteria were applied in the study of the industry output reported annually in Scrip Magazine (for example it includes esters and pro-drugs of previously marketed compounds as well as vaccines, which are excluded from this study), it corroborates the findings of this study. For 2002, only two of the NASs reaching the world market appear to be real first-in-class therapies, compared with ten in the previous year (Lloyd, 2003). However, in 2003 the launch of eight first-in-class therapies was reported (26% of the total industry output in 2004), suggesting that 2002 was an anomaly rather than the start of a new trend. Innovative NASs reaching the market in 2003 include Roche and Trimeris' fusion inhibitor Fuzeon (enfuvirtide), a novel HIV therapy aimed at preventing entry of HIV-1 into cells, and Genentech/Novartix/Tanox's Immunoglobulin E antagonist Xolair (omalizumab), the first drug to target the underlying inflammatory response to allergic asthma (Lloyd, 2004; Read and Sculthorpe, 2004).

Hypothesis 3: Biotechnology has made a considerable contribution to the pharmaceutical industry's new medicine output and this has increased from 1993 to 2002

Considering the growing biotechnology industry and the continuing quest from pharmaceutical companies for innovative medicines, it seems logical to expect that an increasing proportion of new medicine launches was derived through biotechnological processes. The outcome of this study supports this hypothesis for the nine-year period 1993-2001, but not for the duration of the study, due to the low proportion of biotech-derived NMEs launched in 2002. Based on the three-year moving average, calculated to minimise year-on-year fluctuations, the proportion of biotechnology-derived products increased steadily from just over 10% for the period 1993-1995 to almost 25% in the three-year period 1999-2001. Despite an observed decrease in the proportion of biotech compounds in 2002 (which witnessed the launch of only three biotechnology-derived NMEs), the overall trend in the proportion of biotech compounds was upwards for the duration of this study. Read and Sculthorpe (2004) reported that in 2003, 15% of the industry's NME output was biotechnology-derived, suggesting that the observed drop in 2002 might be the first sign of a changing trend, rather than a one-off exception to an overall increase in biotechnology's contribution.

In addition to biotechnology's contribution to the quantity of the industry's annual NME output, quality aspects were investigated as well. The contribution of biotechnology to the one aspect of quality investigated in this study was examined in more detail by re-calculating the proportion of NMEs that were 1st or 2nd in class excluding biotech compounds. A similar proportion of 1st or 2nd in class compounds was observed for all NMEs first launched; compared to when biotech compounds were excluded from the calculation over the duration of this study, with the exception of 2001. In this year the proportion decreased by excluding biotech compounds, suggesting that for this year the proportion of novel compounds was higher for biotech compounds than for non-biotech compounds. For all other years, the proportion of novel biotech compounds was similar to the overall proportion, suggesting that biotechnology contributes to innovation to the same extent as do more traditional compounds.

Ashton (2001), investigating biotechnology products introduced onto the world market between 1982 and 1998, found that the contribution of biotechnology-derived pharmaceuticals to the annual NME output of the industry had steadily increased since the introduction of the first biotech product in 1982. Until 1998, biotechnology had however failed to meet even the lower estimates of Drews (1995), who predicted that biotechnology would contribute between 13 and 24 NMEs per year by the beginning of the 21st century. Nine biotechnology products (excluding recombinant vaccines) had been the largest number of biotechnology products launched in any one year to date over the time period studied. The results of this study demonstrate a continuation of this increasing contribution of biotech compounds to the industry's output: a record 12 biotechnology derived NMEs made it to the market in 2001. However, the contribution of biotechnology was still not sufficient to reverse the decline in annual NME output.

Hypothesis 4: "Major" companies are responsible for the majority of new medicines reaching the market

"Major" companies (i.e. those spending US$ 1bn or more on ethical pharmaceutical R&D) accounted for over 62% of global R&D expenditure in 2002. It therefore seems logical to expect that this cohort of companies is responsible for the development and marketing of the majority of new medicines reaching the market. However, the outcome of this study suggests that this is not the case. Based on the 2002 company grouping, "major" companies were responsible for just over half the industry's NME output in only three of the ten years examined in the study. For the remaining seven years, only a minority of new product launches could be attributed to this cohort of companies. The lowest proportions were observed for 1994, 2000 and 2001, when "major" companies marketed less than one-third of the industry's annual NME output. Overall, "major" companies were responsible for only 41% of all new medicines launched between 1993 and 2002. The number of new products is only half of the output equation; equally important is the revenue generated by these products, which is dependent on their commercial value. If the combined value of the limited number of products marketed by "major" companies exceeds that of the products launched by smaller companies, it could be argued that the

development process of "major" companies is more successful, despite the relative low number of new products. With only one-third of products recovering the cost of its R&D (Grabowski *et al.* (2002) a strategy of focusing on those products with high potential commercial value might prove to be more profitable for the "major" companies in the long term.

The above highlights the declining R&D productivity in its full extent. The business model of the large, well-integrated pharmaceutical company, highly dependent on the income derived from blockbusters, has served the industry well over the last 40 years, but with declining output, increasingly aggressive generic competition and falling stock values, it has been suggested that increasing the R&D budget will no longer suffice and that it might be time for the big pharmaceutical companies to revise their business model (DeLamarter, and Fumero, 2001; Truelove, 2003; Gilbert *et al.*, 2003).

Hypothesis 5: The overall development time for new medicines, from first synthesis to first launch, has decreased between 1993 and 2002

The impetus in the middle and late 1990s was on cutting both development times and regulatory review times (Thomas *et al.*, 1998; DiMasi, 2001b; FDA, 2003), with big pharmaceutical companies predicting reductions in development times by a third. It therefore seems reasonable to expect a downward trend in development times. Over the time period investigated (1993-2002), the median development time from first synthesis to first launch was 11.0 years. Year-on-year variations were observed, with annual medians ranging between 9 and 13.3 years. Overall, only a slight increase of less than 0.5 year was observed based on the best fit which was found not to be significantly different from a situation of no change, refuting the hypothesis that overall development times have decreased over the duration of the study.

Interesting observations were made when investigating subsets of the data for changes over time. Development times for NMEs marketed by "major" companies decreased from over 12 years in 1993 to less than ten years in 2002. Over the same period of time, development times for NMEs marketed by "other" companies significantly increased from around 11 years during the mid-1990s

to more than 14 years from first synthesis to launch for the years 2001 and 2002. Several trends over this period of time might have contributed, to some degree, to the observed decline in development times for "major" companies: the number of NMEs marketed for CNS indications, shown to have longer development times than other therapeutic areas, decreased for this cohort of companies, whereas the proportion of NMEs for which Europe was the region of choice for first world launch declined more steeply for "major" companies than for "other" companies. However, this only provides a partial and potential explanation for the observed decline. Could it also be an indication that size does matter with regards to the efficiency of drug development? While "other" companies have proven to be capable of developing quickly (ten NMEs marketed by this cohort reached the market within 5 years of first synthesis, compared to eight NMEs marketed by "major" companies), larger companies are apparently able to consistently speed up their R&D processes. It should be taken into account that development time is not the only performance measure contributing to R&D efficiency. Development times should be examined in the light of success rates, since sufficiently low attrition could balance longer developments in such a way that it could still result in a higher number of products reaching the market. Success rates have been investigated in detail in the study reported in Chapter six.

Investigating the number of new molecular entities reaching the market will only provide a partial picture of the industry's output. Ultimately, it is the combined commercial value of these new products, as well as any potential additional income that can be generated through life cycle management and geographical expansion, that determines the industry's future income, and therefore its viability. And despite all challenges facing the industry, many doom predictions and no substantive increase in numbers of new launches, in the real world growth has been achieved (Walton, 2000).

SUMMARY

- The outcome of this study showed a significant decrease in the industry's NME output over the ten-year period 1993-2002.

- No overall increase was demonstrated in the proportion of NMEs that were first or second in class ('novel') over the duration of the study.

- A continuing increase was observed in the proportion of biotechnology NMEs reaching the market, culminating in a record of 12 biotech compounds launched in 2001. Biotechnology's contribution was not sufficient to halt the industry's declining NME output.

- Major companies, although accountable for 62% of global ethical pharmaceutical R&D expenditure in 2002, were responsible for only 41% of all new medicines launched between 1993 and 2002, highlighting the full extent of the declining R&D productivity.

- No decrease was observed in the time from first synthesis to first launch. Significant differences were observed between "major" and "other" company cohorts, with development times for "major" companies decreasing and those for smaller companies increasing from 1993 to 2002.

- The number of NMEs reaching the market per year is not the only measure against which to assess the industry's output. Other aspects to take into account include the number of line extension products reaching the market and product value in terms of sales and geographic expansion.

CHAPTER FIVE

EVALUATION OF GLOBAL PHARMACEUTICAL COMPANIES' PIPELINES – A LONGITUDINAL STUDY

INTRODUCTION

The pharmaceutical industry's overall successful performance in the late 1990s has led to high financial expectations of pharmaceutical companies in the early years of the 21st century. Shareholders and other interested parties have generally come to expect double-digit growth in profits (Fletcher, 2000). One of the key drivers of a company's growth is sales derived from the newly launched products. According to Fletcher (2000) major companies could be required to bring five to six new products to market each year to maintain double-digit growth, whereas more conservative estimates were provided by Andell (2003) who indicated that companies would need to achieve one new product launch per two years for every percentage point market share. For Pfizer, with a market share of around 9% in 2003 (Anon, 2004m; Truelove, 2004), this would translate into the requirement of launching four to five new products each year, whereas a company the size of AstraZeneca (~4% market share) would need to launch two new products annually. Assessments of output required to sustain future growth need to take into account commercial value as well as incorporate a measure for estimated return on investment. Most estimates of required future output are based on an average peak sales value of US$ 300-400Mn (Drews and Ryser, 1996; Horrobin, 2000; Banerjee *et al.*, 2001). As such, the launch of one blockbuster product (sales exceeding US$ 1bn) would make a contribution to a company's revenue similar to that of two to three average-sized products. Higher commercial values will of course increase the chance of recovering the investment made in the research and development (R&D) of the product. Grabowski *et al.* (2002) studied the returns on R&D for 118 new chemical entities (NCEs) introduced onto the US market between 1990 and 1994 and found that only one-third of the new drug introductions had present values in excess of average R&D cost, indicating that the risk involved in drug development does not stop at product launch. Drews and Ryser found that the overall number of new chemical entities launched by the Top 50 companies in theory was too small to sustain healthy growth in this group (Drew and Ryser, 1996; Drews, 1998a)

Press communications in early 2004 highlighted a careful optimism for the

future amongst certain companies. Roche announced that it had 12 drugs either already on the market or in the late-stage pipeline with the potential to become blockbusters and generate more than 1 billion Swiss francs apiece and similarly, US firm Merck & Co announced that it will be filing for a range of new product approvals in the near future (Anon, 2004n; 2004o). This optimism was also apparent for Novartis, with analysts forecasting strong headline results for the first quarter of 2004. However, they cautioned that without any major new product launches in 2004 the company will remain dependent on its more established products to meet its 2004 target of delivering top-line growth in the high single digit range and ahead of the market (Anon, 2004p).

The analysts view on Novartis' predicted performance confirms that the financial community also views the number of new product launches as an important indicator for the future success of a pharmaceutical company. The composition of a company's current development pipeline can be used as an indicative measure of its future success in terms of the number of new product launches. Ultimately, the number and phase distribution of new active substances (NASs) in development, in combination with success rates and cycle times are the metrics that determine the number of NASs reaching the market. All of these metrics can, in turn, be influenced by several factors, including level and timing of investment as well as the efficiency of the drug development and decision-making processes. Analysis of the current pipeline can provide a tentative indication as to whether a continuous output of new products can be sustained. Additionally, details of the current pipeline can provide insights into current industry strategies, for example the impact of biotechnology as a source of new medicines or the role of external sources, through licensing-in or acquisition.

The output of the pharmaceutical industry cannot be measured in terms of numbers only. The overall objective of a company is to secure continuous income through product sales. New products are required to compensate for loss of income from existing products due to generic competition or competition from "me-too" products. The economic value of each new product in combination with the number of products launched will determine the income that can be generated.

Increasing pressures from governments and regulatory authorities to demonstrate improved safety and efficacy over and above existing treatments as well as pharmaco-economic benefits means that product innovation is key to maximising the economic value of a product. Only those products that carry substantial advantages over existing therapeutics can command premium prices upon introduction (Drews and Ryser, 1996). For any product there are many characteristics that could differentiate it from others, one of them being the novelty of the mode of action.

A study has been developed to examine the pipeline of the large and medium-sized pharmaceutical companies in detail. Companies participating in the study were asked to provide information on all NASs in preclinical or clinical development or under regulatory review, specifying details such as the type and origin of the active substance, as well as the indication and the novelty of the pharmacological mode of action.

OBJECTIVES

Data collected in this study are used to evaluate the ethical pharmaceutical development pipeline between 1998 and 2002 in order to generate evidence to test the following hypotheses:

1. Companies increased the size of their pipeline between 1998 and 2002.
   Against a background of increasing R&D expenditure in the industry's continued drive to reverse the downward trend in the number of new medicines reaching the market, it is reasonable to expect that some if not all of this investment can be accounted for by an increased development effort in terms of the overall pipeline size

2. The distribution of products in the pipeline, i.e. the proportion of NASs per phase of the development process, has changed between 1998 and 2002.
   If companies are to maximise their future output they cannot afford to

focus on one characteristic of the development process only. It is therefore postulated that in addition to the increased number of NASs as suggested in the first hypothesis, companies are also focusing on improving late stage success rates which would be likely to result in a shift in the phase distribution of the development pipeline.

3. Biotechnology has made a positive contribution to the industry's pipeline in terms of the number of biotech compounds in development over the period examined.
   Considering the growing biotechnology industry and the increased licensing and partnering activities between this industry and the pharmaceutical industry (Dyer, 2002), it seems logical to expect that biotechnology compounds account for an increasing proportion of the development pipeline.

4. Companies have increasingly focused on the development of innovative medicines between 1998 and 2002.
   It is not unreasonable to expect that in addition to increasing the number of new product launches, the industry is attempting to maximise the medical and thereby commercial value of its output by focusing on the development of innovative NASs.

5. During the period of the study, companies have increasingly focused on a smaller number of therapeutic areas.
   Due to the intrinsic differences between therapeutic areas, different skill sets and knowledge will be required for the development of NASs in different areas. Since experiences are rarely transferable across therapeutic areas it is logical to expect that in order to improve efficiency, companies are focusing their resources on a smaller number of therapeutic areas (Gilbert et al., 2003).

METHODS

The study of the global ethical pharmaceutical development pipeline was conducted by means of an annual questionnaire-based approach, which was initiated with a pilot study in 1996 (MacFarlane *et al.*, 1997; MacFarlane, 1998). Subsequent rounds of data collection have been enlarged to encompass the top pharmaceutical companies by R&D expenditure, as well as the leading biotechnology companies. Invitations to participate were sent to at least the Top 20 pharmaceutical companies and the Top five biotechnology companies, based on pharmaceutical R&D expenditure in the year over which data were to be collected. References for annual pharmaceutical R&D expenditure were obtained from the annual September issues of MedAdNews Magazine (Anon, 1999b; 2000b; 2001b; 2002; 2003c). This list of Top 20 pharmaceutical companies and Top five biotechnology companies was complemented with any other company undertaking ethical pharmaceutical R&D that had expressed an interest in this type of study in the past and within which a suitable contact could be identified. Companies invited to participate for one or more years are listed by name in Table 2.1 with an overview of the number of companies invited year on year provided in Table 5.2. For this chapter, data collected for the years 1998-2002 are analysed in detail.

Data collection

The study focused on new ethical (prescription only) pharmaceuticals, excluding any additional activities such as line extensions, veterinary medicines or over-the-counter products. Companies were asked to provide information on all NASs that were in active clinical development, or for which a dossier was either in preparation or had been submitted to a regulatory authority, by 31st December of each year. For the year 1998, an NAS in active development was defined as one that had been administered to humans, and whose development had not been terminated. Data collection for later years was extended to include NASs in preclinical development, with NASs considered to be in active development in a given year from the completion of the first animal toxicity study required for the first ever administration to humans, up to and including submission, but which had not been approved for marketing before 31st December of that year. The development stage (as of 31st December) of each

NAS in active development was requested annually. The content of the questionnaire was assessed annually to ensure that up-to-date and relevant information was collected. Definitions were provided along with the questions to encourage consistent responses between companies and across years. An overview of how the questionnaire evolved for the years 1998-2002 is provided in Table 5.1. The questionnaire used for data collection for 2001 is provided in Appendix VI. Companies that had participated in the study in previous years were supplied with data provided in these years and asked to confirm and update the information.

Table 5.1 Aspects of the global ethical development pipeline requested in the annual study for each NAS in active development, 1998-2002

Question	1998	1999	2000	2001	2002
Generic name	✓	✓	✓	✓	✓
Pharmacological mode of action	✓	✓	✓	✓	✓
Novelty of the pharmacological mode of action		✓	✓	✓	✓
Therapeutic area					
Therapeutic area (open-ended question)	✓	✓	✓	✓	
WHO ATC code					✓
NAS type					
Biotech compound yes/no	✓				
NAS type		✓	✓	✓	✓
Position in the pipeline (lead or back-up)	✓				
Projected peak sales	✓	✓	✓	✓	
NAS origin	✓	✓	✓	✓	✓
Development stage	✓	✓	✓	✓	✓
Whether the company routinely prioritised their compounds		✓	✓	✓	
Level of priority		✓	✓	✓	✓
Whether the NAS was terminated		✓			✓
If terminated, termination date			✓	✓	✓
If terminated, termination reason					
Scientific & business considerations, one reason only		✓	✓	✓	
Scientific & business considerations, up to three reasons					✓
Drug discovery technologies used for NASs entering development			✓		

Data collection took place in the first half of the year following the calendar year in which activities took place, e.g. the questionnaires used for collecting data on activities in 1998 were made available to all companies invited to participate between January 1999 and June 1999. Each company was contacted prior to sending out of the questionnaire to ascertain the most appropriate person to

receive the questionnaire. Recipients of the questionnaire were subsequently contacted to ascertain the likelihood of their participation in the study. The level of completeness of the questionnaires returned by the participants varied per company per year, depending on both the internal availability of the information as well as the willingness to share externally such detailed and confidential data.

External data sources

Annual R&D expenditure data were obtained from CMR International's Global R&D Expenditure Database (GLOBEX). GLOBEX holds detailed information on annual ethical pharmaceutical R&D expenditure, capital expenditure, R&D full-time equivalents (FTEs) and sales from over 80 companies. Since its inception in 1982, the database has been kept up to date with confidential data obtained directly from pharmaceutical companies through the annual R&D Expenditure and Sales study, supplemented with company confirmed data from the public domain.

Data processing and analyses

The questionnaire on 1998 activities was made available in paper format only. In later years, companies were given a choice to submit their data either on paper or by use of an electronic, Microsoft Excel™-based or Microsoft Access™-based, questionnaire. The use of electronic questionnaires greatly improved the quality of the data collected by eliminating the need for additional data handling steps, such as interpreting handwriting and manually entering data into the database, as such participants were encouraged to provide data using Access™ (first choice) or Excel™ (second choice) rather than by returning the Word™ questionnaire.

Data were processed using Microsoft Access™. Both Microsoft Access™ and Microsoft Excel™ were used to obtain descriptive statistics of the data. SPSS™ for Windows™ was used to run statistical analyses on the data:

- *Linear regression* was used to test whether the proportion of licensed in/acquired NASs changed over time for each of the four development phases.
- *Chi-square tests* were applied to test for significant differences in the

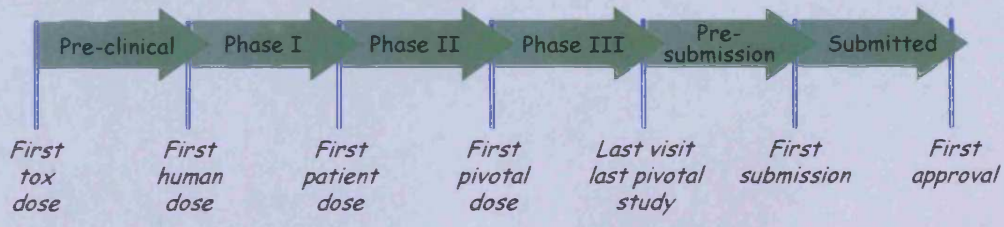
proportion of biotech NASs and licensed-in/acquired NASs by therapeutic area, and to test the relationship between biotech and non-biotech vs. licensed in/acquired and non-licensed in/acquired.

- The *Wilcoxon Signed Rank* test was applied to test for significant changes between the years 1998 and 2002 in pipeline size, the number of therapeutic areas and the number of NASs per therapeutic area.
- The differences in the proportion of novel NASs in development by company size have been tested using an independent 2-sample *t-test*, since normal distribution of the data was demonstrated.
- *Repeated measures one-way analysis of variance (ANOVA)* was used to test the statistical significance of changes over time in pipeline size

Determination of development stage

The development stage of each NAS in (pre)-clinical development was identified in one of two ways. Either the company made an assessment of the development phase of each of their NASs, or the company provided milestone data for key R&D activities, which were subsequently used to assign the development stage of each NAS on 31st December of each year. Figure 5.1 illustrates the start and end milestone defining each of the development phases.

Figure 5.1 Phase definitions



For definitions of the milestones, see Glossary of Terms on page X.

Observation of confidentiality agreement

Data collected in this study were covered by a confidentiality agreement with respondent companies, preventing the presentation of identifiable individual company data. To assess whether any of the trends or developments observed differed between larger and smaller companies, respondent companies were characterised according to their level of global R&D expenditure in ethical pharmaceuticals in 2002. Companies for which 2002 ethical pharmaceutical

R&D expenditure equalled or exceeded US$ 1bn were classified as "major" companies, whereas those companies for which this expenditure was less than US$ 1bn were classified as "other" companies.

Trend analysis

Where historical data are presented, the activities of companies that now form part of a larger company, due to merger and acquisition activities, have been attributed to the company grouping as it was in 2002. For trend analyses, only companies were included for which the required information for all years included in the analysis was available. Where relevant to the interpretation of the data, the cohort of companies included in the trend analysis was defined by the proportion of global R&D expenditure and / or sales it represented in 2002.

Determination of novelty of pharmacological mode of action

In 1999, a new question was added to the study asking companies to indicate for each NAS in active development whether the pharmacological mode of action was established or novel. Novel NASs were defined as those NASs for which no compounds with the same pharmacological mode of action had been marketed previously. Although participants perceived this to be an important characteristic with potential influence on performance metrics such as development time and success rate, they were not always able to provide the requested information, due to a combination of unavailability of the information and this information being perceived by some companies as too sensitive to be divulged. To cater for the limited availability of this information, three parameters were calculated to assess the proportion of novel NASs in the pipeline: the actual proportion (by excluding NASs with unknown novelty), the minimum proportion (by assuming all NASs with unknown novelty were established) and the maximum proportion (by assuming all NASs with unknown novelty were novel). The minimum and maximum proportions were then used to present a range of the possible proportion of novel NASs in the pipeline, around the actual proportion.

Therapeutic area classification

For the years 1998, 1999, 2000 and 2001, information on therapeutic area and / or indication was obtained by means of an open-ended question, enabling

participants to provide as much or as little detail as they considered appropriate. This information was then used to consistently classify all NASs using the World Health Organisation (WHO) anatomical therapeutic and chemical code (ATC code) system (WHO, 2002). In 2002, companies were asked to select the ATC code that they perceived to be most appropriate. Additional validation was still applied to ensure consistency across companies. For example, vaccines being developed for the treatment of certain types of cancer within one company could have been assigned the ATC code for vaccines (J07), whereas a second company might have classified a similar NAS as an oncology treatment, e.g. L01. Appendix VII provides an overview of the different therapeutic areas and the associated WHO ATC codes.

RESULTS

Response rate

A total of 52 companies participated in the study for one or more of the years 1998-2002, based on the company grouping as it was in 2002. In any given year in this five-year period, a minimum of 34 companies participated in the study, with a maximum of 49 companies participating in 1999 (Table 5.2). On average, over the whole period of the study, respondent companies represented a minimum of 72% of annual global R&D expenditure. For the calendar year 2002, 34 companies provided information on their pipeline activities, including all 14 companies with R&D expenditure exceeding US$ 1bn ("major" companies), representing 80% of global R&D expenditure in 2002. For

Table 5.2 Number and description of study respondents (1998-2002).

Year(s)	Number of companies invited	Number of respondent companies	% of Global R&D expenditure (number of companies for which data available)
1998	67	46	>66% (34)
1999	80	49	>73% (35)
2000	100	43	>75% (34)
2001	63	38	>67% (28)
2002	34	34	80% (34)

Based on company grouping and cohort as in year over which data were collected. Not all companies provided R&D expenditure data. The percentage of R&D expenditure was calculated for those companies for which information was available and presented as a minimum of the percentage of R&D expenditure for which the responding companies were responsible.

a cohort of 26 companies (13 "major" and 13 "other" companies) data are available for all five years 1998-2002. This cohort was responsible for 71% of global R&D expenditure in 2002. Non-respondent companies chose not to participate for one or more of the following reasons: (1) the requested information in line with the definitions provided was not readily available within the company, (2) the requested data could not be made available within the given time frame for data collection, or (3) the company was not willing to provide the requested data. For the years 1998-2001, the questionnaire was sent to a large number of companies in the hope that they would provide data. For data collection over the calendar year 2002, however, the questionnaire was only sent to companies previously committing to participation, explaining the drop in the number of companies invited for that year. Since this cohort of companies already represented 80% of global pharmaceutical R&D expenditure, there was no need to extend data collection to other companies

Overall size of the development pipeline

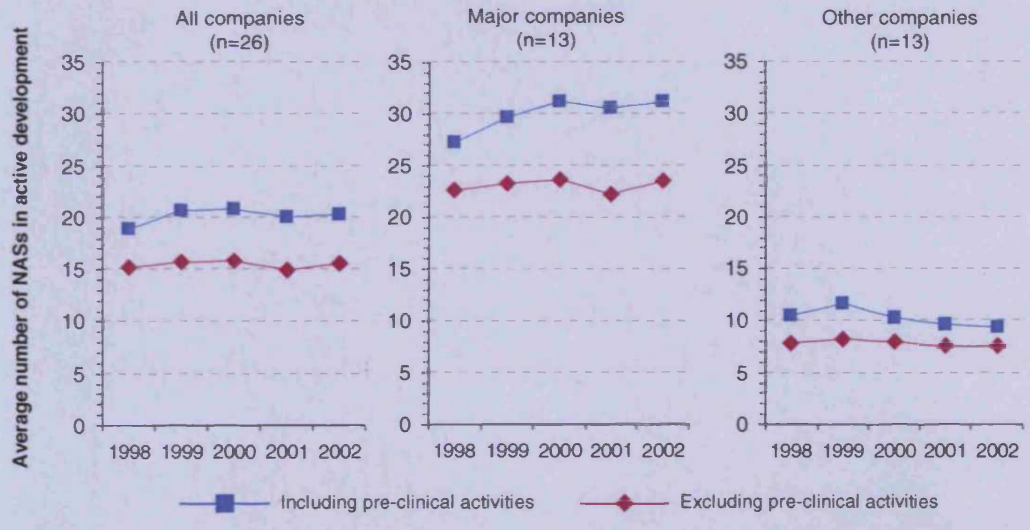
Thirty-four companies reported a total of 618 NASs in active development on 31st December 2002, with 436 of the 618 NASs (71%) being in development within 14 "major" companies. Development activities in each company's pipeline were attributed to an average of 18 NASs. Not surprisingly, the average pipeline size for "major" companies (31 NASs) was far greater than that of smaller companies (nine NASs). Table 5.3 shows a breakdown of pipeline size by phase in 2002 for all companies and for the "major" and "other" company cohorts.

Twenty-six companies provided data for all five years 1998-2002 (Figure 5.2). This cohort of companies accounted for the active development of a total of 488 NASs in 1998, 536 NASs in 1999, 537 NASs in 2000, 521 NASs in 2001 and 526 NASs in 2002. Over the period 1998-2002, this cohort increased their combined R&D expenditure on ethical pharmaceuticals by at least US$ 5.7bn (based on data from 19 of the 26 companies). Despite this increase in investment, the average number of NASs in active development has remained relatively stable, at around 20 NASs. For 13 "major" companies a slight increase in the average pipeline size was observed, from 27 NASs in 1998 to 31 NASs in

Table 5.3 Phase distribution of NASs in active development on 31st December 2002 by company size

Latest development stage	Total NASs for respondent companies	Proportion of Total NASs	Mean per company
All respondents (n=34)			
Preclinical	143	23%	4.2
Phase I	216	35%	6.4
Phase II	177	29%	5.2
Phase III	44	7%	1.3
Presubmission	13	2%	0.4
Submitted	25	4%	0.7
Total	**618**	**100%**	**18.2**
"major" respondents (n=14)			
Preclinical	109	25%	7.8
Phase I	157	36%	11.2
Phase II	116	27%	8.3
Phase III	29	7%	2.1
Presubmission	6	1%	0.4
Submitted	19	4%	1.4
Total	**436**	**100%**	**31.1**
"other" respondents (n=20)			
Preclinical	34	19%	1.7
Phase I	59	32%	3.0
Phase II	61	34%	3.1
Phase III	15	8%	0.8
Presubmission	7	4%	0.4
Submitted	6	3%	0.3
Total	**182**	**100%**	**9.1**

Figure 5.2 Average pipeline size per year (1998-2002).



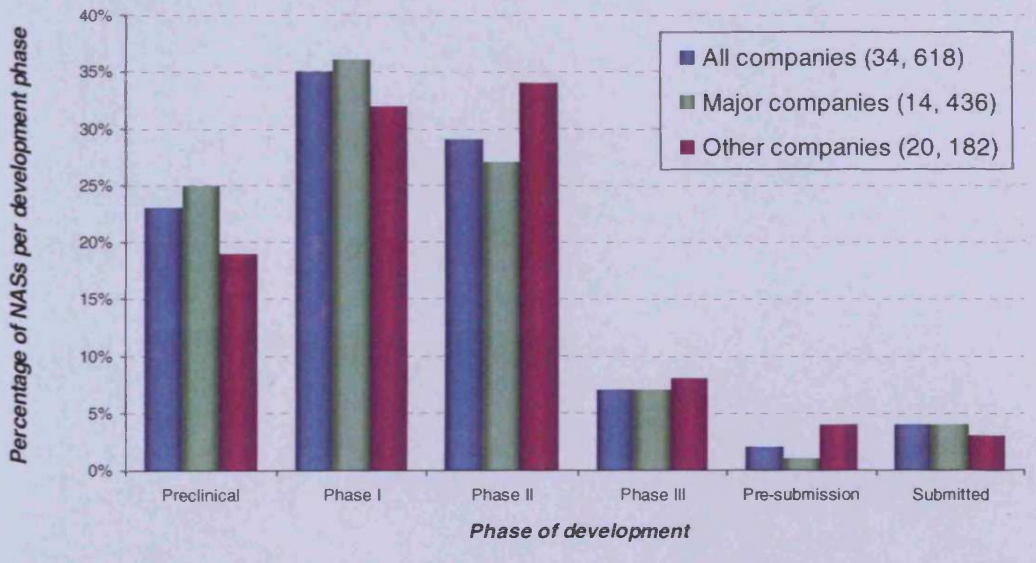
(n) is the number of companies. Statistical analysis of these data using a repeated measures ANOVA model shows that there was no significant change over time in overall pipeline size (p>0.05).

2002. For the 13 "other" companies, the average pipeline size remained virtually unchanged during this five-year period (around 10 NASs, Figure 5.2). Analysing changes in the size of the clinical pipeline only, by excluding NASs in preclinical development, resulted in similar patterns for "other" companies and all companies. The slight increase observed in the average size of the combined preclinical and clinical pipeline was not observed in the clinical pipeline for the "major" companies, suggesting the observed increase was driven by extended preclinical activities.

Distribution of the pipeline by development phase

The distribution of NASs in active development is presented in Figure 5.3 as the percentage of NASs per phase of the development process. Over 80% of the 618 NASs (536 NASs) in active development on 31st December 2002 were in one of the early development phases: preclinical development, clinical phase I and clinical phase II. Of all phases, Phase I is the most highly populated: 216 NASs (35%) were reported to be in this phase of the development process, with Phase II as a close second, accounting for 29% of all NASs (177 NASs) in development in 2002. Twenty-three percent of all NASs (143 NASs) were reported to be in preclinical development and an additional seven percent (44 NASs) and two percent (13 NASs) of all NASs were reported to be in clinical

Figure 5.3 Pipeline size by phase as of 31st December 2002 by company cohort



The phase distribution presented in this graph is based on data from 34 companies (14 "major" and 20 "other" companies).

Phase III or in the pre-submission phase, respectively. The remaining 25 NASs (4%) had been submitted to a regulatory authority and were still awaiting authorisation for marketing on 31st December 2002.

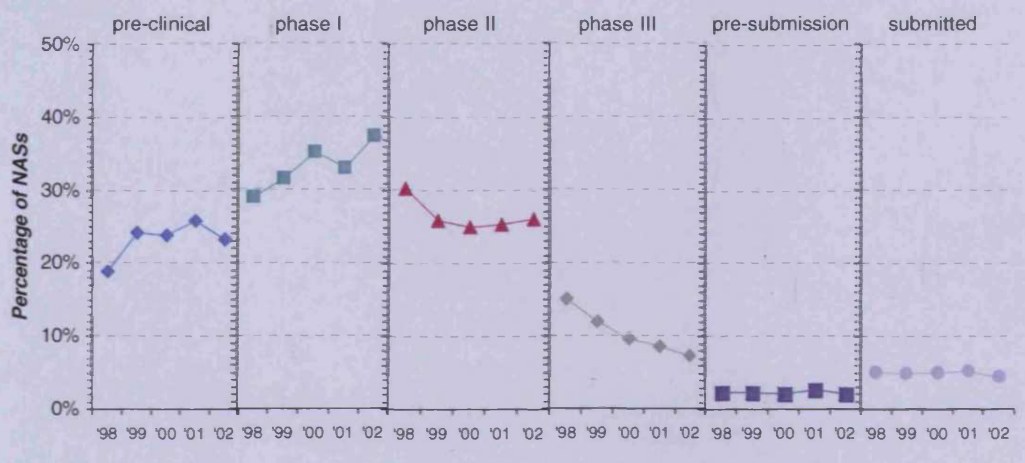
The overall distribution for the 14 "major" companies displayed a similar pattern, although the difference in size between the preclinical phase and phase II was smaller for "major" companies (two percentage points) than the difference observed for all 34 companies (six percentage points). Twenty "other" companies reported a total of 182 NASs in development, one-third of which were reported to be in clinical Phase I (59 NASs). A similar proportion of NASs was observed to be in phase III of the development process (61 NASs). The preclinical phase accounted for 19% of their overall pipeline (34 NASs). The main difference between "major" and "other" companies was the relative size of Phase I and Phase II. "Other" companies reported the development of 1.0 NAS in Phase II for every NAS in Phase I, whereas "major" companies reported a ratio of 0.7 NAS in phase II for every NAS in Phase I in 2002.

Although no changes were observed in the average pipeline size per year over the period 1998-2002, fluctuations were observed in the phase distribution of the active development pipeline (Figure 5.4). For the 26 companies that provided data for all five years, the proportion of NASs in Phase I was almost equal to the proportion of NASs in phase II in 1998 (29% and 30%, respectively), with Phase III representing 15% of the pipeline. In the four years that followed, the proportion of NASs in phase I gradually increased to 37% by 2002, with the exception of 2001 (33%). Over the same time period, a steady decrease was observed in the proportion of NASs in Phase III, reaching a low of only 7% in 2002. After an initial drop in 1999, the proportion of NASs in phase II remained relatively stable around 26% of all NASs in active development. No changes were observed in the proportion of NASs in the pre-submission phase or those awaiting approval for marketing.

Origin of NASs in development

Information relating to the origin of NASs was provided for 599 of the 618 NASs (97%) in active development on 31st December 2002 (Figure 5.5). Of these,

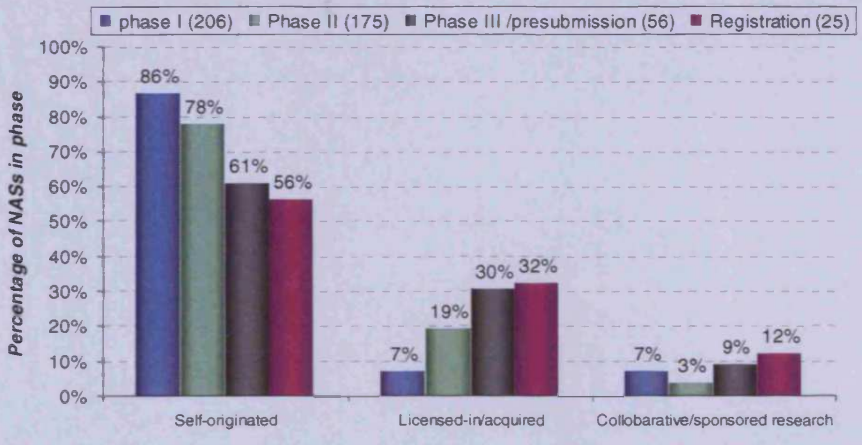
Figure 5.4 Phase distribution of NASs in active development (1998-2002)



The phase distribution presented in this graph is based on data from 26 companies (13 "major" and 13 "other" companies) that provided data for all five years 1998-2002.

80% (479 NASs) originated from internal research activities, 14% (84 NASs) were obtained through licensing or acquisition activities and 6% (36 NASs) originated from collaborative or sponsored research. Eighty-six percent of NASs in Phase I were self-originated, a percentage that declined with every subsequent phase of the development process; of the 25 NASs awaiting

Figure 5.5 Origin of NASs by phase, 2002

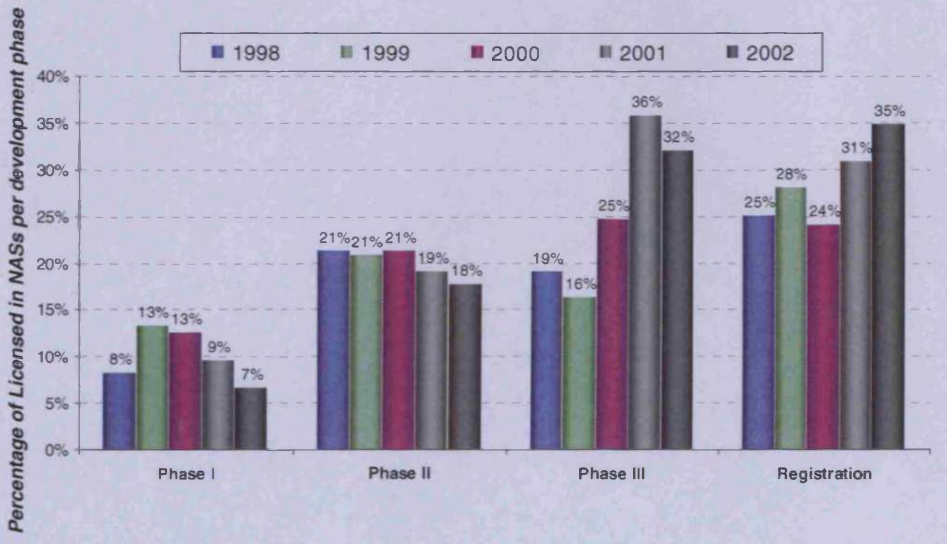


registration only 56% were self-originated. Licensing and acquisition activities are increasingly important in later phases, with around 30% of NASs in Phase III and of those awaiting registration being reported as derived through these type of activities.

The percentage of NASs obtained through licensing-in or acquisition activities by phase over time for the 26 companies that provided data for all five years

1998-2002 is presented in Figure 5.6. This graph represents the number of licensed-in NASs in development at the end of each year as the percentage of the total number of NASs with known origin in development at that time; it does not represent the number of NASs licensed-in or acquired during the year per phase. The proportion of licensed-in NASs in Phase I of the development process by the end of 1998 is similar to this proportion at the end of 2001 and 2002 (around eight percent). At 13% this proportion was slightly higher in 1999

Figure 5.6 Percentage of licensed-in NASs per development phase by year, 1998-2002



Statistical analysis of these data using a linear regression model shows that there was a significant decrease in the proportion of licensed-in NASs in Phase II ($p<0.05$). No significance was shown for any of the other phases.

and 2000. For Phase II, the percentage of licensed-in NASs remained relatively stable around 21%, although a slight decrease was observed for the years 2001 and 2002, with 18% of NASs in development at the end of 2002 in this phase classified as licensed-in. Although year-on-year fluctuations are present, the percentage of licensed-in NASs in Phase III has increased steadily over the time frame observed, from 19% in 1998 to 32% in 2002. A similar increasing trend has been observed for the last phase described, from a quarter of all NASs awaiting regulatory approval originating from licensing-in or acquisition activities at the end of 1998 to over one-third in 2002. Statistical analysis using a linear regression model demonstrated a significant decrease ($p<0.05$) in the proportion of NASs in Phase II that had been licensed-in, but no significant changes could be demonstrated for any of the other phases.

Compound type

Of the 565 NASs in active development on 31st December 2002 for which the compound type was identified, by far the majority were classified as new chemical entities (504 NASs). Six percent were derived from biotechnology (36 NASs) and a further 3% were classified as biologicals (19 NASs). Only one of the 565 NASs was identified as a gene therapy product (Table 5. 4).

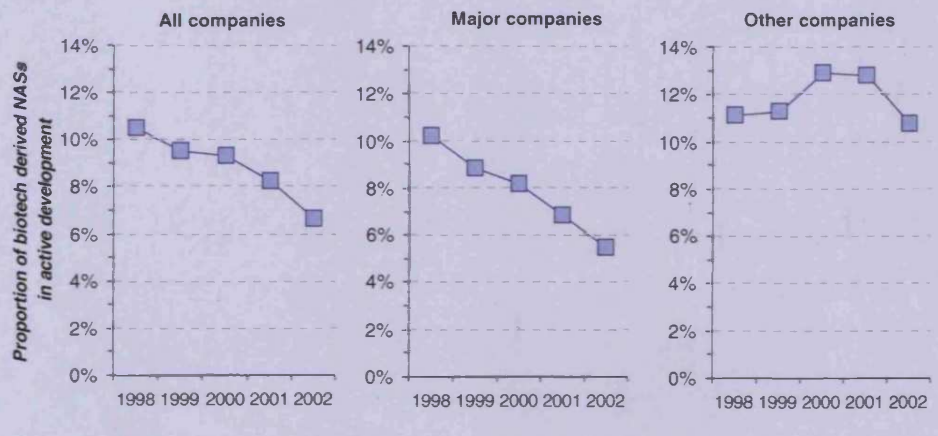
Table 5. 4 Distribution of NASs by type of compound in active development as of 31st December 2002

Type of compound	Number of NASs	Proportion of total NASs
New Chemical Entities (NCEs)	504	89.2%
Biotech derived	36	6.4%
Biologicals	19	3.4%
Gene therapy	1	0.2%
Other	5	0.9%
Total NASs	**565**	**100%**

Data provided by 13 "major" companies for the years 1998-2002 indicated that the contribution of biotechnology to the ethical pharmaceutical pipeline is on the decline. In 1998, biotech compounds represented around 10% of this cohort's overall pipeline compared to only 5% in 2002. For the 13 "other" companies, biotechnology has made an equal contribution to their pipeline throughout the five years 1998-2002. Around 12% of the combined pipeline of "other" companies was reported as being derived through biotechnological processes (Figure 5.7).

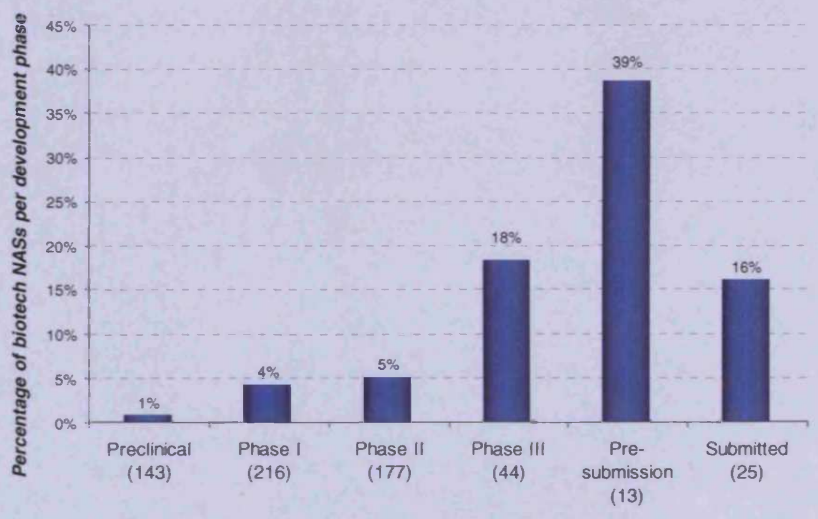
An interesting observation was made regarding the proportion of biotechnology-derived NASs per phase of the development process. With each consecutive phase, the proportion of NASs in development that were derived from biotechnology rises (Figure 5.8). Only 1% of the 143 NASs in preclinical development on 31st December 2002 were reported to have originated from biotechnological processes, compared to 4% of the 216 NASs in Phase I and 5% of the 177 NASs in Phase II of the development process. For Phase III, 8 of the 44 NASs (18%) were reported to be of biotechnological origin. The

Figure 5.7 Proportion of biotech-derived NASs by company size in active development as of 31st December 1998-2002



The proportion of biotech NASs presented in these graphs is based on data from 26 companies (13 "major" and 13 "other" companies) that provided data for all five years 1998-2002.

Figure 5.8 Percentage of biotechnology derived NASs by phase (2002)

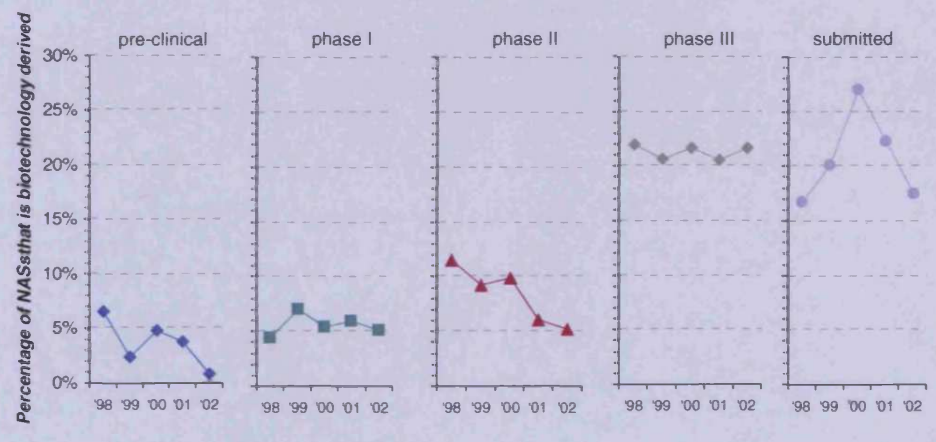


This graph represents data from 34 companies (14 "major" and 20 "other" companies). (n) is the total number of NASs in each development phase.

highest percentage of biotech NASs in 2002 was reported for the pre-submission phase; 39% of the 13 NASs. The percentage of the 25 submitted NASs that were derived through biotechnological processes was lower at 16%. A combination of lower attrition rates and a tendency to license-in biotech NASs during later stages of development may be underlying the higher proportion of biotech NASs in the later phases of the development process.

Analysis of the above breakdown over time for the 26 companies that provided data for all five years 1998-2002 showed a decrease in the percentage of biotech NASs in preclinical development, from 7% in 1998 to 1% in 2002. A similar downward trend was observed for Phase II where the proportion of NASs derived from biotechnology more than halved, from 11% in 1998 to 5% in 2002. No change was observed in the proportion of biotech NASs in Phase I and Phase III of the development process (around 5% and 21%, respectively). For NASs under regulatory review, the percentage of biotech NASs increased from 16% in 1998 to reach a peak of 27% in 2000, followed by a decrease for 2001 and 2002 back to the original percentage observed in 1998 (Figure 5.9).

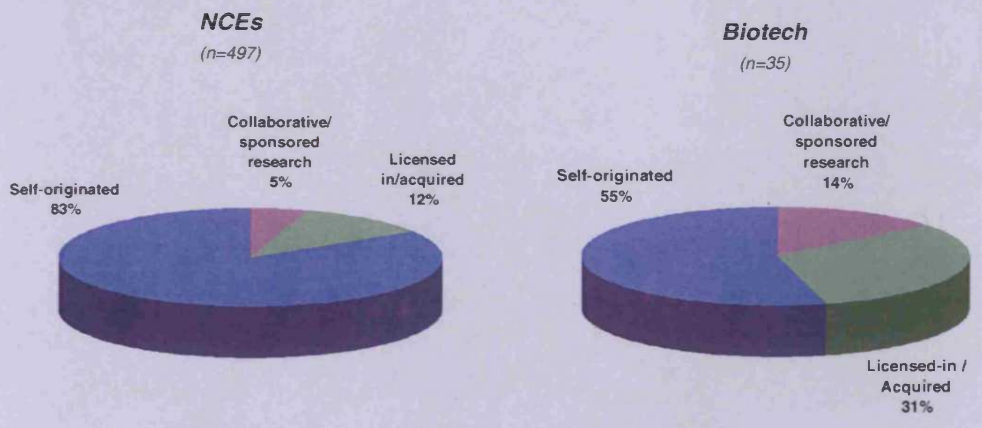
Figure 5.9 Percentage of biotechnology derived NASs by phase (1998-2002)



These graphs are based on data from 26 companies (13 "major" and 13 "other" companies) that provided data for all five years 1998-2002.

A distinct difference can be observed in the origin of biotechnology products and chemical entities. Of the 497 chemical entities in development at the end of 2002 by far the majority (83%) was self-originated. Only 12% were obtained through in-licensing or acquisition and the remaining 5% originated from collaborative or sponsored research activities. In contrast, almost half of the 35 biotechnology compounds in development were obtained from sources other than the company's own research activities. Fourteen percent resulted from collaborative or sponsored research activities, and almost a third was obtained externally (31%, Figure 5.10). Statistical analysis using a Chi-square test showed that the proportion of licensed-in NASs is significantly higher for biotech compounds than for non-biotech compounds ($p<0.01$).

Figure 5.10 Origin of NCEs and biotech-derived NASs in active development as of 31st December 2002



(n) represents the number of NCEs/biotech-derived NASs in active development on December 31st, 2002.

Novel versus established mode of action

In 1999, a new question was added to the study asking companies to indicate for each NAS in active development whether the pharmacological mode of action was established or novel. Novel NASs were defined as those NASs for which no compounds with the same pharmacological mode of action had been marketed previously. Due to a combination of unavailability of this information and the information being perceived by some companies as too sensitive to be divulged, this characteristic was only specified for a subset of the data. For example, for only 310 (50%) of the 618 NASs in development was the pharmacological mode of action identified as either established or novel. To cater for the limited availability of this information, three parameters were calculated to assess the proportion of novel NASs in the pipeline: the actual proportion (by excluding NASs with unknown novelty), the minimum proportion (by assuming all NASs with unknown novelty were established) and the maximum proportion (by assuming all NASs with unknown novelty were novel). The minimum and maximum proportions were then used to present a range of the proportion of novel NASs in the pipeline, around the actual proportion.

For 2002, it was estimated that around 53% of NASs in development by 34 companies had a novel mechanism of action, with a potential range from a minimum of 27% to a maximum of 77%. The actual percentage of novel NASs

in development (excluding NASs of unknown novelty) was lower for "major" companies (41%) than for "other" companies (71%). This difference seems to be corroborated when NASs with unknown novelty were taken into account; the proportion of novel NASs in "other" companies' aggregated pipeline ranged from 49% to 80%, whereas the proportion of novel NASs in the 14 "major" companies' aggregated pipeline falls between 17% and 75% (Table 5.5).

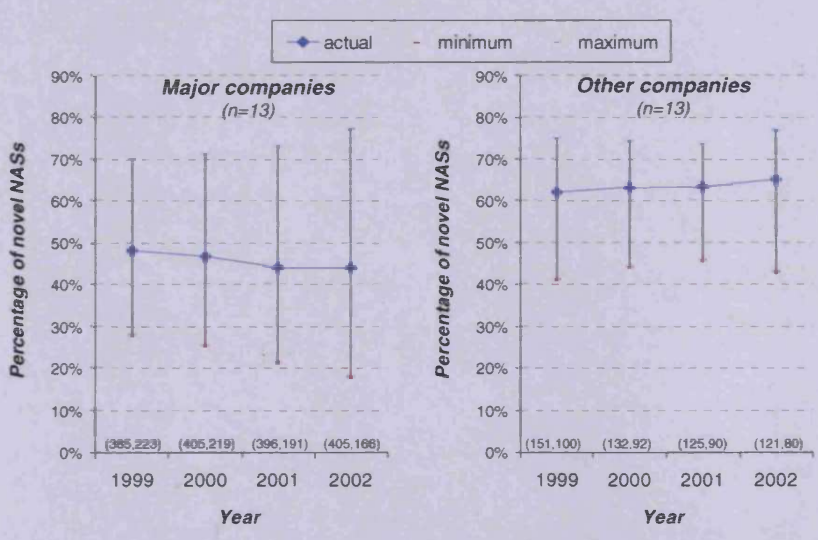
A cohort of 26 companies, representing 71% of global R&D expenditure, participated in the study for all four years 1999-2002 (Figure 5.11). The actual

Table 5.5 Proportion of NASs with novel mode of action in active development as of 31st December 2002 by company size

	Actual	Minimum-Maximum	All NASs	NASs with known novelty
All companies (n=34)	53%	27% - 77%	618	310
"major" companies (n=14)	41%	17% - 75%	436	185
"other" companies (n=20)	71%	49% - 80%	182	125

Statistical analysis of these data using an independent t-test did not show significant differences between "major" and "other" companies in the proportion of novel NASs in development (p>0.05)

Figure 5.11 Proportion of NASs in active development with novel mode of action by company size (1999-2002)

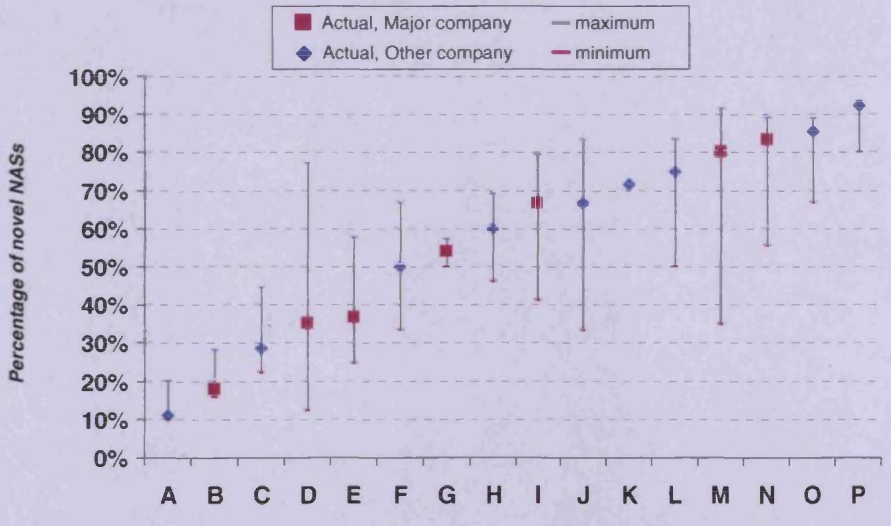


The actual value is calculated by excluding NASs for which the novelty of mode of action is not provided. The maximum value is calculated by assuming that all NASs with unknown novelty are novel. The minimum value is calculated by assuming that all NASs with unknown novelty are established. (n,n) = total number of NASs in development, number of NASs with known novelty of mode of action. Statistical analysis of these data using a linear regression model showed a significant increase in the proportion of novel NASs in development by "other" companies (p<0.05). No significance could be demonstrated for "major" companies.

proportion of novel NASs in the aggregated pipeline for this cohort remained constant over the time period studied (around 51%). However, when taking into account those NASs for which no information was provided on the novelty of the pharmacological mode of action, the range between the minimum and maximum percentage of novel NASs widened from 40 percentage points in 1999 to 53 percentage points in 2002 (between 31.5% and 71.3% and between 23.4% and 77%, respectively), indicating that the high proportion of NASs with unknown novelty prevents any meaningful conclusions to be drawn from this analysis. Statistical analysis of NASs with known novelty ('actual proportion') demonstrated a significant increase in the proportion of novel NASs in development by "other" companies ($p<0.05$). No significant change over time was demonstrated for "major" companies.

Although no trend could be observed in the overall proportion of novel NASs in development, distinct differences were found between individual companies. Figure 5.12 shows the minimum, maximum and actual proportion of novel NASs in development per company. Of 16 companies examined, the pipeline of six companies consisted of over 70% novel NASs (based on actual proportion). At

Figure 5.12 Proportion of NASs in active development with novel mode of action by company size (2002)

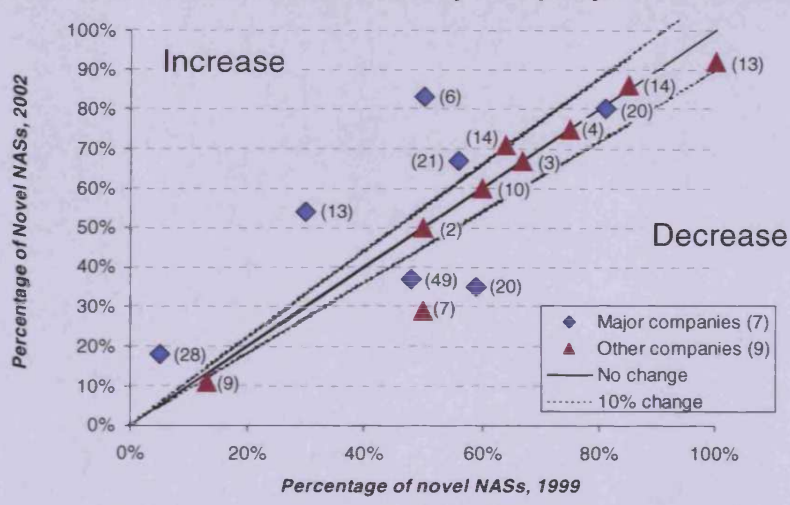


The actual value is calculated by excluding NASs for which the novelty of mode of action is not provided. The maximum value is calculated by assuming that all NASs with unknown novelty are novel. The minimum value is calculated by assuming that all NASs with unknown novelty are established. Companies that only provided information on established or novel NASs but not on both are excluded from this analysis.

the other end of the scale, for three companies less than one-third of their pipeline in 2002 was novel when NASs with unknown novelty are excluded. When taking into account those NASs for which no information was provided on the novelty of the pharmacological mode of action it was still apparent that the proportion of novel NASs widely varies per company. Two "other" companies were identified as developing a pipeline containing at least 70% novel NASs (companies K and P), whereas the pipelines of one "major" and one "other" company contained a maximum of 30% of novel NASs (companies A and B), demonstrating the extent of the differences found between companies.

The percentage of novel NASs in development in 1999 is plotted against the percentage of novel NASs in development in 2002 for individual companies in Figure 5.13. Of the 16 companies included in this analysis, the pipelines of four "major" companies and one "other" company contained a higher proportion of

Figure 5.13 Percentage of novel NASs by company, 1999 vs. 2002



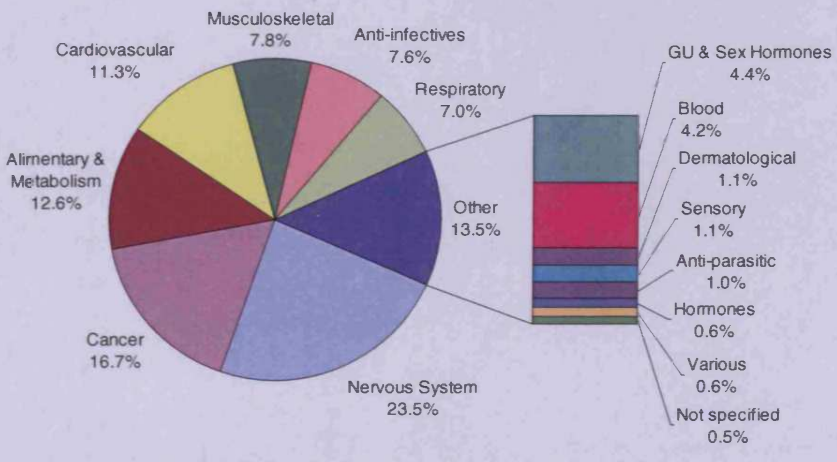
The percentage is calculated by excluding NASs for which the novelty of mode of action was not provided. Companies that only provided information on established or novel but not both types of NASs are excluded from this analysis. (n) is the number of NASs for which information was available in 2002. Statistical analysis of these data using a t-test showed no significant differences between 1999 and 2002, for either company cohort (p>0.05).

novel NASs in 1999 than in 2002. For four companies (two "major" and two "other" companies), a decrease in the proportion of novel NASs in development was observed between the end of 1999 and the end of 2002. For the remaining seven companies, the level of novelty of the pipeline in 2002 was within ten percentage points of the percentage of novel NASs in development in 1999.

Pipeline distribution by therapeutic area

Based on the WHO ATC classification, NASs were assigned to one of fourteen therapeutic areas. In 2002, over two-thirds of pipeline activities could be attributed to four therapeutic areas: Nervous System, Oncology & Immunomodulators, Alimentary & Metabolism and Cardiovascular System (see Figure 5.14). The main therapeutic area, Nervous System accounted for 24% of all NASs in active development on 31st December 2002.

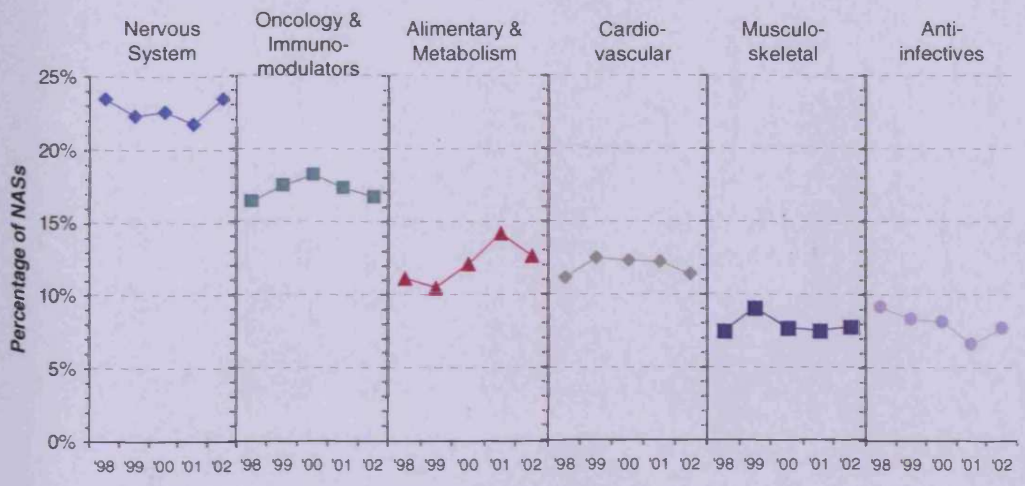
Figure 5.14 Therapeutic breakdown of new active substances in development on 31st December 2002



Based on 618 NASs in development on December 31st, 2002.

For the 26 companies that provided data for all five years 1998-2002, the aggregated percentage of NASs in development per therapeutic area for the six main areas is presented in Figure 5.15. NASs in development for Nervous System indications, the largest therapeutic area, represented 22-23% over this five-year period, with the second-largest therapeutic area (Oncology & Immunomodulators) representing around 17% of all NASs in development over this period of time. The proportion of NASs in development for Alimentary & Metabolism indications by this cohort of companies increased slightly, from 11% in 1998 to 14% in 2001, although this proportion decreased slightly in 2002 (to 13%). The importance of the cardiovascular area in terms of the proportion of NASs in development has remained stable at 11-12% of the pipeline. The same stable trend was observed for the Musculoskeletal and Anti-infectives therapeutic areas, with both areas representing around 8% of all NASs in development for each year of the five-year period 1998-2002.

Figure 5.15 Therapy area distribution of NASs in active development (1998-2002)



These graphs are based on data from 26 companies (13 "major" and 13 "other" companies) that provided data for all five years 1998-2002. This cohort of companies accounted for the active development of a total of 488 NASs in 1998, 536 NASs in 1999, 537 NASs in 2000, 521 NASs in 2001 and 526 NASs in 2002.

Considerable variation between therapeutic areas was found in the proportion of biotech compounds and the proportion of licensed-in or acquired NASs (Table 5.6). The lowest percentage of biotech-derived NASs was observed for the largest area, Nervous System (<1%), whereas 15% of NASs in the second-largest therapeutic area (Oncology & Immunomodulators) were derived through biotechnology. This area was also the area for which the highest percentage of licensed-in and acquired NASs was observed (27%). The lowest dependence on this type of activities as a source of NASs was observed for the therapeutic area GU & Sex hormones (4%). Another parameter for which differences were found between therapeutic areas was novelty. Table 5.6 reports on the minimum, maximum and actual percentage of novel NASs in development in each therapeutic area. Statistical analysis showed significant differences between therapeutic areas for all three characteristics assessed (novelty, $p<0.001$; biotech, $p<0.01$; licensed-in, $p<0.01$). The proportion of novel NASs in development was significantly lower for Anti-infectives and GU/sex hormones and significantly higher for cardiovascular indications ($p<0.05$). Further tests on the differences between therapeutic areas in the proportion of biotech NASs and the proportion of licensed-in NASs were non-conclusive.

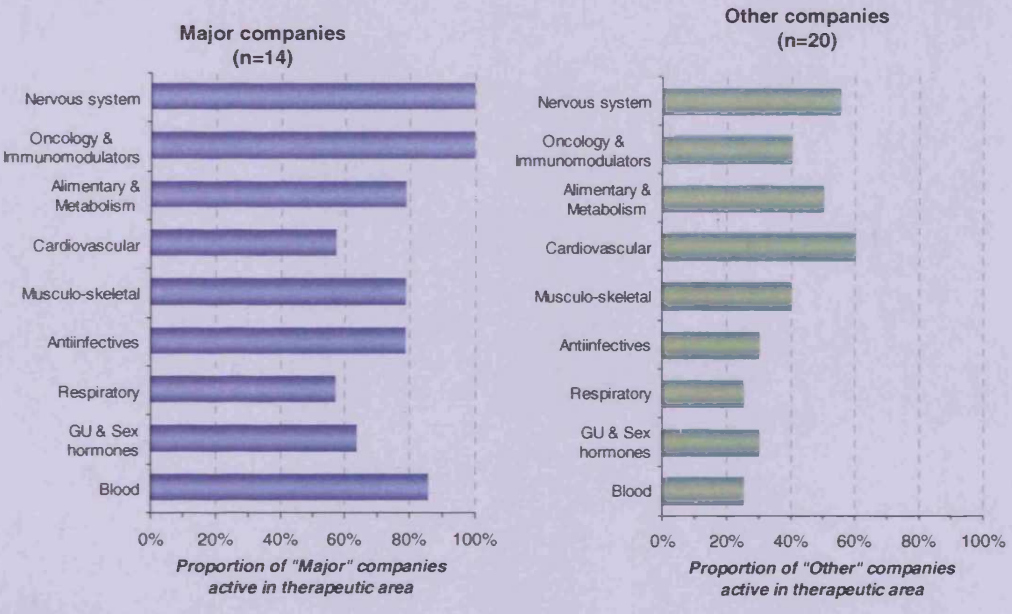
When assessing the number of companies active per therapeutic area, it was identified that all "major" companies and a substantial number of "other" companies have one or more NASs in development for the two largest therapeutic areas, Nervous System and Oncology & Immunomodulators. More surprising is the large number of companies with development activities in the smaller therapeutic areas. For example, the 27 NASs in development within the therapeutic area GU & Sex hormones in 2002 could be attributed to the combined activities of a total of 15 companies. This would mean that there are several companies developing only one NAS within this therapeutic area (Table 5.6 and Figure 5.16).

Table 5.6 Pipeline characteristics by therapeutic area 2002

Therapeutic area	Size		Biotech NASs	Licensed -in NASs	Novel mode of action
	Number of NASs	% of pipeline[a]	% of TA[b]	% of TA[b]	% of TA[c]
Nervous System	145	23.5%	0.7%	12.4%	58% (31%-77%)
Oncology & Immunomodulators	103	16.7%	14.6%	27.2%	60% (24%-83%)
Alimentary & Metabolism	78	12.6%	6.4%	12.8%	50% (33%-67%)
Cardiovascular	70	11.3%	5.7%	4.3%	66% (39%-80%)
Musculoskeletal	48	7.8%	4.2%	4.2%	50% (19%-80%)
Antiinfectives	47	7.6%	8.5%	17.0%	30% (15%-66%)
Respiratory System	43	7.0%	2.3%	14.0%	55% (28%-77%)
GU/Sex Hormones	27	4.4%	3.7%	3.7%	20% (7%-70%)
Blood	26	4.2%	11.5%	11.5%	55% (23%-81%)
All NASs	618	100%	5.9%	13.6%	53% (27%-77%

[a]Calculated as the proportion of all NASs in development, including 3 NASs for which the therapeutic area was not specified. [b]Calculated as the proportion of NASs in development for that therapeutic area, including NASs for the compound type/origin was not provided. [c]See page 121 for more information about the calculation of the percentage of NASs with a novel mode of action. Statistical analysis of these data using a Chi-square test showed significant differences between therapeutic areas in the proportion of biotech NASs ($p<0.01$), the proportion of licensed-in/acquired NASs ($p<0.001$) and the proportion of NASs with a novel pharmacological mode of action ($p<0.01$). The proportion of novel NASs was significantly lower for the therapeutic areas GU/Sex hormones and anti-infective and significantly higher for the cardiovascular area ($p<0.05$). It was not possible to identify which therapeutic areas were significantly different for the other two characteristics.

Figure 5.16 Number of companies active per therapeutic area as of 31st December 2002



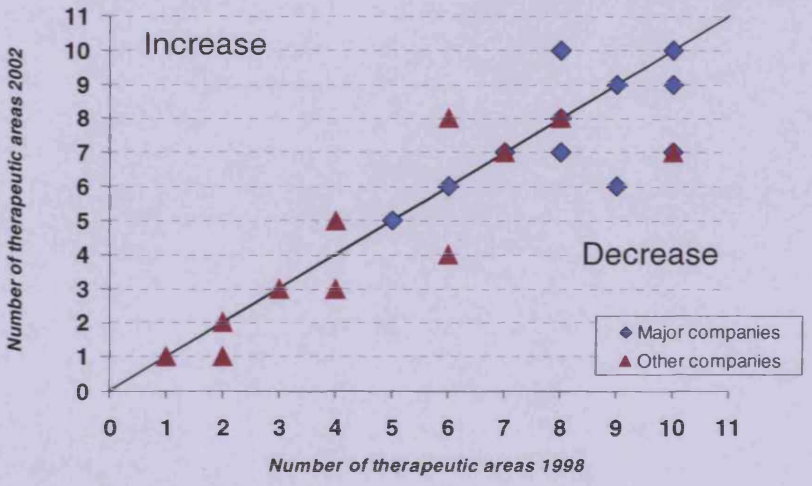
Therapeutic areas ordered by decreasing number of NASs in development on December 31st, 2002.

In 2002, respondent companies were developing NASs in an average of six therapeutic areas each. The average "major" company spread its development activities over 31 NASs in seven therapeutic areas, whereas "other" companies, on average, focused their activities on nine NASs in four therapeutic areas. The WHO ATC codes system divides indications into 14 therapeutic areas; none of the participating companies was undertaking development activities in all 14 areas simultaneously. In 2002, three of the 36 companies undertook development activities in ten therapeutic areas, the highest number of areas reported. Of the 26 companies that participated in the study in all five years 1998-2002, ten companies (four "major" and six "other" companies) were active in fewer therapeutic areas in 2002 than they were in 1998 (Figure 5.17). Only three companies (one "major" and two "other" companies) increased the number of therapeutic areas in which they were active over this period of time.

The total size of the pipeline is closely linked to the number of therapeutic areas in which a company is undertaking development activities, since in order to be considered active in a therapeutic area, at least one NAS has to be in development for an indication within that area. Figure 5.18 presents the number

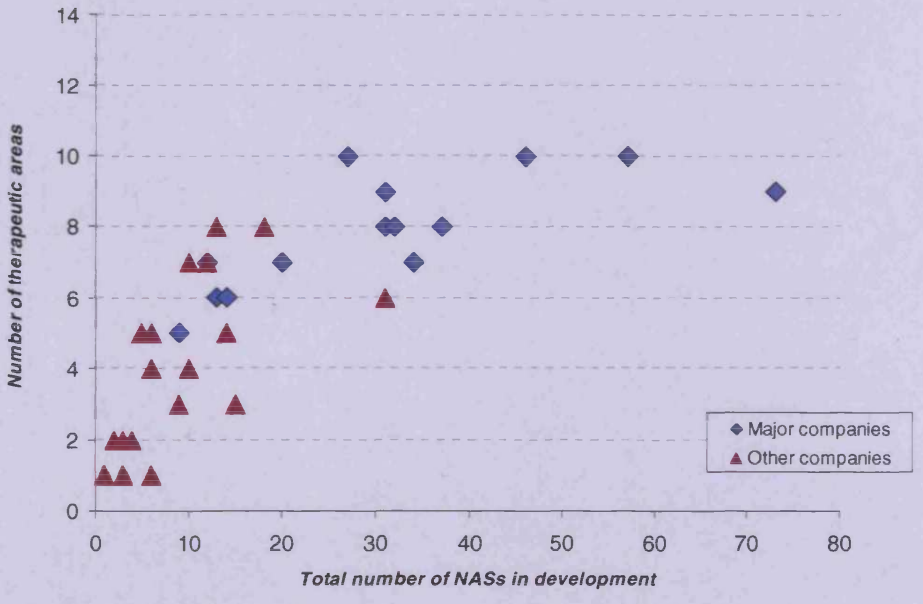
of therapy areas plotted against the total number of NASs in development per company and demonstrates the general relationship between these two parameters. Interestingly, however, when comparing companies with similar pipeline sizes substantial differences are observed in the number of therapeutic areas for which these NASs are being developed. For example, five companies reported the development of 13-15 NASs at the end of 2002. For these companies, the number of therapeutic areas varied from three to eight. On

Figure 5.17 Number of therapeutic areas in which companies are active, 1999 vs. 2002



The maximum number of therapeutic areas in which a company can be active is 14.

Figure 5.18 Number of therapeutic areas per company vs. pipeline size, 2002



The maximum number of therapeutic areas in which a company can be active is 14.

average, each of the 34 companies participating in 2002 was developing 18.2 NASs for 5.6 therapeutic areas, with an average ratio of 3.3 NASs per therapeutic area. For "major" companies this ratio was higher (3.8 NASs per therapeutic area) than for "other" companies (2.4 NASs per therapeutic area).

The average number of NASs in development at the end of 1998 and 2002 is presented in Table 5.7 for the 26 companies that provided data for all years 1998-2002. The table also describes the average number of therapeutic areas for which these NASs were being developed and the average number of NASs per therapeutic area. In 1998, these 26 companies developed an average of 18.8 NASs for an average of 6.4 therapeutic areas, i.e. an average of 2.7 NAS

Table 5.7 Mean number of NASs in preclinical and clinical development per therapeutic area by company size (1998 vs. 2002)

	Therapeutic areas	NASs in development	NASs per Therapeutic area
1998 – mean numbers per company (preclinical and clinical development)			
All companies (n=26)	6.4	18.8	2.7
"major" companies (n=13)	8.3	26.9	3.1
"other" companies (n=13)	4.5	9.9	2.3
2002 – mean numbers per company (preclinical and clinical development)			
All companies (n=26)	6.0	20.2	3.2
"major" companies (n=13)	7.8	31.2	3.8
"other" companies (n=13)	4.2	9.3	2.6

Statistical analysis of these data using a Wilcoxon Signed Rank test indicated that there was no significant difference between the two years investigated for either characteristic (number of therapeutic areas, number of NASs and number of NASs per therapeutic area) for either company cohort (all, "major" and "other" companies) (p>0.05).

per therapeutic area. For 2002, this had increased to an average of 3.2 NASs per therapeutic area, suggesting that companies are focusing their development activities on a smaller number of therapeutic areas. This shift appeared to be more pronounced for "major" companies than for "other" companies. For "major" companies the average number of NASs per therapeutic area increased from 3.1 to 3.8, a 23% increase over the five-year period. For "other" companies an increase of 13% was observed, from 2.3 NASs per therapeutic area in 1998 to 2.6 in 2002. Statistical analysis showed that none of the observed changes over time were significant (p>0.05).

The results of a similar analysis based on NASs in preclinical development are presented in Table 5.8. For the 18 companies that reported preclinical development activities in both 1998 and 2002, the ratio of NASs per therapeutic area increased by 23% from 1.3 in 1998 to 1.6 in 2002. This increase was limited to "major" companies' activities; the average ratio for ten "major" companies increased by 46%, from 1.3 1998 to 1.9 NASs per therapeutic area in 2002. Over this period of time, the ratio remained unchanged for the eight "other" companies in this analysis (1.3 NASs per therapeutic area for both years 1998 and 2002). Statistical analysis showed that none of the observed changes over time were significant ($p>0.05$).

Table 5.8 Mean number of NASs in preclinical development per therapeutic area by company size (1998 vs. 2002)

	Therapeutic areas	NASs in development	NASs per Therapeutic area
1998 – mean numbers per company (preclinical development)			
All companies (n=18)	3.2	4.3	1.3
"major" companies (n=10)	4.0	5.5	1.3
"other" companies (n=8)	2.3	2.9	1.3
2002 – mean numbers per company (preclinical development)			
All companies (n=18)	3.4	6.3	1.6
"major" companies (n=10)	4.6	9.4	1.9
"other" companies (n=8)	2.0	2.5	1.3

Statistical analysis of these data using a Wilcoxon Signed Rank test indicated that there was no significant difference between the two years investigated for either characteristic (number of therapeutic areas, number of NASs and number of NASs per therapeutic area) for either company cohort (all, "major" and "other" companies) (p>0.05).

DISCUSSION

In this study, the ethical development pipelines of 34 large and medium-sized international pharmaceutical companies were examined. Details of all NASs in preclinical and clinical development, as well as NASs undergoing regulatory review were utilised to generate evidence to test five hypotheses.

Hypothesis 1: Companies increased the size of their pipeline between 1998 and 2002

Against a background of increasing R&D expenditure in the industry's continued drive to reverse the downward trend in the number of new medicines reaching the market, it is reasonable to expect that some if not all of this investment will

reflect an increased development effort demonstrated in an increase in overall pipeline size. However, data from this study demonstrate that over the period of the study, 1998-2002, the average pipeline size for 26 companies, representing over 70% of global R&D expenditure in 2002, remained stable around 20 NASs in preclinical and clinical development per company. Over the same period of time, an increase in the average size of the pipeline for 13 "major" companies was observed, whereas the average pipeline size for 13 "other" companies decreased slightly from 1999 to 2002. For both cohorts of companies, this was driven by changes in the size of the preclinical pipeline rather than the clinical pipeline. Therefore, the evidence does not support the null hypothesis that companies increased the overall size of their clinical pipeline between 1998 and 2002.

The lack of increase in pipeline size does not necessarily mean that companies are not developing more NASs, since increasing the size of the development pipeline is not the only means through which companies could potentially increase the number of new product launches. Other strategies that could be employed include decreasing development times, increasing late-stage success rates and increasing the number of compounds taken into man. Any combination of the above could potentially lead to an improved annual output, without necessarily impacting on the overall clinical pipeline size. For example, if a company would succeed in decreasing its clinical cycle times and at the same time increase the number of NASs entering the clinical development process, the number of NASs going through the development process would increase and, assuming constant success rates, so would the number of NASs reaching the market. If the increase in the number of NASs entering development is balanced against the increased rate at which NASs leave the development process, due to decreased cycle times, the overall number of NASs in development at any given moment in time will be the same and no changes in the pipeline size would be observed.

Over the period 1999 to 2001, Lloyd (2002) reported a slight increase in the number of projects in active R&D, attributing this increase to a surge in the number of compounds entering the pipeline. The apparent contradiction with the

present study can be explained by the different inclusion criteria applied in the two studies. Lloyd's findings are based on any project, including line extensions, anywhere in the R&D process, whereas the data set investigated in this study is limited to new active substances in clinical development and under regulatory review. The observed increase in the number of NASs in preclinical development, as well as increased expenditure on line extension activities by some companies (Chapter three), also supports the hypothesis that the increased number of projects in R&D as reported by Lloyd's results from a increase in line extension activities and preclinical projects.

Hypothesis 2: The distribution of products in the pipeline, i.e. the proportion of NASs per phase of the development process, has changed between 1998 and 2002

It was postulated that in addition to increasing the size of the pipeline (as tested in the first hypothesis) companies were also focusing on improving late stage success rates which would be likely to result in a shift in the phase distribution of the development pipeline. Having established that the outcome of this study does not support the first hypothesis, it is even more important for the future output of the industry that companies have succeeded in improving late-stage success rates.

Data collected in this study supported this view. Over the duration of the study, 1998-2002, a steady increase was observed in the proportion of NASs in clinical Phase I for a consistent cohort of 26 companies, compensated by a decline in the relative number of NASs in Phase III. Most remarkable was the observation that despite a drop of more than 50% in the proportion of NASs in this phase, the number of NASs undergoing regulatory review remained constant during the five-year period.

Three potential developments could be underlying this observation: (a) an increase in the success rates for Phase III, (b) a decrease in the cycle times for Phase III or (c) an increase in the cycle times for the regulatory review stage. Data from the Tufts Center for the Study of Drug Development (CSDD) revealed that the aggregated duration of clinical Phase I to III was 18% faster in the

three-year period 1996-1998 than between 1993 and 1995 (Tufts CSDD, 1999), Getz and De Bruin, 2000). Data from the Centre for Medicines Research (CMR) International on cycle times for new development projects for the years 1997-2003 demonstrated that the duration of Phase III, measured as the time from the first patient dose in the first pivotal safety and efficacy trial to the regulatory submission, remained relatively stable over the period 1998-2002, the duration of this study. Data for 2003, however, disclosed a sharp increase in the duration of clinical Phase III (CMR International, 2004b). Approval times, calculated as time from submission to approval, for both the European Union Centralised Procedure and the US FDA (Food and Drug Administration) rose between 1998 and 2000. Although more promising approval times were observed in 2001, an increase was again observed for both authorities in 2002 (CMR International, 2004a). Together, the USA and Europe were the location of choice for first launch for 75% of NMEs reaching the world market in 2004 (Chapter four). It is therefore not unreasonable to view changes in the US and EU regulatory review times as representative of the global environment for new product launches.

With Phase III times constant over the duration of the study, and only a slight increase in review times, it is likely that an increase in late-stage success rates is the main driver behind the observations. In the study reported in Chapter six trends in both early-stage and late-stage success rates will be examined in more detail.

Hypothesis 3: Biotechnology has made a positive contribution to the industry's pipeline in terms of the number of biotech compounds in development over the period examined (1998-2002)

Considering the growing biotechnology industry and the increased licensing-in and partnering activities between biotechnology and pharmaceutical companies, it seems logical to expect that biotechnology compounds account for an increasing proportion of the pipeline. However, the outcome of this study suggests the opposite. For the 27 companies participating in all five years of this study (1998-2002) the overall percentage of biotechnological compounds in the pipeline decreased from 10% in 1998 to 6% in 2002. The observed decrease was driven by "major" pharmaceutical companies (i.e. those spending

more than US$ 1bn on R&D in 2002). Data for a cohort of 13 smaller companies demonstrated no change with respect to the proportion of biotechnology compounds in development. When studying the results in more detail it becomes apparent that the decline reported for "major" companies is mainly visible in the preclinical phase of the R&D process and clinical Phase III.

Several observations were made in this study providing a more detailed insight into the contribution of biotechnology to the ethical pharmaceutical development pipeline than the proportion of biotech NASs alone. The first observation relates to the proportion of biotechnology-derived NASs by phase. It was observed that this proportion increased with every consecutive phase of the development process, up to and including the regulatory review stage. Secondly, the observation was made that a higher proportion of biotech NASs originated from in-licensing and acquisition activities than was the case for chemical entities. Based on the aggregated data of the 34 companies, 31% of biotech NASs in development in 2002 were licensed-in or acquired compared to 12% of all chemical entities in development in that year. This observation is not surprising since it has been suggested that the majority of biotechnology expertise lies outside the pharmaceutical industry. Thirdly, the observation was made that the proportion of licensed-in and acquired NASs in both Phase I and II had decreased over the duration of the study. In contrast, a considerable increase in this proportion was observed for later phases of the development process. The combination of the above three factors suggests that companies have not lost their interest in biotechnology as the declining proportion of biotech NASs in development initially suggested. Instead, the outcome of the study is most likely to reflect a tendency of companies to license-in biotech NASs later in the development process than has previously been the case, resulting in a decline in the proportion of biotechnology-derived NASs in early development and hence to pipeline overall. Despite the exact hypothesis being disproven in terms of the number of biotech NASs in development, the main thrust of the hypothesis appears to be supported by the outcome of this study, i.e. that biotechnology continues to make an important contribution to the industry's pipeline.

The above theory is corroborated by data collected in a recent repeat of this study. Of the 34 companies participating in the study over 2003 activities, 31 companies reported development activities relating to biotech compounds (CMR International, 2004c), indicating that companies still view biotechnology as important. Today's biotechnology industry is characterised by an increasing number of biotech companies that have become fully integrated, commonly through merger and acquisition activities. In 2000, the biotechnology industry's pipeline appeared fuller than the drug development pipeline of the top 10 pharmaceutical companies combined. (Humphreys, 2000; Anon, 2003d). Most large pharmaceutical companies have recognised that they could achieve greater product output were they to significantly increase their partnerships with biotech companies and they have built a web of alliances over the past decade with innovative biotechnology groups (DeLamarter and Fumero, 2001; Drews and Ryser, 1996). Many of these alliances are of a sophisticated nature (Malone, 2002) with biotechnology companies now taking on more development activities than they would have done five to ten years ago. The pharmaceutical industry seems to be willing to pay the extra money in return for more of the risk being taken by the biotech companies.

Hypothesis 4: Companies have increasingly focused on the development of innovative medicines between 1998 and 2002

In addition to increasing the number of new products launches, the industry is also attempting to maximise the economic value of its output. Increasing pressures from governments and regulatory authorities to demonstrate improved safety and efficacy over and above existing treatments as well as pharmaco-economic benefits mean that product innovation is key to maximising the economic value of a product (Drews and Ryser, 1996). With premium prices upon introduction only possible for those products that carry substantial advantages over existing therapeutics, it seems logical to expect that companies will increasingly be focusing their development activities on innovative NASs.

In this study companies were asked to classify NASs in active development from 1999 onwards as either 'novel' or 'established' based on their

pharmacological mode of action. Although participants perceived this to be a worthwhile characteristic to track, information on the novelty of mode of action was provided for around half of the NASs included in the study, due to a combination of unavailability of the information and this information being perceived by some companies as too sensitive to be divulged. Analysis of the available information might be taken as representative only if it could be proven that companies are as likely to identify novel NASs as they are to identify established NASs. It could be argued that the sensitivity of this data in view of potential competitive advantage applies to a greater extent to novel NASs than to established NASs. However, it is more likely for companies to refrain from providing any data regarding the novelty of mode of action. By excluding companies with limited or no data available for the novelty of mode of action, it was assumed that the impact of incomplete data provision can be reduced. Another reason why this information was only provided for a subset of the data related to the limited availability of the data. In general it will be easier to confirm that the mode of action is established, by identifying at least one NAS with a similar mode of action, than it is to confirm that it is novel since, in theory, this would require confirmation that it is different from the mode of action of all products on the market. As such, the provided data might be slightly skewed towards NASs with an established mode of action, although it is unlikely that this has changed over time, enabling the examination of trends over time with reasonable confidence.

Interestingly, this percentage was observed to be lower for "major" companies (41%) than for "other" companies (71%). The proportion of novel NASs in individual companies' pipelines varied widely; which might explain why only limited changes over time have been observed in the overall proportion of novel NASs in development. However, analysis of the change in this proportion over time for individual companies demonstrated that five of the 16 companies for which sufficient information was available had increased the proportion of novel NASs in 2002 by more than 10% since 1999.

The outcome of the study does not support the hypothesis due to the high proportion of NASs for which the novelty of pharmacological mode of action was

not disclosed. However, based on data from the public domain, it is suggested that there has not been an increased focus on the development of novel NASs, even though Engel (1999) reported that, based on prescription medicines in Phase II clinical trials at the time, a host of new generation medicines was destined to be on the market by 2005. However, more recently, Fumero (2002) indicated that despite the growth of R&D expenditure the number of new drug classes is quite modest. The data collected in this study do not support an assessment of the number of new classes of drugs in development. In order to do so going forward, and make a more definitive assessment as to what extent companies are focusing on the development of innovative NASs, data collection will need to be extended to include a description of the exact pharmacological mode of action.

Hypothesis 5: During the period of the study (1998-2002), companies have increasingly focused on a smaller number of therapeutic areas

The statistical differences between therapeutic areas in pipeline composition by compound type, novelty of mode of action and origin, illustrate the intrinsic differences between therapeutic areas, resulting in different skill sets and knowledge required for the development of NASs in different areas. Since experiences are rarely easily transferable across therapeutic areas it seems logical to expect that in order to improve efficiency and effectiveness, companies are focusing their resources on a smaller number of therapeutic areas (Gilbert *et al.*, 2003).

Development activities from a cohort of 26 companies, that provided data for all years 1998-2002, were evaluated to identify changes over time in the number of therapeutic areas investigated per company. It was observed that for this cohort of companies, ten companies reported preclinical and clinical development activities in fewer therapeutic areas in 2002 than in 1998. Only three companies reported activities in an increased number of therapeutic areas, providing support for the hypothesis that companies are focusing their development activities in a smaller number of therapeutic areas. In line with the above observation, a decline in the average number of therapeutic areas per company was demonstrated for both "major" and "other" companies.

There are many areas on which pharmaceutical companies can focus effort to increase the productivity of their R&D process to ultimately improve future output. Many of these efforts are directed towards increasing the efficiency with which available resources are utilised. In this study, pipeline activities from a cohort of 34 companies were investigated to assess whether a number of approaches are currently being employed by the pharmaceutical industry. Summarising the findings in this study, it was concluded that companies have not increased the size of the overall development pipeline over the five-year period studied. Changes were observed in the phase distributions of the development pipeline, which were most likely the result of an improvement of late stage success rates. Biotechnology continues to make a contribution to the industry's pipeline, despite the observed decline in the proportion of biotech NASs in development. This apparent contradiction is best explained by a changing approach to the licensing-in and acquisition of biotechnology products, with the biotechnology industry taking on more of the development activities traditionally undertaken by the pharmaceutical industry. Differences were demonstrated between therapeutic areas in terms of origin, compound type and novelty of mechanism of action. The intrinsic differences between therapeutic areas require specific capabilities that can rarely be transferred across therapeutic areas. It was demonstrated that the number of therapeutic areas per company declined over the duration of this study, suggesting that companies are focusing their resources on a smaller number of therapeutic areas, focusing on 'knowing much about little' rather than 'knowing little about much'.

SUMMARY

- In this study, the pipeline activities of 34 companies representing 80% of global pharmaceutical R&D expenditure were investigated in detail.

- Although companies did not increase the size of the overall development pipeline over the five-year period studied, changes were observed in the phase distribution which suggested an improvement in late stage success rates.

- Biotechnology continues to make a contribution to the industry's pipeline, despite the observed decline in the proportion of biotech NASs in development.

- Significant differences were demonstrated between therapeutic areas in terms of origin, compound type and novelty of mechanism of action.

- A slight decline was observed in the number of therapeutic areas per company over the duration of the study (1998-2002), suggesting that companies are focusing their resources on a smaller number of therapeutic areas, focusing on 'knowing much about little' rather than 'knowing little about much'.

CHAPTER SIX

AN ASSESSMENT OF CLINICAL SUCCESS RATES AND THEIR CONSEQUENCES – A LONGITUDINAL STUDY

INTRODUCTION

In previous chapters, it has been demonstrated that over the last five to ten years research and development (R&D) expenditure increased exponentially, the number of new medicines reaching the market declined and pipeline sizes remained relatively constant, suggesting a decreasing efficiency in pharmaceutical development. Reliable success rates to market and phase attrition rate estimates are an important tool for the evaluation of the efficiency with which the pharmaceutical industry conducts clinical development (DiMasi, 2001a). Not only do success rates provide insight into the proportion of compounds entering development that will make it to market, the cost of new drug development is also critically dependent on the proportion of active substances that fail in clinical testing (DiMasi *et al.*, 1991; 1995a; 1995b).

A limited number of studies have examined pharmaceutical success rates in the past. The Tufts Center for the Study of Drug Development (CSDD) first reported on success rates in the United States in 1984 (Sheck *et al.*, 1984). Three updates of this study have been published since (Bienz-Tadmer *et al.*, 1992; DiMasi, 1995; 2001a). In their latest publication, success rates were calculated for new chemical entities for which an investigational new drug (IND) filing was submitted in the USA and therefore focused on drug development in the United States only. The study described in this chapter is unique in that it assesses success rates for the international pharmaceutical industry, taking into account chemical entities as well as biotechnology products and biologicals.

In this study, success rates for the international pharmaceutical industry are investigated in detail for the period 1994-2002. The impact of characteristics such as therapeutic area and company size on success rates, as well as the relationship between the duration of clinical phases and success rates has been examined. Furthermore, the derived success rates data will be used to investigate whether current R&D practices have the potential to support a reversal of the declining number of new medicines reaching the market.

OBJECTIVES

In this study, success rates for new active substances (NASs) in development between 1994 and 2002 were investigated in detail, addressing the following five research questions:

1. What is the current probability of success to market for NASs entering clinical development?
2. Have the efforts undertaken by the industry to increase R&D efficiency resulted in an improvement in success rates?
3. To what extent do compound and company characteristics impact on success rates?
4. What, if any, is the relationship between duration in phase and success rates?
5. What can the industry do to positively influence its output in terms of the number of NASs reaching the market?

METHODS

The study of pharmaceutical development success rates and their consequences in terms of potential future output was based on data collected for the study of the global ethical pharmaceutical development pipeline, as described in Chapter five.

Data set

The data set from the Global Ethical Development Pipeline study included development activities for all NASs, where an NAS was defined as an active substance that had not been previously available for therapeutic use in humans and was destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans. The analyses in this study were based on NASs in development between 1994 and 2002 by companies participating in the 2002 round of data collection. An overview of the data points included in this study for individual NASs is provided in Table 6.1.

Table 6.1 Details of each NAS used in the study of success rates

Characteristics	Details	
Milestone dates	First human dose	First submission
	First patient dose	First launch
	First pivotal dose	Termination date
Compound characteristics	Novelty of mechanism of action *(novel; established)* Origin *(self-originated; licensed-in/acquired; collaborative/sponsored research, other)* Compound type *(chemical entity; biotech; biological, gene therapy product, other)* Developing company	
Therapeutic area	Based on the WHO ATC code system (see Appendix VII)	

External data sources

Annual R&D expenditure data were obtained from the study reported in Chapter three, to which data from the Centre for Medicines Research (CMR) International's Global R&D Expenditure Database (GLOBEX) were added. GLOBEX holds detailed information on annual ethical pharmaceutical R&D expenditure, capital expenditure, R&D full-time equivalents (FTEs) and sales from over 80 companies. Since its inception in 1982, the database has been kept up to date with confidential data obtained directly from pharmaceutical companies through the annual R&D Expenditure and Sales study, supplemented with company confirmed data from the public domain.

Information on the historical number of annual new product launches was taken from the study reported in Chapter four. Cycle time information used in future output predictions was taken from the report "*Performance metrics in global pharmaceutical R&D. Incorporating 2000-2002 company analyses*" by Van den Haak *et al.* (2003b)

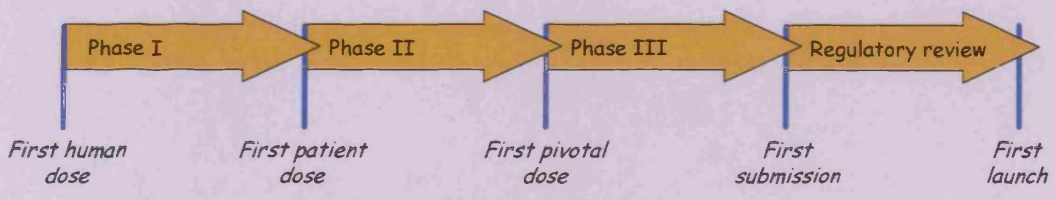
Data processing and analyses

Data were processed using the database programme Microsoft Access™. Descriptive statistics of the data were obtained using Microsoft Access™ and the spreadsheet programme Microsoft Excel™. SPSS™ for Windows™ was used to run statistical analyses on the data. *Chi-square tests* were applied to test for significant differences in between-phase success rates over time, as well as by characteristics such as therapeutic area and company size. No suitable statistical test was identified to test for statistically significant changes in the probability of success to market.

Success rate analyses

In this study, success rates have been calculated by development phase (Figure 6.1), where a NAS was considered successful if it progressed to the next development phase and to have failed if development activities were terminated prior to entry into the subsequent phase.

Figure 6.1 Phase definitions based on key R&D milestones



For definitions of the milestones, see Glossary of Terms on page X.

'Entry' methodology

In this study, success rates were calculated using the 'entry' methodology. This methodology provides more current success rates than the 'longitudinal' methodology and unlike the 'progression-decision' methodology, took into account NASs still in phase at the end of the tracking period.

'Longitudinal' methodology

The 'longitudinal' methodology, which generates actual success rates from 'first human dose' to market, was used to validate the probabilities of success estimated with the 'entry' methodology. Detailed information on success rate methodologies is provided in Chapter two.

For the calculation of current success rates, NASs entering a phase between 1997 and 1999 were tracked until they progressed to the next phase of development, or were terminated, or until the end of 2002 – whichever event occurred first. To obtain a large enough dataset to calculate robust success rates by therapeutic area, however, the time frame for entry into phase was extended to cover 1994-1999, with the fate of each NAS again being assessed at the end of 2002. For trend analyses, the duration over which each NAS was tracked following entry into phase was kept constant to ensure comparability of the data. For example, the fate of NASs entering a phase between 1994 and

1996 was assessed at the end of 1999; the fate of NASs entering a phase between 1995 and 1997 was assessed at the end of 2000 and so on.

Relationship between cycle times and success rates

Two aspects of the relationship between the duration of clinical phases and success rates were investigated in this study. Firstly, the relationship between the time spent in a phase and the probability of successfully completing that phase was examined. The duration in a phase was calculated as the time from entry into that phase to the point in time that the decision was made to either progress the NAS to the next phase, or to terminate further development activities. As a consequence, this calculation only takes into account NASs with a known fate. The likelihood of successful completion of the phase after X years in a phase was calculated as the success rate for all NASs where the duration in the phase exceeded X years.

The second aspect of the relationship between the duration of clinical phases and success rates that was investigated in this study related to the time spent in one phase and the likelihood of success in the next phase. The duration in a phase was calculated as the time from the start of the phase to the end of the phase, using the phase definitions as illustrated in Figure 6.1. The phase duration was calculated for all NASs completing the phase between 1997 and 1999. Based on the 25th, median and 75th percentile duration for this cohort of NASs, NASs were divided into four quartiles (cohorts):

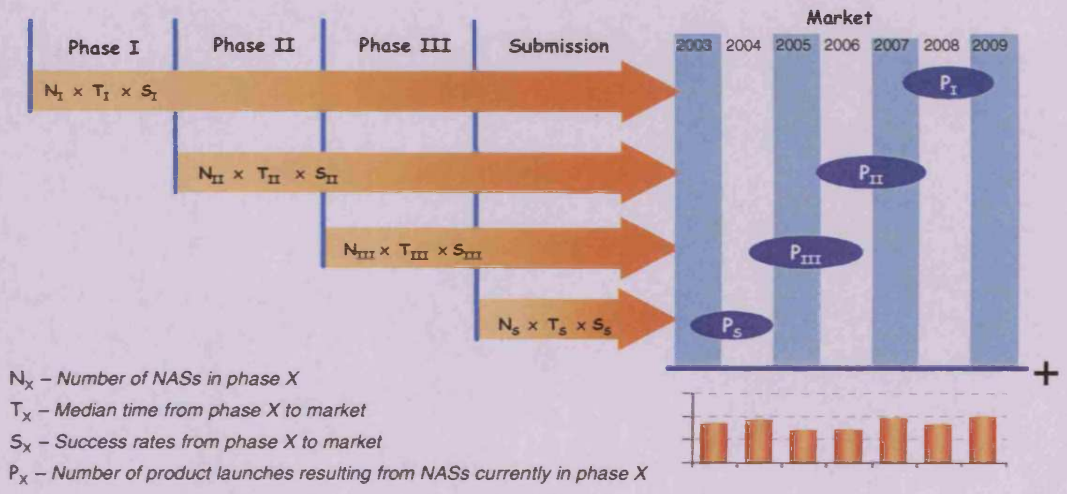
- First quartile: NASs for which the duration in phase was less than or equal to the 25th percentile for all NASs;
- Second quartile: NASs for which the duration in phase exceeded the 25th percentile, but was less than or equal to the median duration for all NASs;
- Third quartile: NASs for which the duration in phase exceeded the median duration, but was less than or equal to the 75th percentile for all NASs;
- Fourth quartile: NASs for which the duration in phase exceeded the 75th percentile for all NASs.

For each of these quartiles the current, minimum and maximum success rate was calculated for the phase subsequent to the phase for which the duration was calculated.

Future output predictions

Future output in terms of the number of new medicines reaching the market will depend on three variables: (1) development time to market, (2) success rates to market and (3) pipeline size. Based on the current (2002) values of these three variables, a model was developed to predict future output (Figure 6.2). Future output was predicted by applying between-phase success rates calculated using the 'entry' methodology, based on NASs entering a phase between 1997 and 1999, whose fate were assessed at the end of 2002. Cycle times were based on phases completed between 2000 and 2002 as reported by Van den Haak *et al.* (2003b). Using these two metrics, an assessment was made of

Figure 6.2 Graphical representation of future output model



the proportion of NASs in active development on 31st December 2002 that would reach the market, and the time within which they would do so. For example, assuming a success rate of 90% from 'first submission' to market, and a median cycle time for the regulatory review stage of 2 years, 90% of NASs under regulatory review on 31st December 2002 is predicted to reach the market between 1st January 2003 and 31st December 2004. Based on the assumption that the NASs were equally distributed with respect to the time that they had already spent in this phase, it was calculated that half of the NASs predicted to reach the market would do so in 2003 and the other 50% in 2004. A similar assessment was made for clinical Phases I, II and III to obtain an estimate of the overall number of NASs reaching the market per year.

RESULTS

Response rate and data set characteristics

For the calendar year 2002, 34 companies provided information on their pipeline activities, including all 14 companies with ethical pharmaceutical R&D expenditure exceeding US$ 1bn ("major" companies). The data for this cohort, which is responsible for 80% of global pharmaceutical R&D expenditure in 2002, provided the basis for all analyses in this chapter, with the exception of trend analyses. Trend analyses were based on data from a cohort of 19 companies (13 "major" and 6 "other" companies) that provided data for all years 1994-2002. This cohort of companies represented 65% of global pharmaceutical R&D expenditure in 2002.

Clinical success rates

Of the 323 NASs achieving 'first human dose' between 1997 and 1999, 293 NASs had either achieved 'first patient dose' (i.e. progressed) or had been terminated prior to achieving this milestone by 31st December 2002. Based on this NAS cohort the success rate from 'first human dose' to 'first patient dose' was calculated to be 61% (Figure 6.3). The fate of the remaining 30 NASs was still unknown at the end of 2002. By including these NASs a minimum and maximum success rate could be calculated based on the assumption that either

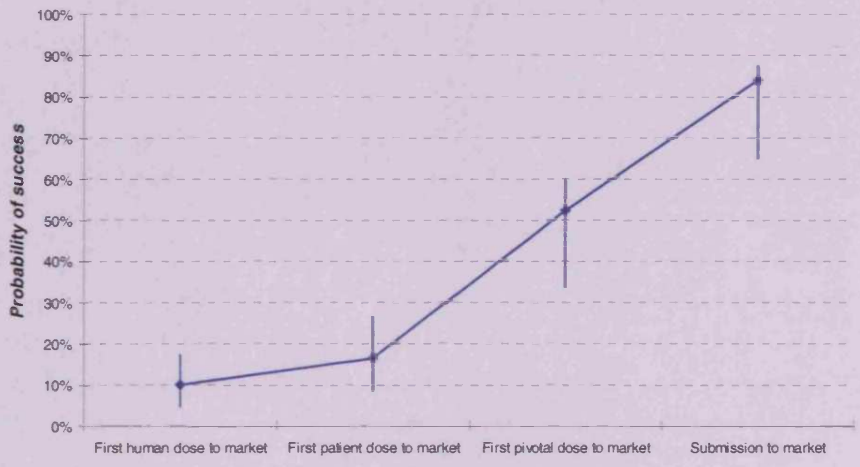
Figure 6.3 Success rates between phases (1997-1999)

High-low lines represent the range of possible success rates (min-max). Success rates calculated for NASs entering a phase between 1997 and 1999, with the fate assessed at the end of 2002, using the 'entry' methodology.

all NASs with unknown fate would be terminated (minimum success rate) or that they would all progress to the next phase by achieving 'first patient dose' (maximum success rate). The minimum and maximum success rates from 'first human dose' to 'first patient dose' were calculated to be 58% and 65%, respectively. The success rate from 'first patient dose' to 'first pivotal dose' was calculated to be 31% (ranging from 26% to 44%), from 'first pivotal dose' to 'first submission' to be 62% (ranging from 52% to 68%) and from 'first submission' to market to be 84% (ranging from 65% to 88%).

Using the between-phase success rates (Figure 6.3), the probability of success from the start of each phase to market was calculated (Figure 6.4). Based on NASs entering a phase between 1997 and 1999, the current probability of success from 'first human dose' to market was 10%, i.e. an estimated ten NASs

Figure 6.4 Probability of success to market (1997-1999)



High-low lines represent the range of possible success rates (min-max) Based on between-phase success rates calculated for NASs entering a phase between 1997 and 1999, with the fate assessed at the end of 2002, using the 'entry' methodology.

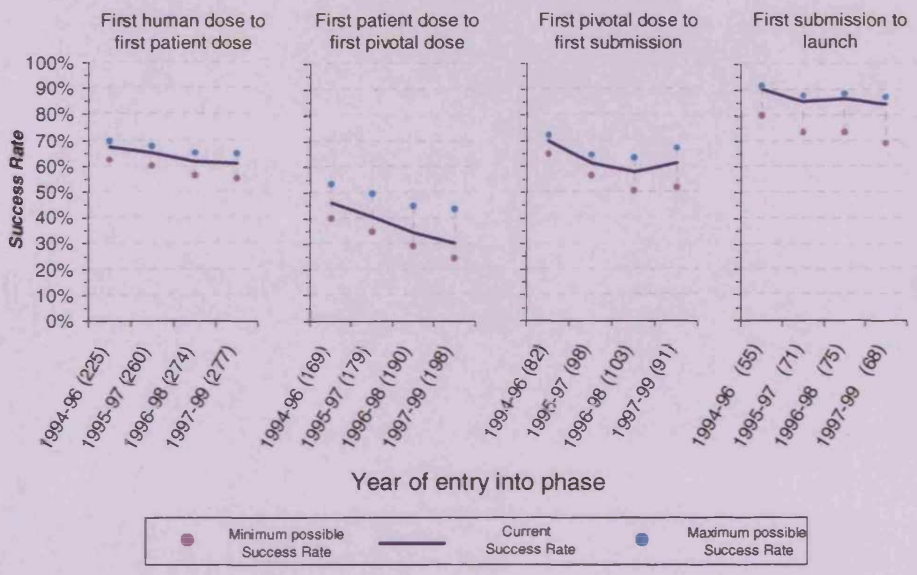
would have to be taken into man in order to achieve one product launch. The probability of success to market increased with each subsequent phase: from 'first patient dose', 'first pivotal dose' and 'first submission' the probability of success to market was estimated to be 16%, 52% and 84%, respectively.

Trends over time

To examine in detail how success rates have changed over time, the progress of NASs in development within a cohort of 19 companies (that provided data for

each year 1994-2002) has been tracked. Between-phase success rates have been plotted by three-year time windows to increase the size of each data set and minimise year-by-year fluctuations (Figure 6.5). An overall decline in success rates, during the time period examined, was evident for all four phases considered. However, there are indications that by increasing the hurdle for entry into Phase III (as suggested by the considerable decline in success rate at

Figure 6.5 Trends in success rates between phases (1994-1999)



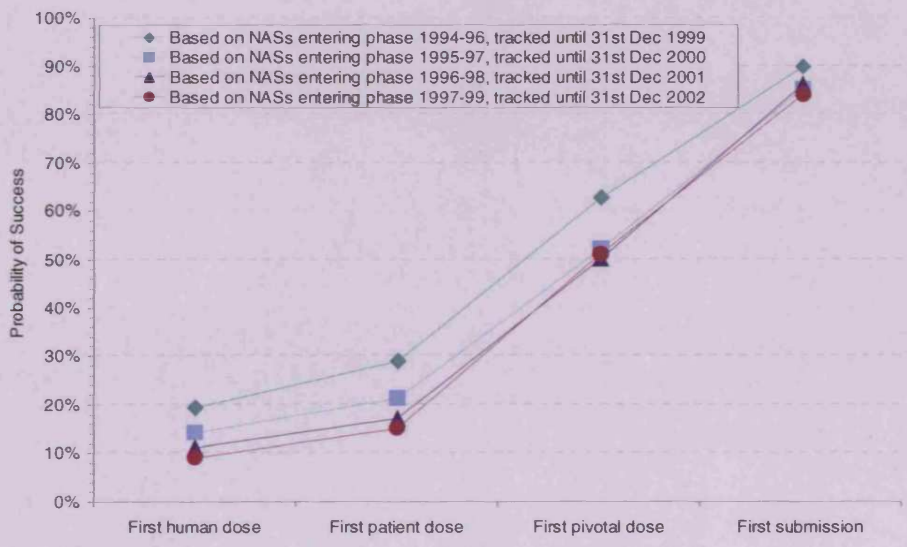
(n) is the number of NASs entering phase. Statistical analysis of these data using Mantel-Haenszel Chi-square tests showed the changes in success rates from 'first human dose' to 'first patient dose' ($p<0.05$), from 'first patient dose' to 'first pivotal dose' ($p<0.01$) and from 'first pivotal dose' to 'first submission' to be significant ($p<0.05$).

Phase II), companies have succeeded in halting the decline in success rates from 'first pivotal dose to 'first submission'. Although success rates of 61% are still low for this advanced stage of the development process, it is a positive sign that the declining trend observed in preceding years has been halted. Statistical analyses demonstrated significance in the changes over time for success rates from 'first human dose' to 'first patient dose', from 'first patient dose' to 'first pivotal dose' and from 'first pivotal dose' to 'first submission'.

Using the current between-phase success rates presented in Figure 6.5 (i.e. excluding NASs for which the fate remained unknown), trends over time in the probability of success to market were investigated (Figure 6.6). The probability of success from 'first human dose' to market decreased considerably over the time period studied, from 19% based on NASs entering a phase between 1994

and 1996 to only 9% for NASs entering a phase between 1997 and 1999. A comparable downward trend was observed for the probability of success from 'first patient dose' to market (from 29% to 15%, respectively). It is encouraging to note, however, that following an initial drop of 10 percentage points, the proportion of NASs entering clinical Phase III ('first pivotal dose') predicted to reach the market has remained constant for the last three year-ranges studied (around 51%). Similarly, the likelihood of NASs that entered the regulatory review stage ('first submission') subsequently reaching the market has not decreased over the last three year-ranges studied (~85%).

Figure 6.6 Trends in probability of success to market (1994-1999)

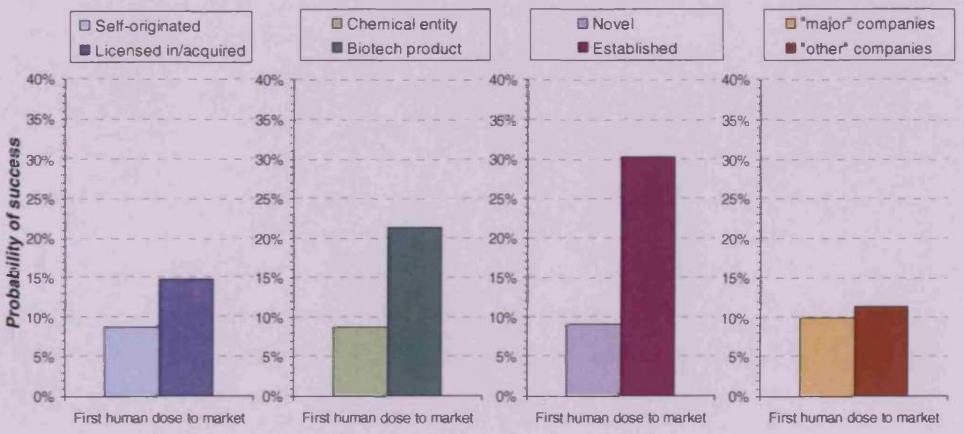


Impact of compound and company characteristics

The impact of a number of compound and company characteristics on between-phase success rates and on the probability of success to market has been investigated in detail. The probability of success from 'first human dose' to market by novelty of mode of action, origin, compound type and company size based on NASs entering a phase between 1997 and 1999 is presented in Figure 6.7. The probability of success from 'first human dose' to market could be calculated for eight therapeutic areas based on NASs entering a phase between 1994 and 1999 (Figure 6.10). Table 6.2 shows details of the between-phase success rates used to calculate the probability of success to market displayed in Figure 6.7 and Figure 6.10, as well as the number of NASs included in each calculation. Trends over time in between-phase success rates

are shown in Figure 6.8, with the resulting trends in probability of success from 'first human dose' to market depicted in Figure 6.9 and Figure 6.11. All trend analyses were based on data from the 19 companies that provided data for all years 1994-2002.

Figure 6.7 Probability of success from 'first human dose' to market by compound characteristic and company size (1997-1999)



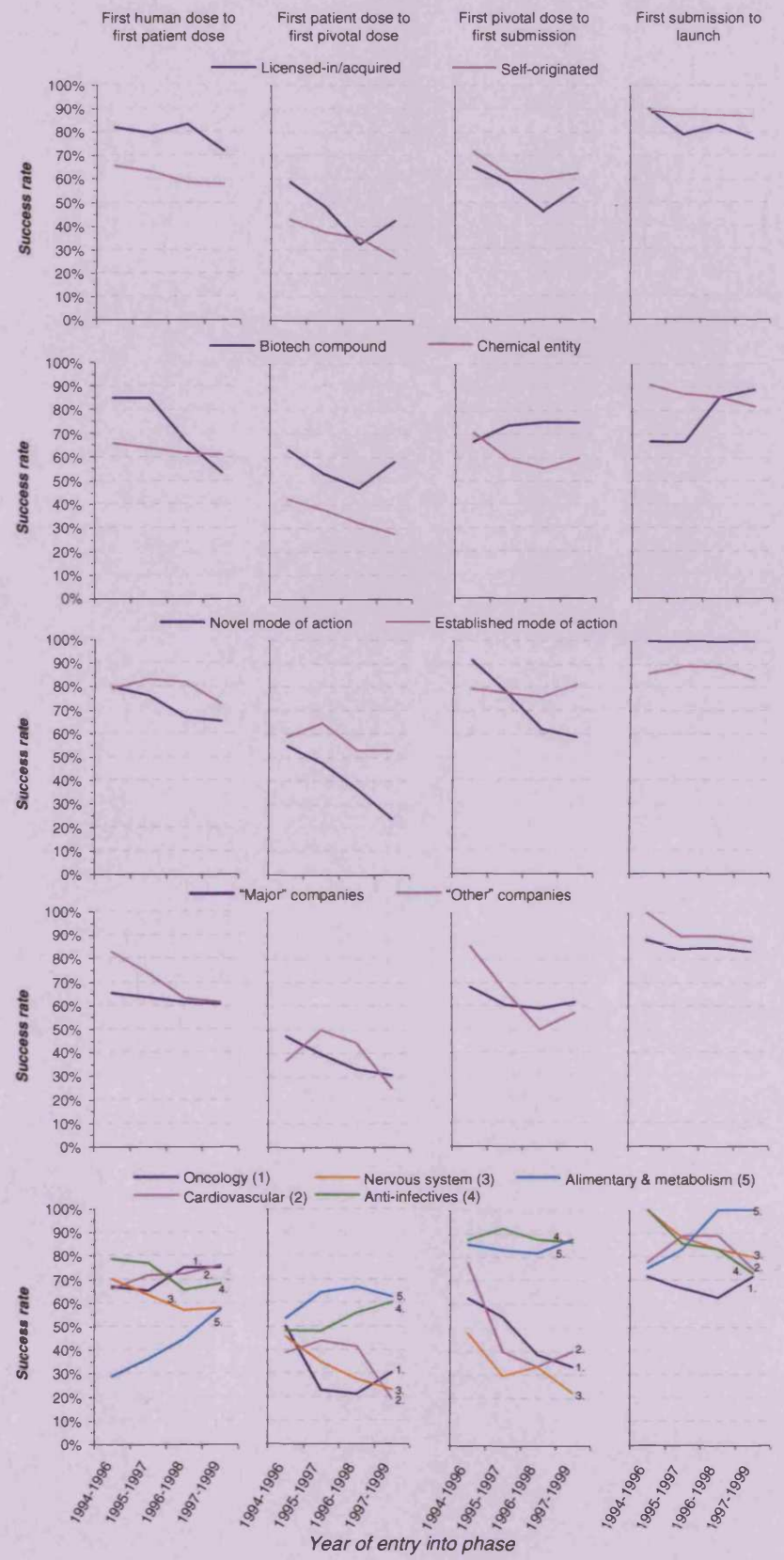
Based on between-phase success rates calculated for NASs entering a phase between 1997 and 1999, with the fate assessed at the end of 2002, using the 'entry' methodology.

A breakdown of the data set by origin demonstrated that for compounds entering a phase between 1997 and 1999, licensed-in NASs exhibited a superior probability of success from 'first human dose' to market than NASs discovered in-house (15% vs. 9%, respectively, Figure 6.7). Higher success rates in early clinical development (i.e. between 'first human dose' and 'first pivotal dose') underpinned this difference, since in later phases (i.e. from 'first pivotal dose' onwards) success rates between phases for self-originated NASs slightly exceeded those for licensed-in NASs (Table 6.2). Analyses of trend over time demonstrated that this profile was present from 1994 onwards, with the exception of the period 1996-1998 (based on date of entry into phase) when the success rates for licensed-in NASs for phase II (i.e. 'first patient dose' to 'first pivotal dose') were slightly lower than that for self-originated NASs (Figure 6.8) The difference in overall probability of success to market between self-originated compounds and those that are licensed-in became less pronounced over the time period investigated. Based on NASs entering phase between 1994 and 1996, the difference was ten percentage points (28% for licensed-in vs. 18% for self-originated) compared to five percentage points based on NASs

Table 6.2 Success rates between phase by characteristic

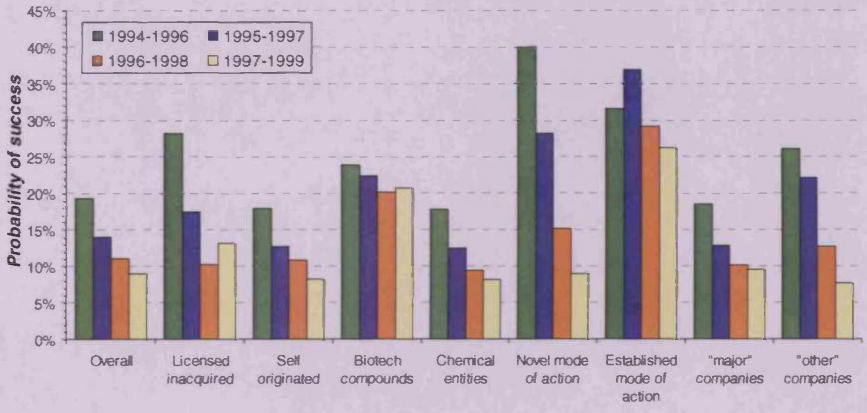
	Success rate			*n*	Success rate			*n*	Success rate			*n*	Success rate			*n*
	Current	Min	Max		**Current**	Min	Max		**Current**	Min	Max		**Current**	Min	Max	
Industry	*Based on NASs entering phase between 1997 and 1999*															
Industry	**61.4%**	55.7%	65.0%	*323*	**31.4%**	25.6%	44.0%	*234*	**62.4%**	52.3%	68.5%	*111*	**83.9%**	65.0%	87.5%	*80*
Therapeutic area	*Based on NASs entering phase between 1994 and 1999*															
Alimentary & metabolism	**47.6%**	42.9%	52.9%	*70*	**53.3%**	47.1%	58.8%	*34*	**76.5%**	72.2%	77.8%	*18*	**92.9%**	76.5%	94.12	*17*
Anti-cancer	**76.0%**	67.9%	78.6%	*56*	**35.5%**	30.6%	44.4%	*72*	**47.8%**	40.7%	55.6%	*27*	**68.8%**	61.1%	72.2%	*18*
Anti-infective	**78.0%**	74.2%	79.0%	*62*	**55.1%**	54.0%	56.0%	*50*	**85.7%**	77.4%	87.1%	*31*	**84.2%**	76.2%	85.7%	*21*
Blood	**55.0%**	52.4%	57.1%	*21*	**52.9%**	45.0%	60.0%	*20*	**38.5%**	38.5%	38.5%	*13*	**100%**	60.0%	100%	*5*
Cardiovascular	**72.3%**	67.1%	74.3%	*70*	**34.0%**	30.8%	40.4%	*52*	**64.0%**	55.2%	69.0%	*29*	**78.6%**	52.4%	5.75%	*21*
Musculoskeletal	**66.0%**	63.6%	67.3%	*55*	**50.0%**	43.8%	56.3%	*32*	**77.8%**	73.7%	79.0%	*19*	**100%**	83.3%	100%	*12*
Nervous system	**60.9%**	56.8%	63.5%	*148*	**31.6%**	25.5%	44.7%	*94*	**37.1%**	33.3%	43.6%	*39*	**92.0%**	85.2%	93.6%	*27*
Respiratory	**66.7%**	58.8%	70.6%	*51*	**19.4%**	17.7%	26.5%	*34*	**66.7%**	66.7%	66.7%	*12*	**83.3%**	83.3%	83.3%	*6*
Compound type	*Based on NASs entering phase between 1997 and 1999*															
Chemical entity	**61.0%**	56.0%	64.2%	*282*	**28.2%**	23.1%	41.2%	*199*	**62.0%**	50.6%	69.0%	*87*	**80.9%**	62.3%	85.3%	*61*
Biotech compound	**63.2%**	52.2%	69.6%	*23*	**52.9%**	40.9%	63.6%	*22*	**70.6%**	63.2%	73.7%	*19*	**90.0%**	64.3%	92.9%	*14*
Origin	*Based on NASs entering phase between 1997 and 1999*															
Self-originated	**57.6%**	52.9%	61.1%	*257*	**27.2%**	21.4%	42.8%	*173*	**64.9%**	53.6%	71.0%	*69*	**85.7%**	66.7%	88.9%	*45*
Licensed-in	**77.5%**	70.5%	79.6%	*44*	**43.6%**	39.5%	48.8%	*43*	**55.6%**	48.4%	61.3%	*31*	**78.3%**	60.0%	83.3%	*30*
Mode of action	*Based on NASs entering phase between 1997 and 1999*															
Novel	**64.6%**	56.4%	69.1%	*110*	**23.3%**	14.7%	51.5%	*68*	**60.0%**	48.4%	67.7%	*31*	**100%**	86.4%	100%	*22*
Established	**73.0%**	65.7%	75.8%	*99*	**58.1%**	51.4%	62.9%	*70*	**84.6%**	71.7%	87.0%	*46*	**84.0%**	65.6%	87.5%	*32*
Company size	*Based on NASs entering phase between 1997 and 1999*															
"major" companies	**61.0%**	55.6%	64.5%	*234*	**31.3%**	26.7%	41.3%	*172*	**61.0%**	52.2%	66.7%	*90*	**84.3%**	68.3%	87.3%	*63*
"other" companies	**62.5%**	56.2%	66.3%	*89*	**31.8%**	22.6%	51.6%	*62*	**68.8%**	52.4%	76.2%	*21*	**81.8%**	52.9%	88.2%	*17*

Figure 6.8 Trends in success rates by phase by characteristic (1994-1999)



entering a phase between 1997 and 1999 (13% vs. 8%, respectively, Figure 6.9). Statistical analysis of the data using Chi-square tests showed significant differences in success rates by origin from 'first human dose' to 'first patient dose' ($p<0.05$).

Figure 6.9 Trends in probability of success from 'first human dose' to market by compound characteristics and company size (1994-1999)



A breakdown of success rates by compound type demonstrated that products of biotechnology enjoyed a higher probability of success from 'first human dose' to market than chemical entities (21% vs. 9%, Figure 6.7). This difference was mainly driven by the success rate from 'first patient dose' to 'first pivotal dose' (Phase II), aided by smaller differences for later phases. As shown in Table 6.2, biotech compounds were almost twice as successful in Phase II as chemical entities (53% vs. 28%, respectively). For both Phase III and the regulatory review stage a difference of around nine percentage points was observed in favour of biotech compounds. Interesting changes over time were observed when success rates were broken down by compound type (Figure 6.8). The success rates from 'first human dose' to 'first patient dose' (Phase I) for biotech compounds decreased considerably over the time period studied, reaching a level below that of chemical entities for the latest year-range (1997-1999). The reverse was observed for success rates by compound type from 'first submission' to market, which increased from only 67% based on NASs entering this phase between 1995 and 1997, to 89% in the latest year-range investigated.

The changes over time in between-phase success rates resulted in only a minor decline in overall probability of success to market for biotechnology products

over the time period studied (from 24% to 21%). For chemical entities, the observed decline was much steeper, from 18% based on NASs entering a phase between 1994 and 1996, to only 8% for NASs entering a phase between 1997 and 1999, the latest year-range investigated (Figure 6.9).

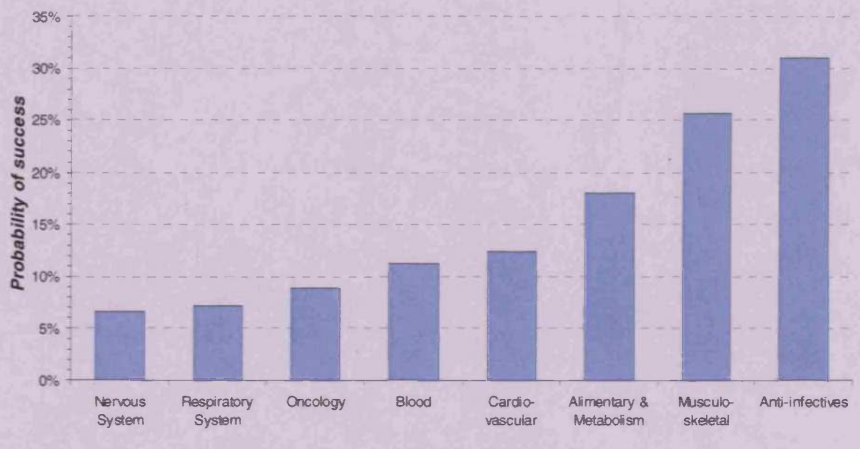
As might be expected, compounds with an established mode of action (i.e. if another NAS had already been licensed for marketing when the compound in question entered the clinic) had a higher probability of reaching the market from 'first human dose' than those with a novel mode of action (30% vs. 9%, respectively, Figure 6.7). Compounds with an established mode of action enjoyed superior success rates at every clinical phase (Table 6.2). However, compounds with a novel mode of action have proven to be much more successful during the regulatory review stage than those that represent less of a pharmacological breakthrough. Over the period studied, all novel NASs submitted for regulatory review had subsequently made it to market, compared to 84% of NASs with an established mode of action. The probability of success to market from 'first human dose' for NASs with a novel mode of action fell steeply from 1994 onwards, demonstrating the increasing risk of drug development (Figure 6.9). Based on NASs entering phase between 1994 and 1996, 40% of novel NASs entering clinical development were predicted to reach the market. In the last year-range studied (1997-1999) this had fallen to only nine percent. Over the same period of time, the probability of success to market for NASs with an established mode of action demonstrated only a slight decline. Statistical analysis of the data using Chi-square tests showed significant differences in success rates by novelty of mode of action from 'first patient dose' to 'first pivotal dose' ($p<0.01$) and from 'first pivotal dose' to 'first submission' ($p<0.05$).

To investigate the impact of company size on success rates, companies were divided into two cohorts based on their R&D expenditure in 2002. Little difference was observed in the probability of success from 'first human dose' to market for the two company cohorts. For companies with a 2002 R&D budget of less than US$ 1bn ("other" companies) this was observed to be 11%, whereas "major" companies were estimated to bring 1 NAS to market for every 10 NASs

entering clinical development (10%, based on NASs entering phase between 1997 and 1999, Figure 6.7). Success rates from 'first pivotal dose' to 'first submission' showed the greatest difference between the two cohorts, where smaller companies enjoyed success rates of 69%, compared to 60% for "major" companies (Table 6.2). However, examining trends over time for these two cohorts demonstrated that the success rates for the two company cohorts have not always been similar. Based on NASs entering phase between 1994 and 1996 from a cohort of 19 companies that provided data for all years 1994-2002, smaller companies were more successful in every phase apart from Phase II ('first patient dose' to 'first pivotal dose', Figure 6.8). As a result, their probability of success from 'first human dose' to market exceeded that of the "major" companies by 7 percentage points (26% vs. 19%, respectively, Figure 6.9) This picture changed considerably within the time span of four years, with success rates for "other" companies declining for both Phase I ('first human dose' to 'first patient dose') and Phase III ('first pivotal dose' to 'first submission'), resulting in a decrease in the probability of success to market for compounds entering clinical development to only 8% (1997-1999). The overall probability of success to market also decreased for "major" companies over this period of time, but not as dramatically as for the smaller companies, reaching 10% in the latest year-range examined.

Utilising the full data set available, (1994-2002), success rates could be calculated for eight therapeutic areas (Table 6.2 and Figure 6.10). Based on NASs entering phase between 1994 and 1999, 'Anti-infectives' was observed to be the therapeutic area with the lowest risk with a probability of success from 'first human dose' to market of 31%, followed by 'Musculoskeletal' (26%) and 'Alimentary & Metabolism' (18%). For all other therapeutic areas the probability of success was estimated to be below 13%, indicating that more than eight NASs would have to be taken into man in order to achieve one product launch in these areas. 'Nervous system' and 'Respiratory system' were found to be the two areas with the highest risks, with a probability of success from 'first human dose' to market of only 7%. For Nervous system indications, low success rates in all three clinical phases underpinned the low probability of success, whereas for 'Respiratory system' reasonable success rates were observed for all phases

Figure 6.10 Probability of success from 'first human dose' to market by therapeutic area (1994-1999)

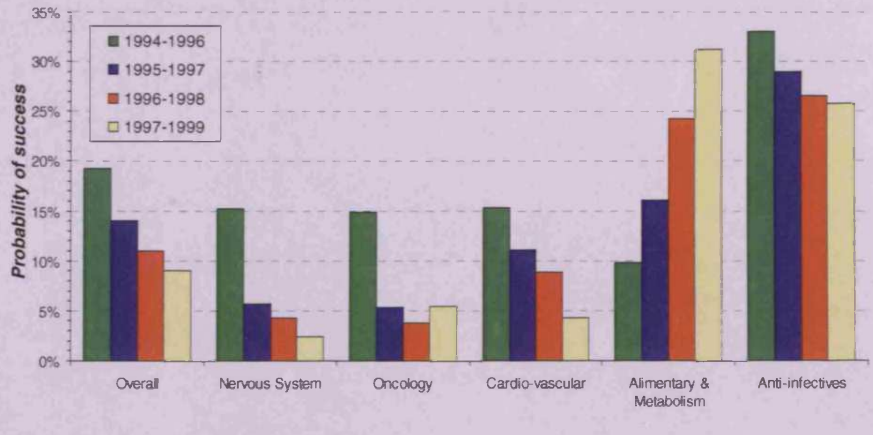


Based on between-phase success rates calculated for NASs entering a phase between 1994 and 1999, with the fate assessed at the end of 2002, using the 'entry' methodology.

but Phase II ('first patient dose' to 'first pivotal dose'), suggesting that the main difficulty in developing medicines in this area could be predicting clinical efficacy and safety (Table 6.2). Statistical analysis of the data using Chi-square tests showed significant differences ($p<0.05$) in success rates between therapeutic areas for all phases apart from the last phase (from 'first submission' to market).

For five therapeutic areas sufficient information was available to examine trends over time in both success rates and probability of success to market; the results are shown in Figure 6.8 and Figure 6.11. Most remarkable were the observations for the therapeutic area 'Alimentary & metabolism'. Based on data

Figure 6.11 Trends in probability of success from 'first human dose' to market by therapeutic area (1994-1999)



from 19 companies, this therapeutic area suffered the lowest probability of success from 'first human dose' to market of all areas investigated in the first year-range (10%, 1994-1996). Data for the latest year-range (1997-1999), however, indicated that with a probability of success of 31% this was the most successful therapeutic area. The improvement in success rate was found for all phases, apart from Phase III ('first pivotal dose' to 'first submission'), where this therapeutic area enjoyed the highest success rates throughout the duration of the study. This therapeutic area includes irritable bowel syndrome (IBS) and obesity, indications for which relatively few therapeutic options exist. Could the unmet medical need be driving the remarkable success in this area?

For the remaining four therapeutic areas, the probability of success to market declined, in line with the overall decline observed for the complete data set (Figure 6.11). Interestingly, the success rate from 'first pivotal dose' to 'first submission' declined considerably for three of the four therapeutic area, the exception being 'Anti-infectives. In this area, the success rate in this phase remained constant, around a remarkable 90%, for all year-ranges examined. One explanation for this could be the relatively low proportion of novel NASs in development in this therapeutic area (as demonstrated in Chapter five), which is most likely driven by the fact that many antibiotics in development only demonstrate minor structural differences from existing drugs to combat drug resistance.

Success rate analyses using the 'longitudinal' methodology

The analyses of probability of success to market presented in this chapter were derived by calculating success rates for each phase of development, and multiplying the between-phase success rates in order to estimate the probability of reaching the market. As such, the analyses reflect likely probabilities of success based on recent industry practice, rather than the actual success rate for a group of compounds that have been tracked all the way from first human dose to market. Since data were available for nine years in total it was possible to calculate success rates using this longitudinal approach. A total of 160 NASs was identified that entered clinical development during 1994 and 1995. The fate of these NASs, as of the 31st December 2002, is detailed in Figure 6.12. Of the

Figure 6.12 Success rates to market using the 'longitudinal' methodology for NASs entering man 1994-1995

NASs first tested in man in 1994/95	Status at the end of 2002					
	Phase I	Phase II	Phase III	Reg review	Launched	Terminated
160	1	4	6	10	15	124
*Probability of reaching market**	*10%*	*16%*	*52%*	*84%*	*N/A*	*0*
Number predicted to reach market	*0.1*	*0.64*	*3.12*	*8.4*	*(15)*	
			12.26			
Likely success rate for NASs first tested in man 1994/95	= ((12.26+15)/160)*100 = 17%					

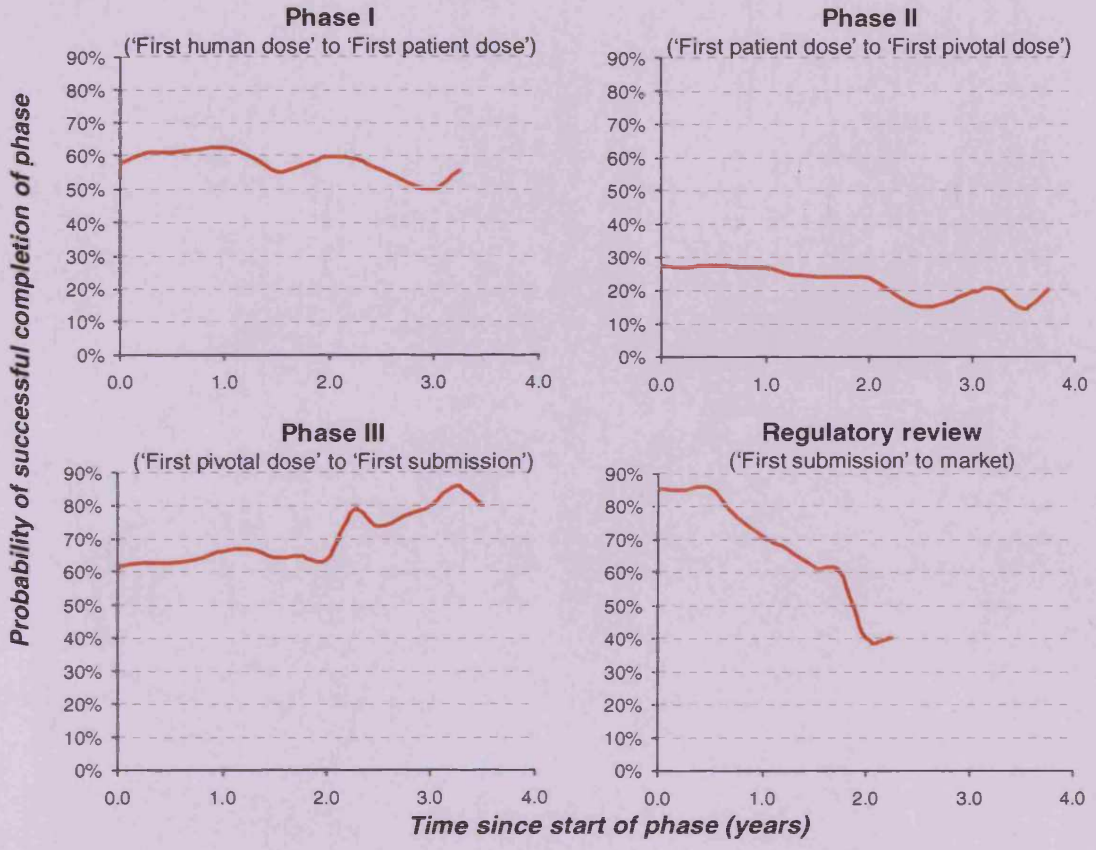
**As calculated based on NASs entering phase between 1997 and 1999 (Figure 6.3).*

160 NASs entering man between 1994 and 1995, 21 were still in active development at the end of 2002. By applying the current probabilities of success (as shown in Figure 6.3) it was estimated that 12 of the 21 NASs will be launched eventually. Adding these 12 to the 15 NASs that have already been launched resulted in a likely success rate to market for the 1994/1995 group of NASs of 17%. While this methodology arrives at a higher success rate to market than that calculated based on success rates by phase (i.e. 10%), it is consistent with the fact that success rates calculated by means of a longitudinal study reflect historical activities and the observation that success rates by phase have declined over the past few years (Figure 6.6).

Influence of duration in phase on success rates

Two aspects of the relationship between the duration of clinical phases and success rates were investigated in this study. Firstly, the relationship between time spent in a phase and the probability of successfully completing that phase was examined, for all three clinical phases (Phase I, II and III) and the regulatory review stage. The outcome of these analyses is depicted in Figure 6.13. For Phases I and II, the probability of successfully completing the phase appears to decrease slightly with increasing time in phase. For NASs that have been in Phase I for one year, the likelihood of successfully progressing to Phase II is observed to be just over 60%. However, for NASs that have been in

Figure 6.13 Relationship between duration in phase and probability of successfully completion of phase



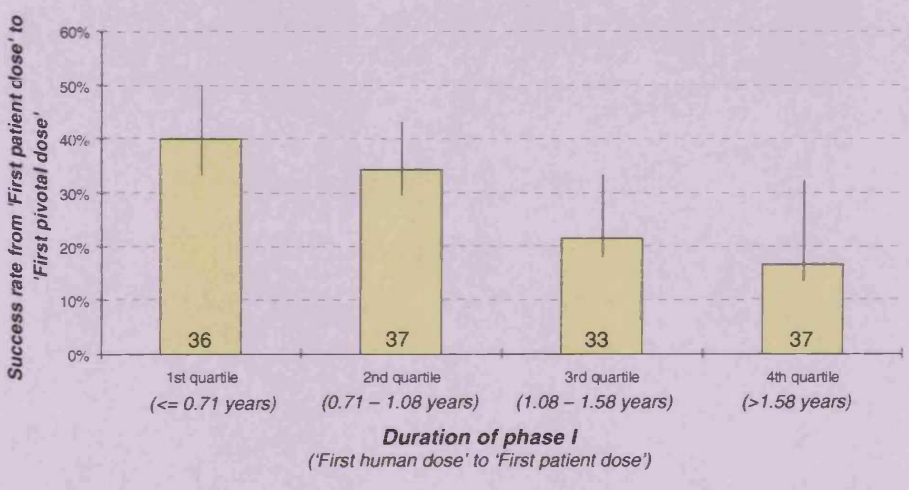
Excluding NASs in development for more than one indication.

Phase I for around three years, the likelihood is around 50%. Similarly, the probability of successfully progressing to Phase III is observed to be around 25% for NASs that have been in phase II for one year, compared to about 15% if the time in Phase II exceeds 2.5 years. For Phase III, a positive relationship appears to exist between time in phase and likelihood of successful completion of the phase. For NASs that have been in this phase for up to two years, the probability is observed to be just over 60%, whereas if the time spent in Phase III exceeds three years, the likelihood of successful completion of this phase rises to 80%. Not surprisingly perhaps, the likelihood of receiving regulatory approval decreases the longer NASs spent in regulatory review. If there are no issues regarding the clinical safety or efficacy of the product approval will be granted relatively quickly. Delays occur however, when doubts arise about the safety and/or efficacy of the product and the company is asked for clarification or even to undertake additional clinical work. Such concerns may ultimately not

be resolved, leading to a non-approvable decision and potentially termination.

The second aspect of the relationship between the duration of clinical phases and success rates that was investigated in this study related to the duration of one phase and the likelihood of success in the next phase. Both the relationship between the duration of Phase I and subsequent success rates for Phase II (Figure 6.14), and the duration of Phase II and success rates for Phase III (Figure 6.15) have been investigated. NASs were divided into four quartiles based on the time taken to complete the first phase. For each of these cohorts of NASs, success rates were calculated as the proportion of NASs that

Figure 6.14 Relationship between duration Phase I and success rate Phase II (1997-1999)

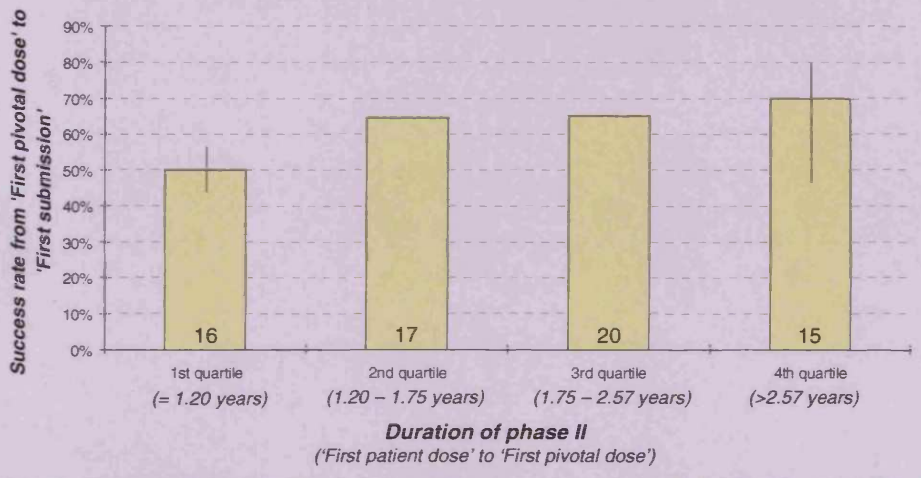


High-low lines represent the range of possible success rates (min-max). n is the number of NASs included in the calculation. Statistical analysis of these data using a Chi-square test showed that there were no significant differences in success rates for the four cohorts(p>0.05).

successfully completed the second phase. A possible range of success rates was calculated by making assumptions about those NASs for which the fate in the second phase was still unknown by the end of 2002. The outcome of this study suggested that there was an indirect correlation between the duration of Phase I and the likelihood of successful completion of Phase II (Figure 6.14). For those NASs with the fastest cycle time in Phase I (<0.7 years), a success rate of 40% was observed for Phase II. For those NASs with Phase I cycle times exceeding 1.58 years, the success rate had decreased to 17%, suggesting that long phase I cycle times may be an indication of increased risk going forwards.

In contrast, a positive correlation was observed between the duration of Phase II and the success rate for Phase III (Figure 6.15). Here the outcome of the study suggested that the likelihood of success in Phase III was seen to increase with increasing cycle times in Phase II. For NASs completing Phase II within 1.2 years the success rate in Phase III was calculated to be 50%. For NASs where Phase II cycle times exceeded 2.57 years, the likelihood of successfully completing Phase III had increased to 70%.

Figure 6.15 Relationship between duration Phase II and success rate Phase III (1997-1999)



High-low lines represent the range of possible success rates (min-max). n is the number of NASs included in the calculation. Statistical analysis of these data using a Chi-square test showed that there were no significant differences in success rates for the four cohorts($p>0.05$).

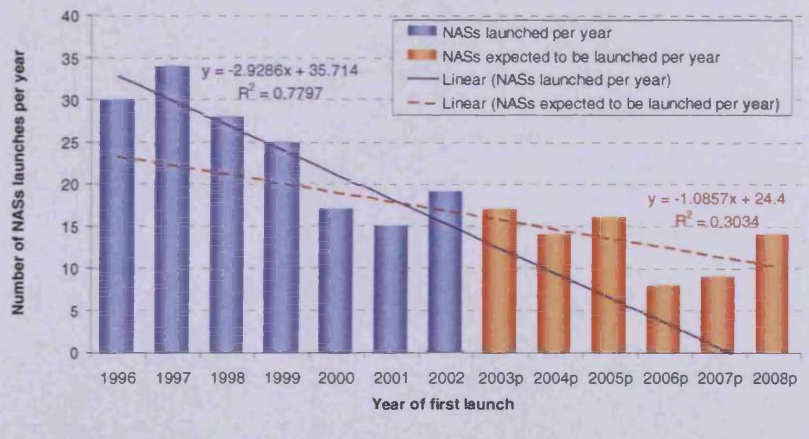
Future output predictions

Future output in terms of the number of new medicines reaching the market will depend on three variables: (1) development time to market, (2) success rates to market and (3) pipeline size. Based on the 2002 values for these three variables, a prediction could be made of potential future output using the model depicted in Figure 6.2 on page 158. The success rates were based on calculations presented in Figure 6.4. Cycle times were taken from Van den Haak *et al.* (2003b). For the predictions shown in Figure 6.16, the median cycle times for each phase were used separately. For Table 6.3, Table 6.4 and Table 6.5, the estimated number of NASs to reach the market was assessed using the cumulative median time taken from clinical phase I to first launch (i.e. the sum of median durations of each phase).

Figure 6.16 shows the historical and predicted future output of the 34 companies that provided data for 2002. For this cohort, a downward trend in the number of new product launches was observed over the period 1996-2002, in line with industry observations over that period of time. Based on current pipeline size, development times and success rates, it was predicted that this downward trend is likely to continue in the near future for this cohort of companies (Figure 6.16). On average, these 34 companies were predicted to achieve the launch of 14.5 NASs per year (Table 6.3), which represents a 50% reduction from NAS output recorded in the late 1990s. It should be noted, however, that the inputs reflect current R&D practices, which are unlikely to remain constant over the next seven years. Similarly, the calculations do not take into account any NASs brought into development through, future, licensing activities. However, although the many dynamics of drug development are acknowledged, it is believed that this model provides a good basis for predicting what the future might bring should current practices be continued.

The 14 "major" companies were predicted to achieve, on average, the launch of 9.7 NASs per year for the next 7 years (Table 6.4). This suggests that they will not be able to achieve the launch of one new medicine per company per year. The 20 "other" companies were predicted to achieve the launch of just 5.2 NASs per year (Table 6.5).

Figure 6.16 Historical and estimated future new product launches per year, 1996-2008



Based on success rates, cycle times and the current development pipeline of 34 companies, representing 80% of global ethical pharmaceutical R&D expenditure in 2002. p = prediction.

Table 6.3 Estimated number of NASs in development in 2002 reaching the market for 34 companies

	Phase I	Phase II	Phase III	Regulatory review	Total
Number of NASs in phase, 31st Dec 2002	216	177	57	25	475
Probability of success based on NASs entering phase between 1997 and 1999	10%	16%	52%	84%	-
Estimated number of NASs reaching the market	21.8	29.1	29.8	21.0	101.7
Cumulative median duration from 1st human dose to market (years)					7.0
Predicted output per year for the next seven years (NASs/year)					14.5
Predicted output per year per company for the next seven years (NASs/year/company)					0.43

Based on data from 34 companies representing 80% of global pharmaceutical R&D expenditure in 2002.

Table 6.4 Estimated number of NASs in development in 2002 reaching the market for 14 "major" companies

	Phase I	Phase II	Phase III	Regulatory review	Total
Number of NASs in phase, 31st Dec 2002	157	116	35	19	327
Probability of success based on NASs entering phase between 1997 and 1999	10%	16%	51%	84%	-
Estimated number of NASs reaching the market	15.4	18.7	18.0	16.0	68.1
Cumulative median duration from 1st human dose to market (years)					7.0
Predicted output per year for the next seven years (NASs/year)					9.7
Predicted output per year per company for the next seven years (NASs/year/company)					0.69

Based on data from all 14 "major" companies (i.e. spending US$ 1bn or more on ethical pharmaceutical R&D in 2002).

Table 6.5 Estimated number of NASs in development in 2002 reaching the market for 20 "other" companies

	Phase I	Phase II	Phase III	Regulatory review	Total
Number of NASs in phase, 31st Dec 2002	59	62	22	6	148
Probability of success based on NASs entering phase between 1997 and 1999	11%	18%	56%	82%	-
Estimated number of NASs reaching the market	6.6	10.9	12.4	4.9	34.8
Cumulative median duration from 1st human dose to market (years)					6.7
Predicted output per year for the next seven years (NASs/year)					5.2
Predicted output per year per company for the next seven years (NASs/year/company)					0.26

Based on data from 20 "other" companies (i.e. spending less than US$ 1bn on ethical pharmaceutical R&D in 2002).

By changing the parameters fed into the model, it was possible to simulate the potential impact of improvements to the drug development process such as maximising success rates, decreasing cycle times or increasing the number of NASs entering clinical development. The simulated future output predictions shown in Table 6.6 all describe theoretical situations in which only one or two parameters were changed at a time. Although these parameters are unlikely to change in isolation in real life, the approach taken provides valuable insight into the extent to which the three metrics, success rates, cycle times and pipeline size, impact on future output. Increasing pipeline volume appeared to have the smallest impact on future output. Increasing the number of NASs taken into man by 10% only leads to an additional 0.3 NASs reaching the market annually. A total of 16 NASs was predicted to reach the market annually when increasing the number of NASs entering Phase I by 50%, although the likelihood of this occurring in practice is questionable in view of capacity restrictions.

The outcome of the simulations suggested that improving cycle times could potentially have more of an impact on industry output. By reducing industry cycle times to the current 10th percentile values instead of the median phase cycle times, the annual output could potentially be doubled, reaching an

Table 6.6 Simulated impact of process improvements on estimated future output for a cohort of 34 companies

Situation	Estimated output
• Current industry success rates, median cycle times and pipeline size	14.5 NASs/year
*Improving cycle times**	
• 10% decrease in median cycle times	16.1 NASs/year
• Industry 10th percentile cycle times	29.9 NASs/year
*Increasing pipeline volume**	
• 10% increase in NASs entering clinical development	14.8 NASs/year
• 50% increase in NASs entering clinical development	16.0 NASs/year
*Improving success rates**	
• 10% increase in success rates	18.5 NASs/year
• Between-phase success rates from company with highest probability of success from 'first human dose' to market ('best case')	30.2 NASs/year
*Improving success rates and cycle times**	
• Industry 10th percentile cycle times AND 'best case' success rates	62.3 NASs/year

** Assume all other parameters remain constant*

estimated 30 NASs per year. However, the feasibility of achieving this improvement at either industry or company level is again questionable. These cycle times have been achieved for some NASs, but not consistently for all phases for all projects. A reduction in total development time of 10% might be a more realistic target. According to the model used in this study, this would result in an additional 1.6 NASs reaching the market annually.

The greatest impact on NAS output was associated with improvements in success rates. Two situations have been simulated with regards to this parameter. In the first situation, an improvement of 10% in the between-phase success rates for all four phases was assumed, resulting in an estimated average annual output of 18.5 NASs. In the second simulation, between-phase success rates were used that were consistent with the company that had the highest probability of success from 'first human dose' to market', based on NASs entering phase between 1994 and 1999 (28%, 'best case'). This company, which can not be named for reasons of confidentiality, achieved success rates of 72% from 'first human dose' to 'first patient dose', 39% from 'first patient dose' to 'first pivotal dose' and 100% for the last two stages (i.e. 'first pivotal dose' to 'first submission' and 'first submission' to market). Applied to the total pipeline size of the 34 companies included in these calculations, and using the industry cycle times, these success rates result in an average output of 30.3 NASs per year. Taking the simulations one step further by combining the two most successful situations (i.e. 10^{th} percentile cycle times and 'best case' success rates) resulted in a simulated output of 62.3 NASs per year: almost two NASs per company per year. However, in order to achieve this, cycle times would have to be halved and the probability of success to market would almost have to be tripled, for all companies, suggesting that an output of two NASs per year per company is highly unlikely based on current development processes, even with greater efficiencies.

DISCUSSION

In this study, pharmaceutical development risk is assessed in terms of success rates between phases as well as probability of success to market. NASs in

clinical development by a cohort of 34 large to medium-sized international pharmaceutical companies between 1994 and 2002 have been investigated in detail in order to address five research questions as detailed on page 154.

Research questions:

- **What is the current probability of success to market for NASs entering clinical development?**
- **Have the efforts undertaken by the industry to increase R&D efficiency resulted in an improvement in success rates?**

Based on NASs entering development phases between 1997 and 1999, within a cohort of 34 companies, the current probability of success from 'first human dose' to market was observed to be 10%, i.e. only one out of ten NASs taken into clinical development is estimated to reach the market. It was found that the main bottle neck in achieving launch was Phase II; only one in three NASs entering this phase progressed to Phase III. Once in Phase III, only two out of three achieved regulatory submission and a further 16% of NASs that were submitted to a regulatory authority were subsequently terminated.

Based on data from a cohort of 19 companies that provided data for all years in the analysis, the probability of success to market from 'first human dose' was found to have fallen over the duration of this study from 19% for NASs entering development phases between 1994 and 1996 to only 9% for NASs entering between 1997 and 1999. Although this decline was to some extent observed for all four phases, it is encouraging to note that success rates for Phase III (from 'first pivotal dose' to 'first submission') after an initial decline from 62% to 52%, displayed a small increase in the last year-range investigated. The steepest decline in between-phase success rates was observed for Phase II ('first patient dose' to 'first pivotal dose'), which decreased by over a third from its original value of 46% for NASs entering phase between 1994 and 1996.

DiMasi (2001a) used data from 24 companies to investigate success rates for new chemical entities (NCEs) in the USA. Based on NCEs for which an IND was submitted between 1990 and 1992, a success rate of 17% from IND filing to approval was calculated. DiMasi also found that the success rates for NCEs

that were first tested in humans in the USA were much lower than the success rates for NCEs where first testing in humans took place anywhere in the world, suggesting that a certain amount of pre-screening has taken place for those NASs that were tested in humans elsewhere in the world first - presumably a result of the additional clinical experience gained with the latter NASs prior to IND submission. Because of this, it is not possible to establish whether the differences between the probability of success observed in this study (10%) and the success rate reported by DiMasi (17%) results from the different methodology employed, DiMasi's focus on the US market, or whether it reflects a real change in success rates over time. However, DiMasi did observe a decline in success rates over the duration of his study, from 23% based on NASs for which a first IND was filed between 1981 and 1983 to 17% for NASs where the first IND was filed in the period 1990-1992. This could suggest that the decrease in success rates observed in the present study might represent a continuation of a declining trend that started as early as the 1980s.

If the industry was able to reverse this decline, for example by the development of preclinical studies with a better predictive value, the financial benefits could be significant since the clinical cost for some research failures will not be borne. It has been suggested that improving success rates from one in five to one in three (based on DiMasi's calculations) will reduce total costs by approximately 30% (Tufts CSDD, 2003). However, these savings will have to be balanced against traditional costs associated with a better preclinical screening process (DiMasi, 2001a). Other strategies that could be applied to reduce failure rates of products or concepts include increasing the alignment between clinical and biology expert groups to validate novel drug mechanisms early or by licensing validated compounds, technologies or concepts from other organisations (Schmid and Smith, 2004).

Research question: To what extent do compound and company characteristics impact on success rates?

In this study, the impact of origin, compound type, novelty of mode of action, company size and therapeutic area has been examined. It was found that self-originated NASs were less successful in early development than licensed-in or

acquired NASs. Although in later phases the reverse was observed with self-originated NASs enjoying superior between-phase success rates, this was not sufficient to make up for the lower success rates in earlier phases and so the overall probability of success from 'first human dose' to market was higher for licensed-in NASs (15%) than for those that originated from within the organisation's discovery function (9%).

Companies may repeat some early development work when licensing in a compound, which may contribute to the higher success rates observed for licensed-in NASs in Phase I and II. However, when the success rates calculation is limited to NASs for which one or more development phases have already been conducted by the licensee, success rates for licensed-in compounds still exceeded those for self-originated compounds in both Phase I and II (Kola and Landis, 2004); Van den Haak, 2004).

Steven (2002) suggested that when licensing-in is used to fill gaps in the pipeline, lower hurdles for progression through development may be permitted for these compounds than those set for internal investigational drug assets, resulting in higher success rates for licensed-in compounds. However, since all products, regardless of origin, have to meet regulatory requirements for safety and efficacy, lower internal hurdles for the progression of licensed-in NASs are unlikely to account for the differences in success rates reported in this study. Indeed, the view has also been expressed that products considered for licensing are subjected to a more stringent selection process – a selection process that is also more impartial due to a lack of internal history (Booth *et al.*, 2004; Lam, 2004a). Furthermore, the cost of the act of licensing-in is much more visible than the cost of internal development. As such, the failure of a licensed-in compound might have a much higher impact on shareholders' views of the company, again causing companies to be more selective with respect to their licensing decisions. In many companies, the selection of compounds for licensed-in is made by a different part of the organisation than the department responsible for internal project selection (Booth *et al.*, 2004). Studying the differences between the criteria used in the two processes might provide some insight as to how the success rates for self-originated NASs could be improved.

The outcome of this study suggested that less risk is involved in the development of biotech compounds than in the development of chemical entities. Twenty-one percent of biotech compounds entering clinical development were estimated to make it to market, compared to 9% of chemical entities. Biotechnology derived compounds have outperformed chemical entities in terms of success rates over the duration of this study. The overall probability of success to market for biotech-derived NASs demonstrated only a slight decline, from 24% (1994-1996) to 21% (1997-1999), whereas for chemical entities, the probability of success to market more than halved, from 18% (1994-1996) to only 8% in the latest year-range investigated (1997-1999). In part, this reflects the nature of biotechnology derived NASs, many of which are naturally occurring proteins with specific pharmacological profiles and defined physiological mechanisms of action (Gosse and Mannochia, 1996). For these reasons, the clinical evaluation of a biotechnology NAS can be less prone to trial and error than the evaluation of chemical entities (Van Brunt, 2000).

The risk associated with the development of NASs with a novel mechanism of action was higher than that of more established NASs. However, the extent to which this differs might be somewhat surprising. The probability of success from 'first human dose' to market was three times lower for novel than for established NASs (9% vs. 30%). However, the regulatory authorities' focus on the approval of products with a distinct advantage over existing treatments was apparent in the success rate from 'first submission' to 'first launch' (market). All 24 novel NASs entering the regulatory review stage between 1994 and 1999 subsequently achieved 'first launch', compared to 84% of NASs with an established mode of action. The observed widening of the gap between success rates for novel and established NASs was driven by increasing risk for the development of NASs with a novel mechanism of action. The probability of success for this cohort of compounds dropped from 40% (1994-1996) to less than 10% (1997-1999). This decrease might be related to an increasing focus on untreated, often chronic diseases. This will require the development of drugs against new targets and usually involves diseases with complex pathophysiology, complicating any prediction of clinical safety and efficacy during preclinical development.

Only minimal differences were found between success rates for companies spending over US$ 1bn on annual pharmaceutical R&D expenditure ("major" companies) and those spending less ("other" companies). In the mid-1990s, "other" companies achieved slightly higher success rates. Based on NASs entering a phase between 1996 and 1998, a probability of success to market of 26% was calculated for this cohort, compared to 19% for "major" companies. Over the duration of the study, a decline was observed in between phase success rates for "other" companies, whereas "major" companies were able to limit the damage. As a result, the probability of success for the two cohorts of companies were similar for the last year-range investigated (1997-1999, ~10%).

The outcome of this study indicated that therapeutic area has the biggest impact on success rates. Of the eight areas for which success rates could be calculated based on NASs entering phase between 1994 and 1999, 'Anti-infectives' and 'Musculoskeletal' were the area with the highest probability of success to market. The three areas associated with the highest risk were 'Nervous system', 'Respiratory' and 'Oncology', with probabilities of success to market of less than 10%. For nervous system indications, success rates were low across all four phases, whereas for respiratory indications the main risk appeared to be in Phase II, with a success rate from 'first patient dose' to 'first pivotal dose' of only 19%. The main driver behind the low probability of success for oncology indications appeared to be the success rate from 'first submission' to market. Only 69% of NASs submitted for review subsequently reached the market. What could be underlying these low success rates for anti-cancer medicines at this stage and could some of these late terminations have been prevented? When a company submits a dossier, it will be reasonably certain that the data describes a product that is sufficiently safe and efficient to be made available to patients. The subsequent termination illustrates that this opinion is not shared by those who review the dossier. Has the sponsor company underestimated the required level of safety, assuming that since the indicated disease is life threatening more side-effects might be allowed? Or is the market changing so rapidly with product introductions from competitors that what would have been acceptable at the time the dossier was being prepared, no longer met the requirement of demonstrating sufficient risk-benefit ratio by

the time the review was completed?

The findings of this study suggested that the influence of therapeutic area on success rates has increased over the last two decades. DiMasi (2001a) reported success rates ranging from one in eight (12%) for respiratory indications to one in three (33%) for anti-infectives, whereas the outcome of this study demonstrated a range from one in 14 for nervous system indications to one in three for anti-infectives. Both studies confirmed that anti-infectives was a relatively low-risk area compared to respiratory indications for which low success rates were observed. No direct comparisons could be made regarding success rates for the therapeutic area nervous system, since in DiMasi's study analgesics and anaesthetics were examined as a separate therapeutic area whereas these indications were included as nervous system indications in this study. The higher success rates for licensed-in NASs observed in this study were also reported in DiMasi's study.

In conclusion, the outcome of this study suggests that therapeutic area has the biggest impact on success rates, followed by novelty of mode of action. Biotech compounds demonstrated superior success rates over chemical entities, whereas licensed-in NASs were more successful than self-originated compounds. Company size appeared to have the least impact on success rates, with similar probabilities of success observed for "major" and "other" companies.

Research question: What, if any, is the relationship between duration in phase and success rates?

Two aspects of the relationship between the duration of clinical phases and success rates have been investigated in this study. Firstly, the relationship between time in phase and the likelihood of successful completion of that phase was investigated for all three clinical phases as well as the regulatory review stage. It was found that for three of the four phases the likelihood of successful completion declined with increasing time spent in phase. Phase III displayed the opposite profile, with the likelihood of successful completion increasing with increasing time in phase, suggesting that decisions to terminate development take place relatively early in this phase compared to other phases where

termination decisions might be taken more towards the end of the phase. The timing of termination decisions is further discussed in Chapter seven.

The second aspect of the relationship between duration and success rates investigated addressed the question whether success rates for one phase were influenced by the duration (i.e. effort) of the preceding phase. NASs completing Phase I were grouped into four quartiles based on the cycle time for that phase. For each cohort of NASs ('quartiles') the success rate for Phase II was calculated. Interestingly, it was found that Phase II success rates decreased with increasing Phase I cycle times, although no significant difference could be demonstrated. Could this negative relationship suggest that difficulties encountered in Phase I, requiring more effort to resolve and therefore resulting in longer cycle times, might be an indication of future failure? Alternatively, could the association with short Phase I cycle times and high success rates in Phase II reflect the early prioritisation of NASs with the greatest clinical potential? Investigating the reasons for termination in Phase II for each of the cohorts might provide more insight into this relationship.

In similar analyses conducted to investigate the relationship between Phase II cycle times and Phase III success rates, it was found that longer duration in Phase II appeared to correlate with higher success rates in Phase III. This correlation, although not significant, could potentially suggest that greater effort, as demonstrated by longer cycle times, in Phase II might increase the amount of information available to support the decision to start full development for launch and therefore might attributed to decreasing the number of late-stage terminations.

Research question: What can the industry do to positively influence its output in terms of the number of NASs reaching the market?

The number of new medicines reaching the world market per year is a widely accepted metric for measuring the success of pharmaceutical R&D. To make an assessment of the success of current pharmaceutical R&D practices, a model was developed to estimate future output in terms of the annual number of NASs reaching the market, based on current success rates, cycle times and pipeline

size. For a cohort of 34 companies (representing 80% of global pharmaceutical R&D expenditure in 2002) it was predicted that a total of 14.5 launches per year would be achieved on average over the next seven years - less than 0.5 NAS per year per company. The average 2002 R&D expenditure for the 14 "major" companies exceeded US$ 2bn, five times higher than the average 2002 R&D expenditure for the 20 "other" companies. However, the future output for "major" companies (0.7 NAS per company per year) is predicted to be only two times higher than that for "other" companies (0.3 NAS per company per year), suggesting that larger companies might be less efficient in pharmaceutical R&D. It remains to be seen how this will influence the overall pharmaceutical market. In 2002, "major" companies were responsible for only half of all new product launches (Chapter five).

In a recent survey by Accenture it was estimated that up to nine NCEs per company would have to be generated for the largest companies to achieve their desired growth (Kola and Landis, 2004). The outcome of this study, which was corroborated by earlier findings by Drews and Ryser (1996) suggests that with current success rates, cycle times and pipeline volume, this is not achievable. It should be noted that this comparison does not take into account the potential economic value of those products that reach the market. The number of new medicine launches required to survive is highly dependent on the sales and profitability generated by these products. It could be argued that a company achieving the launch of one blockbuster in three years is more successful as a business than a company bringing a new product to market each year in those years, but with peak sales of around US$ 200Mn each. However, with only 3 out of every 10 product launches providing a return on investment (Grabowski *et al.*, 2002), it is still important for the industry to improve the number of new products reaching the market. Since the 1980s, companies have become increasingly aware of the low return on investment which is reflected in a change of strategy. Where portfolio reviews and decision-making were medically driven in the past, these now take into account additional economic aspects to ensure that the products in development have an increased chance of generating revenue over and above their R&D cost.

Future output can be increased by improving any of the three parameters that influence it, i.e. by increasing success rates, decreasing cycle times and/or increasing pipeline size. Using the model, the impact of any of these improvements on future output was simulated. Out of the three available options, increasing pipeline size appeared to have the smallest effect. The small impact on output, combined with the high levels of additional investment required, either to extend internal capacity or contract more external resources to cope with the increased workload, makes this an unlikely option. The results of this study suggested that improving cycle times would be more effective than increasing pipeline size. However, improvements were required in the order of a 50% reduction in cycle times in order to double the predicted output. Although such cycle times have been demonstrated in the past for individual projects, it seems highly unlikely that the industry will be able to consistently achieve such efficiency improvements without loss of quality and escalating expenditure.

Increasing success rates was found to have the greatest impact of any of the three potential improvements. Using the between-phase success rates of the company with the highest probability of success to market over the period studied the predicted future outcome per company increased to almost one NAS per year. Mathematically, by altering both cycle times and success rates, it should be possible to increase average output to almost two NASs per year per company. However, in order to achieve this, average industry cycle times would have to be halved and the probability of success would need to be tripled. Since this is highly unrealistic, it is suggested that an output of two NASs per year per company is not achievable with the current way of conducting pharmaceutical R&D, even with improved efficiency.

The above simulations suggest that there is a maximum growth in output that can be achieved by the current industry. The notion of the existence of a certain 'ceiling' in growth rates that can be achieved is shared by Hank McKinnell, the CEO of Pfizer, who recently predicted that the pharmaceutical industry is entering a period where average annual growth rates are likely to hover at about 8%. These predictions are much lower than the 20% annual growth rate

that was considered the benchmark for the big pharmaceutical companies during most of the 1990s (Anon, 2004q).

SUMMARY

- The current probability of success from 'first human dose' to market is 10%. Phase II is the main bottleneck for clinical development: only 31% of NASs entering this phase subsequently progress to Phase III.

- The probability of success to market decreased from over the period studied (1994-2002). However, it was encouraging to note that an increase in Phase III success rates was observed in the last year-range investigated.

- The outcome of this study suggests that therapeutic area has the biggest impact on success rates, followed by novelty of mode of action. Biotech compounds demonstrated superior success rates over chemical entities, whereas licensed-in NASs were more successful than self-originated compounds. Of the variables examined, company size appeared to have the least impact on success rates.

- The likelihood of successful completion of the phase decreased with increasing time in phase for Phase I and II, and for the regulatory review stage. For Phase III, the likelihood was observed to increase with increasing duration.

- It was found that the longer the length of time NASs spent in Phase I, the lower the success rate for Phase II, whereas the longer the duration of Phase II, the higher the success rate at Phase III.

- For a cohort of 34 companies, a downward trend in the number of new product launches was observed over the period 1996-2002. Based on current pipeline size, development times and success rates, this downward trend is likely to continue in the near future for this cohort of companies.

CHAPTER SEVEN

EVALUATION OF CLINICAL DEVELOPMENT FAILURES – A LONGITUDINAL STUDY

INTRODUCTION

For every medicine brought to the market, many compounds will have become 'stranded' somewhere in the development process. The pharmaceutical industry historically is, and always will be, a high-risk industry and as outlined in Chapter six, the current probability of success from first human dose to market is 10%, requiring ten new active substances (NASs) to be taken into clinical development in order to achieve one product launch.

Although it might be unavoidable that for the majority of compounds taken into man, development will have to be terminated, companies can develop a strategy that will determine to some extent the timing within which this is done. Eliminating failures earlier in the process will limit the cost of developing a specific NAS, as well as free up resources for the development of other, potentially more promising, products. As a result, more NASs can be investigated with the same amount of resources, increasing the efficiency of the development process (Tufts CSDD, 2001; Lam, 2004a). Data from the Tufts Center for the Study of Drug Development (CSDD) indicate that if just five percent of all Phase III failures were terminated in Phase I, total development costs could drop with as much as six percent (DiMasi, 2002)

The pharmaceutical industry, while facing rapidly rising development costs, is under growing pressure to make an early decision as to which active substances in their development portfolios to pursue and which to terminate (Tufts CSDD, 2004). It is therefore important to understand in more detail the risks and issues involved in drug development (DiMasi, 2001a; Kola and Landis, 2004). Valuable information can be obtained from investigating recent development failures and by focusing on why and when the decision was made to terminate (Doogan, 2003). In understanding what the high-risk areas are, effort should be directed towards investigating these areas first and thereby identifying potential problems early.

A limited number of studies have examined drug development failures in the past. Parrish (1989) studied development activities of seven UK-owned

research-based pharmaceutical companies between 1964 and 1987, including limited information on the timing of and reason for termination, as well as the influence of therapeutic area. Drasdo (2003) investigated late-stage terminations in 2002, focusing on termination decisions for individual NASs, as well as studying companies' overall approach to termination. Several other studies report on comparisons of termination reasons and attrition rates (DiMasi, 2001a; Kola and Landis, 2004). However, this study is unique in the comprehensiveness with which drug development failures within the international pharmaceutical industry are investigated. Commonalities between NASs terminated during preclinical and clinical development or during regulatory review between 1998 and 2002 were examined in terms of the timing of failure and the reasons. Similarities and differences between different types of NASs were assessed, as well as the impact of therapeutic area. Furthermore, company performance in terms of success rates, development times and the number of new product launches was studied in relation to termination strategy to increase their insight into the reasons for and timing of failure in pharmaceutical development.

OBJECTIVES

In this study ethical pharmaceutical development failures between 1998 and 2002 were studied in detail to gain an understanding of reasons and characteristics influencing attrition to help companies identify failures earlier. Specifically, the following three objectives were pursued in this study:

1. To examine in more detail termination in terms of timing, reason and the influence of project characteristics in order to identify how companies can terminate failures earlier, by investigating:
    a. Where in the development process the decision to terminate was made and assessing whether this has changed over the duration of this study
    b. Why the decision to abandon further development activities was made and assessing whether this has changed over the duration of this study

2. To review in more detail, given the high failure rate in Phase III (see Chapter six), the decision-making in Phase II in order to identify what can be improved.
3. To assess the impact of companies approach to attrition on the efficiency of their development function, in terms of development time, success rates and, ultimately, the number of new products reaching the market.

METHODS

The study of drug development failures between 1998 and 2002 was based on data collected in the study reported in Chapter five. Previous outputs from this study primarily focused on the successful development of new ethical pharmaceutical products and as such the data set has been used to report on pipeline sizes (Chapter five) and success rates (Chapter six). Although the study focused on the performance metrics of successful NASs, the data set also included NASs for which development had been terminated, including detailed information on the reason for termination and the stage of the development process during which the decision to terminate was taken. This part of the data set has largely remained un-investigated and this study is the first comprehensive investigation of the collected termination data, focusing on NASs for which development was terminated between 1998 and 2002.

Data set

The data set from the Global Ethical Development Pipeline study included development activities for all NASs, defined as the development of an active substance that had not been previously available for therapeutic use in humans and was destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans. From 1999 onwards, data were collected on NASs that had passed the milestone 'first animal toxicity dose'. Prior to 1999, the milestone 'first human dose' was the entry trigger for inclusion in the data set.

For the purpose of this study, a subset of data has been selected. Eligible for inclusion in this subset were all NASs in clinical development for which development was terminated between 1998 and 2002 and all NASs in

preclinical development for which development was terminated between 1999 and 2002. An overview of the information for each NAS included in this study is provided in Table 7.1. To eliminate the influence of individual company practices on trend analyses, only data from companies participating in the study for all five years 1998-2002 have been included.

Table 7.1 NAS details used in the study of development failures

Characteristics	Details	
Milestone dates	First toxicity dose First human dose First patient dose First pivotal dose Last patient last visit in last clinical trial First submission	First approval First launch Decision to develop for launch Proof of concept Termination date
Termination reasons	Scientific reasons: *reasons relating to (pre)clinical efficacy, differential clinical efficacy, (pre)clinical pk/bioavailability, clinical safety, differential clinical safety, toxicology and unfavourable risk:benefit ratio* Commercial reasons: *reasons relating to commercial value and portfolio considerations* Technical reasons: *reasons relating to formulation, patent or commercial legal issues* Regulatory reasons and Other reasons.	
Compound characteristics	Novelty of mechanism of action *(novel; established)* Origin *(self-originated; licensed-in/acquired; collaborative/sponsored research)* Compound type *(chemical entity; biotech)* Developing company	
Therapeutic area	Based on the WHO ATC code system (see Appendix VII)	

Definitions

For the purpose of this study, an NAS was considered terminated when the decision was made to stop all further development activities for the NAS, either internally or within other organisations. As such, the definition excludes NASs that were subsequently licensed-out for further development by other organisations as well as marketed NASs that were subsequently withdrawn. NASs undergoing regulatory review were only considered terminated if the decision was made to abandon development. Therefore, NASs deemed 'non-approvable' by the regulatory authority or withdrawn from the regulatory review process by the applicant for which further development was ongoing (e.g. for alternative indications or to support re-submission of the dossier) were still considered to be in active development. An overview of other definitions used in this study is provided in Appendix VI.

External data sources

Annual R&D expenditure data were obtained from the study reported in Chapter three, data from which were added to the Centre for Medicines Research (CMR) International's Global R&D Expenditure Database (GLOBEX). GLOBEX holds detailed information on annual ethical pharmaceutical research and development (R&D) expenditure, capital expenditure, R&D full-time equivalents (FTEs) and sales from over 80 individual companies. Since its inception in 1982, the database has been kept up to date with confidential data obtained directly from pharmaceutical companies through the annual R&D Expenditure and Sales study, supplemented with company confirmed data from the public domain. Success rates data were taken from the analyses reported in Chapter six of this thesis. Information on the annual number of new product launches was taken from the study reported in Chapter four.

Data processing and analyses

Data were processed using Microsoft Access™. Both Microsoft Access™ and Microsoft Excel™ were used to obtain descriptive statistics of the data. SPSS™ for Windows™ was used to run statistical analyses on the data:

- *Linear regression* was used to test whether the number of NMEs terminated in each phase had significantly changed over the duration of the study.
- *Chi-square tests* were applied to test for significant differences in the proportion of termination reasons over time and between different characteristics, such as therapeutic area. Success rates were also tested for significance using Chi-square tests.
- Time from 'first human dose' to termination was plotted using *Kaplan-Meier survival curves. Log rank tests* were applied to assess differences between survival plots, e.g. by termination reason or over time. Where differences were found between plots, *Mann-Whitney U-tests* were applied to identify where the differences were.
- *Mann-Whitney U-tests* were applied to test for significant differences in clinical development time.

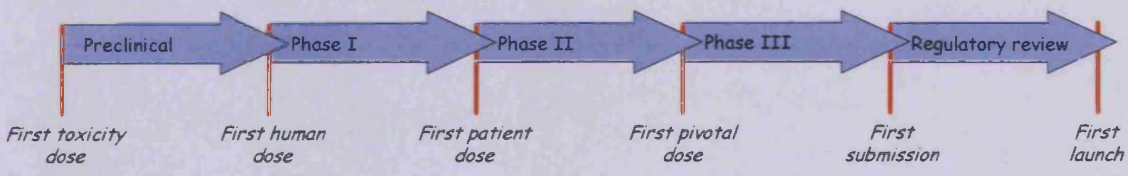
Where historical data are presented, the activities of companies that now form part of a larger company, due to merger and acquisition activities, have been

attributed to the company grouping as it was in 2002. Data collected were covered by a confidentiality agreement with participating companies, preventing the presentation of identifiable individual company data.

Determination of development stage

The milestone dates for key R&D activities were used to assign the development stage of each NAS on the 31st December of each year. Additionally, the milestone dates were used to assess the stage of the development process when the decision to abandon further development activities was taken. Figure 7.1 illustrates the start and end milestone defining each of the development phases. All NASs were assigned to therapeutic areas based on the Anatomical Therapeutic Chemical code (ATC code) system for drugs from the World Health Organization (WHO, 2002). See Appendix VII for an overview of the different therapeutic areas and the associated WHO ATC codes.

Figure 7.1 Phase definition based on milestone data for key R&D activities.



For definitions of the milestones, see Glossary of Terms on page X.

Calculation of the relative number of terminations

The number of terminations over time, overall as well as by phase, could potentially be influenced by changes in pipeline size or distribution. To take these changes into account, the number of terminated NASs is assessed relative to the number of NASs in active development as the ratio of terminated NASs:NASs in active development. The number of NASs in active development in each phase of the development process is calculated as the number of NASs completing the phase, i.e. passing the milestone defining the end of the phase as illustrated in Figure 7.1. For example, the number of NASs in active development in Phase II in 1998 is calculated as the number of NASs completing the milestone 'first pivotal dose' in 1998. The overall number of NASs in active development is calculated as the sum of the number of NASs in

active development in the individual phases. NASs completing more than one phase in a year or year-range will therefore be counted more than once.

Calculation of time to termination

To study the overall clinical time to termination, the time from the administration of the first human dose in the first clinical trial ('first human dose') to the date the decision was made to terminate was calculated in years for individual NASs. NASs were subsequently ranked by increasing time to termination and their relative rank, expressed as a percentage of all NASs included in the calculation and this was plotted against the time to termination. NASs terminated between 1998 and 2002 for which both the date of termination and the date of 'first human dose' were available were included in the analysis. The median time to termination was calculated as the time from 'first human dose' to termination within which 50% of all NASs were terminated, i.e. the duration on the x-axis corresponding to value of 50% on the y-axis of the graph.

Trends over time and between-company differences

To assess whether any trends or developments observed differed between companies, respondent companies were grouped into cohorts. An overview of the criteria applied for the four types of cohorts investigated in this study is provided in Table 7.2. For each of these cohorts of companies, the termination profile has been assessed in terms of:

- The number of NASs terminated;
- The time to termination;
- The top 3 reasons for termination.

In an attempt to assess the potential success of the different approaches to termination, four parameters of R&D performance have been assessed for each company cohort:

- Total clinical development time;
- Late stage clinical success rates;
- Overall clinical success rates;
- The number of new product launches relative to company size.

A detailed explanation of the analysis criteria is provided in Table 7.3. Due to the different year criteria applied to each of the above analyses in combination

Table 7.2 Description of company cohorts assigned

Annual R&D expenditure

Objective: To asses the influence of company size

Calculation: 2002 R&D expenditure on ethical pharmaceuticals taken from GLOBEX (see External data sources)

Companies were grouped into two cohorts:

- "major" companies: R&D expenditure in 2002 >= US$ 1bn
- "other" companies: R&D expenditure in 2002 < US$ 1bn

Phase I success rates

Objective: To assess the differences between companies placing a high hurdle at the of Phase I vs. those placing a lower hurdle at the end of this phase (i.e. those that terminate unless there is a reason to progress vs. those that progress unless there is a good reason to terminate at the end of this phase).

Calculation: Success rate from 'first human dose' to 'first patient dose' (Phase I) for NASs achieving 'first human dose' between 1994 and 1999, with the fate assessed at the end of 31st December 2002.

Companies were grouped into 3 cohorts:

- "low success rates": companies where success rate <= 33rd percentile of success rates for all companies.
- "Medium success rates" companies: companies where success rate >33rd percentile and <= 67th percentile of success rates for all companies.
- "High success rates": companies: companies where success rate > 67th percentile of success rates for all companies.

33rd percentile = 61.5%; 67th percentile = 72.6%

Duration of Phase II

Objective: Duration of phase II was taken as a surrogate measure of the amount of work undertaken in Phase II prior to making the decision to progress to full development for launch.

Calculation: The time from 'first patient dose' to 'first pivotal dose' for NASs achieving 'first pivotal dose' between 1998 and 2002, for which both milestone dates were available. Only companies for which the duration of Phase II could be calculated for two or more NASs were included.

Companies were grouped into three cohorts:

- "Fast" companies: median duration of phase II for company <= 33rd percentile of median duration for all companies.
- "Medium fast" companies: median duration of Phase II for company >33rd percentile and <= 67th percentile of median duration for all companies.
- "Slow" companies: median duration of Phase II for company > 67th percentile of median duration for all companies.

33rd percentile = 1.52 yrs; 67th percentile = 2.12 yrs

Number of NASs taken into clinical development per US$ bn spend

Objective: The relative number of NASs taken into man was taken as a surrogate measure of how stringent the criteria were that were applied by companies when selecting a clinical candidate. The total number of NASs is corrected for company size.

Calculation: Average number of NASs per year passing the milestone 'first human dose' divided by 2002 R&D expenditure on ethical pharmaceuticals (in US$ bn).

Companies were grouped into four cohorts:

- 1-2 NASs/US$ 1bn
- 3 NASs/US$ 1bn
- 4 NASs/US$ 1bn
- >4 NASs/US$ 1bn.

Table 7.3 Analysis criteria for company cohort analyses

Number of terminations
Total number of NASs terminated between 1998 and 2002, while in clinical development.
Time to termination
The time from the date the first human dose was administered in the first clinical trial ('first human dose') to the date the decision was made to terminate. The time to termination was calculated for individual NASs terminated between 1998 and 2002 for which both the date of termination and the date of 'first human dose' were available. The median time to termination was calculated as the time from 'first human dose' to termination within which 50% of all NASs were terminated.
Top three termination reasons
The three most frequently cited reasons for NASs terminated between 1998 and 2002, while in clinical development.
Total clinical development time
Median time in years from 'first human dose' to 'first submission' for NASs submitted between 1998 and 2002 and for which both the date of 'first human dose' and of 'first submission were available. Negative interval durations were excluded from the calculation.
Late stage success rates
Probability of success from 'first pivotal dose' to market for NASs entering phase between 1994 and 1999, with the fate assessed at the end of 2002. A detailed explanation of success rates calculations is provided on page 34.
Overall clinical success rates
Probability of success from 'first human dose' to market for NASs entering phase between 1994 and 1999, with the fate assessed at the end of 2002. A detailed explanation of success rates calculations is provided on page 34.
Relative output
For each cohort the average annual number of NASs reaching the market between 1998 and 2002 was divided by the 2002 ethical pharmaceutical R&D expenditure, to normalise for company size. Where NASs were co-marketed by companies from different cohorts, the NAS was taken into account in the calculation for both cohorts.

with the dynamic character of the pharmaceutical R&D process, there are limitations to the comparability between the different metrics, e.g. an overall clinical success rate from 'first human dose' to market of 10% (based on NASs entering phase between 1995 and 1999) does not directly translate into the requirement of 10 NASs entering Phase I to achieve one product launch. However, the metrics can be meaningfully applied in assessing the commonalities and differences between the company cohorts, which is the primary objective of this set of analyses.

RESULTS

Characteristics of the data source

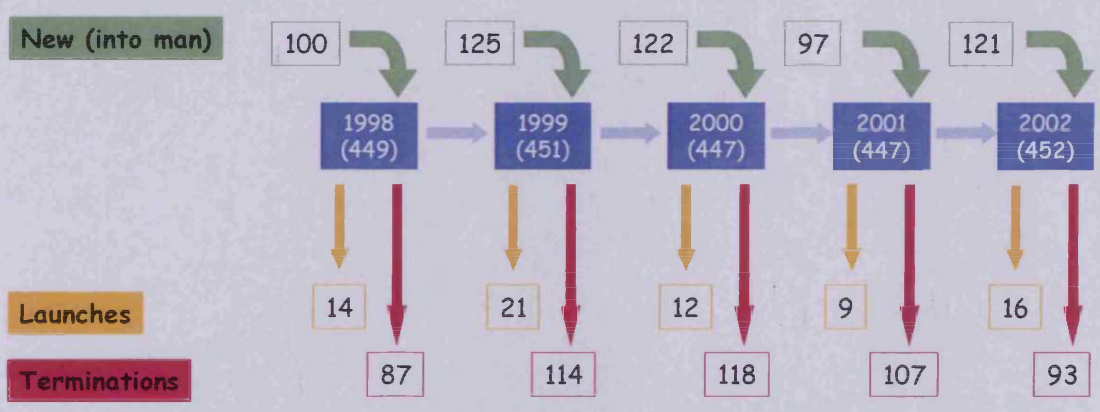
Twenty-eight companies provided data for all five years 1998-2002 (Table 7.4). These companies, including all 14 companies spending over US$ 1bn in 2002 on ethical pharmaceutical R&D ("major" companies), were responsible for 76% of global ethical pharmaceutical R&D expenditure in 2002 (US$ 47.7bn). This cohort of 28 companies terminated a total of 519 NASs during clinical development, i.e. after administration of the first dose in man and prior to receiving marketing authorisation, between 1998 and 2002. The development of an additional 150 NASs was terminated prior to 1st human dose between 1999 and 2002. Over the same period of time (1998-2002) 565 NASs were taken into man by this cohort of companies, 2 of which had reached the market and a further 233 NASs were terminated by the end of 2002.

Table 7.4 Companies included in the study (company groupings as on 31st December 2002)

"Major" companies		"Other" companies	
Amgen	J&J PR&D	Abbott	Merck KgaA
AstraZeneca	Merck & Co	Allergen	Novo Nordisk
Aventis	Novartis	Amersham plc	Procter & Gamble
Bristol-Myers Squibb	Pfizer	Bayer	Sankyo
Eli Lilly	Pharmacia	Boehringer Ingelheim	Sanofi-Synthelabo
F Hoffman-La Roche	Schering Plough	Esteve	Servier
GlaxoSmithKline	Wyeth Pharmaceuticals	Lundbeck	Solvay

An overview of the overall clinical pipeline activities, from 1st human dose to launch, of the 28 companies by year for the period 1998-2002 is provided in Figure 7.2, including the number of NASs taken into clinical development ("into man"), the number of product launches and the number of terminations. The number of NASs taken into clinical development ranged from a high of 125 in 1999 to a low of 97 in 2001. The highest number of NAS launches was observed in 1999, when the combined effort of the 28 companies resulted in the launch of 21 NASs. This was in sharp contrast with the nine product launches reported for 2001. The number of NASs for which clinical development was terminated varied per year between 87 NASs (1998) and 118 NASs (2000). Despite the year-on-year fluctuations of the number of NASs entering and

Figure 7.2 Clinical pipeline activities 1998-2002 for a cohort of 28 companies



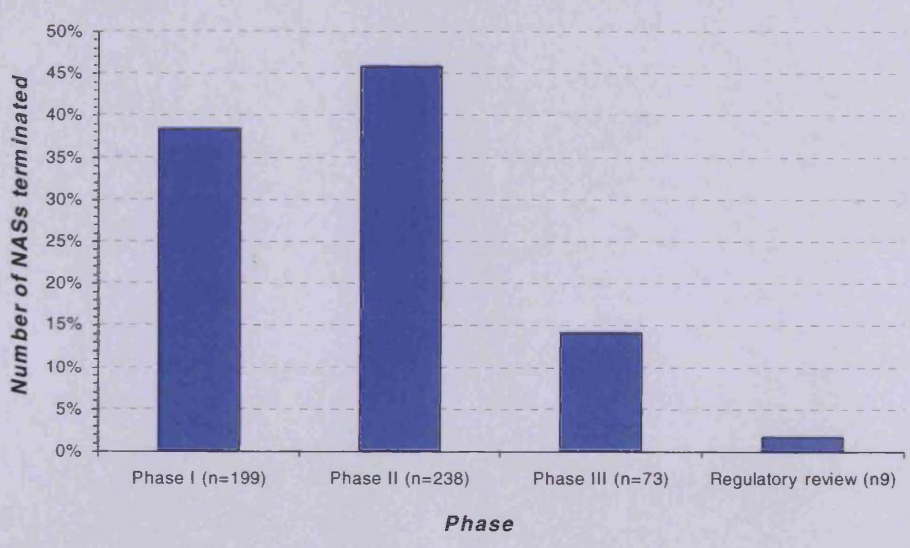
(n) is the total number of NASs in clinical development on 31st December of each year.

leaving the clinical development pipeline, the overall number of NASs in development on the 31st December of each year remained relatively stable around 450 NASs, suggesting that capacity might be a driver for pipeline size.

Terminations by development stage

Figure 7.3 provides a breakdown of the 519 NASs terminated during clinical development by phase. Almost half of the 519 NASs (46%, 238 NASs) were in Phase II when the decision was made to terminate. A further 38% of terminations (199 NASs) took place in Phase I of the development process. Seventy-three NASs (14%) were abandoned while in Phase III and the remaining 2% of terminations took place after submission (nine NASs).

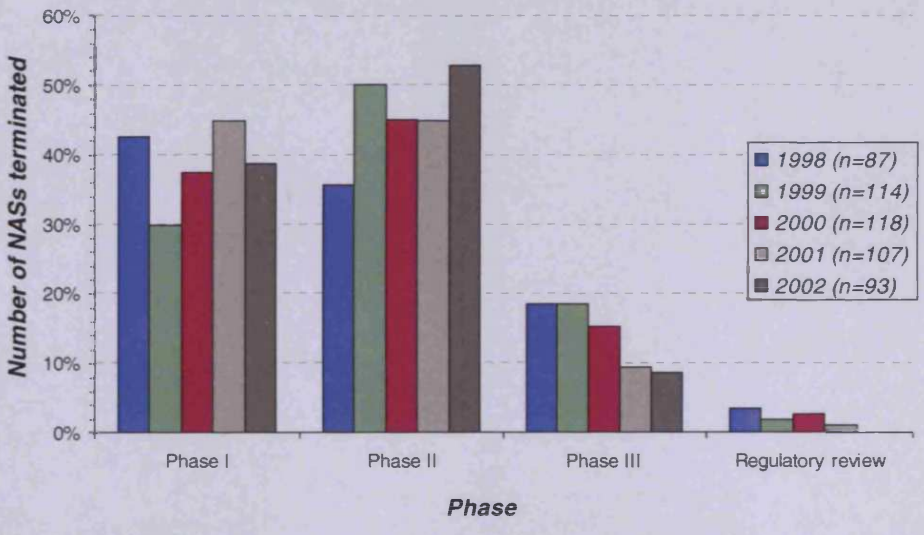
Figure 7.3 Proportion of terminations by phase, 1998-2002



(n) is the number of NASs terminated in each phase

The phase distribution by year over the duration of the study is shown in Figure 7.4. The proportion of NASs terminated in Phase I varied by year, ranging from 30% (34 NASs) of the termination decisions made in 1999 to 45% (48 NASs) in 2001. With the exception of 1999 (50%, 57 NASs), an overall increase in the proportion of NASs terminated in Phase II of the clinical development process was observed, 36% (31 NASs) in 1998 to 53% (49 NASs) in 2002. This increase was in sharp contrast with the decrease of the proportion of NASs terminated in Phase III. In 1998 and 1999, 18% of terminations took place in this phase (16 and 21 NASs, respectively), compared to only half this proportion in 2002 (9%, 8 NASs). The proportion of terminations that took place after submission of the regulatory dossier demonstrated a similar downward trend, from 3% (three NASs) in 1998 to 1% (one NAS) in 2001. In 2002, none of the NASs undergoing regulatory review were terminated.

Figure 7.4 Proportion of terminations by phase per year, 1998-2002

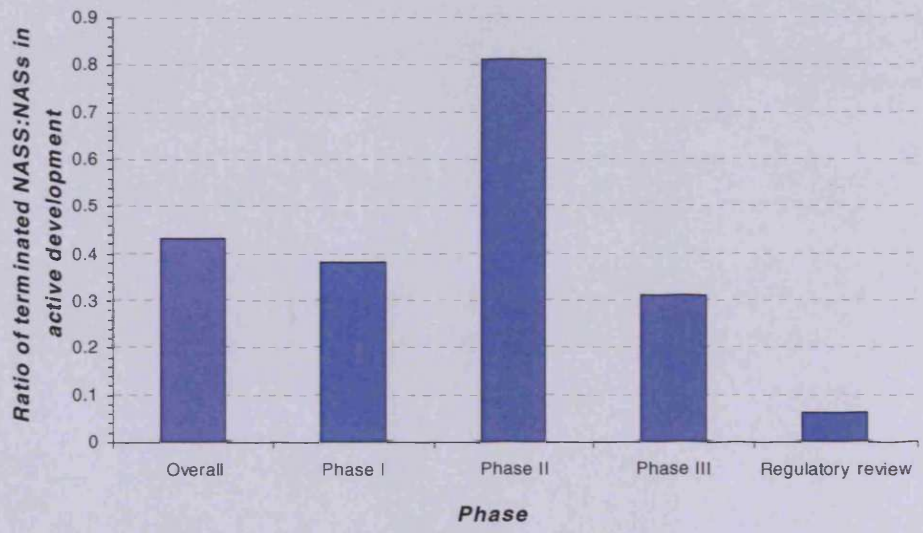


Due to the low number of data points (x=5 for each phase, where x=year), no significant changes could be demonstrated in the number of terminations over time for any of the four phases (linear regression model, p>0.05). (n) is the number of terminated NASs.

The number of terminations relative to the number of NASs in active development is shown in Figure 7.5 as the ratio of terminated NASs:NASs in active development. More information about the methodology of this analysis is provided on page 195. Over the period of the study (1998-2002), 0.4 NASs were terminated for every NAS in active development. This ratio was highest for Phase II (Figure 7.5), where 0.8 NASs were terminated for every NAS in active development. Despite the proportion of terminations in Phase II being only

slightly lower than that in Phase I (Figure 7.3), the ratio in Phase I is less than half the ratio of Phase II, due to the higher number of NASs in active development in Phase I. In Phase III, 0.3 NASs were terminated for every NAS in active development and 0.1 NASs were terminated for every NAS in active development in the regulatory review stage. Although this analysis provides useful insight into the relative number of terminations per phase, more accurate and consistent data is obtained from success rates analyses as provided in Chapter six. In line with the high ratio shown for Phase II in Figure 7.5 success rates were calculated to be the lowest from 'first patient dose' to 'first pivotal dose' (Phase II).

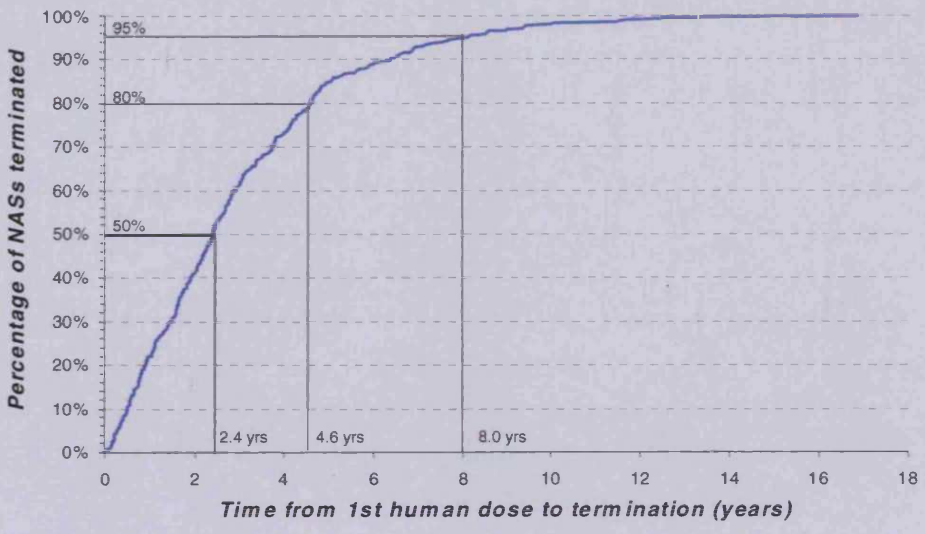
Figure 7.5 Ratio of terminated NASs:NASs in active development by phase, 1998-2002



Time from the start of clinical development to termination

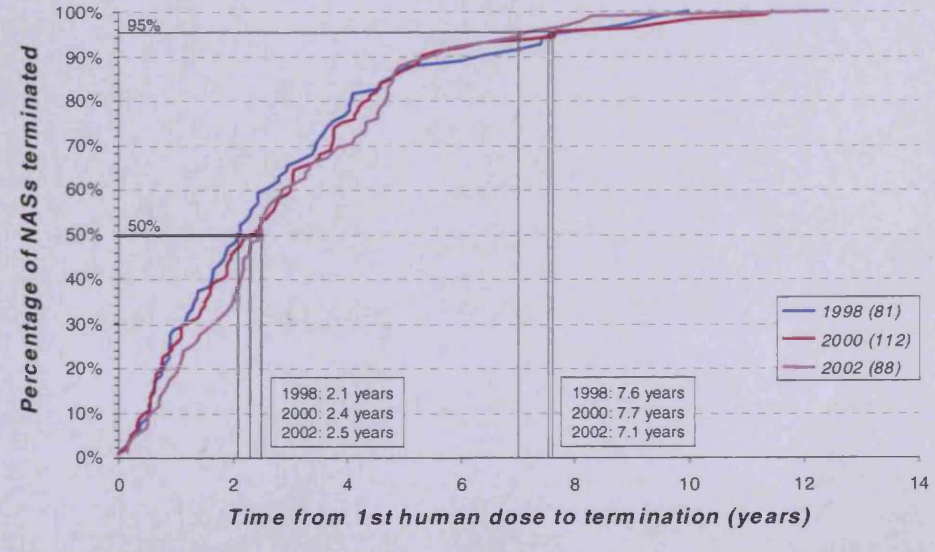
The time to termination, calculated as the time in years from the administration of the first dose in the first clinical trial ('first human dose') to the decision to terminate is shown in Figure 7.6. More information on the methodology of this analysis is provided on page 196. The time to termination could be calculated for 487 (94%) of the 519 NASs terminated during the period 1998-2002. The median time to termination for these 487 NASs was 2.4 years. Although 80% (390 NASs) of all terminations took place within 4.6 years from 'first human dose', 5% of all decisions to abandon development were taken more than eight years after the first clinical activities.

Figure 7.6 Time from first human dose to termination, 1998-2002



In Figure 7.7 the time to termination is shown for NASs terminated in 1998, 2000 and 2002 by year in which the decision to halt development was taken. An increase of the median time to termination over time is observed, from 2.1 years in 1998 to 2.5 years in 2002 (19%). Over the same period of time, a decrease was observed in success rates in Phase II and to a lesser extent in Phase III, with an improvement in phase III success rates observed in the latest year-range (Figure 6.5). Could companies have been focusing on reaching clinical proof of concept before taking the decision to progress to full development for

Figure 7.7 Time from first human dose to termination by year, 1998, 2000 & 2002



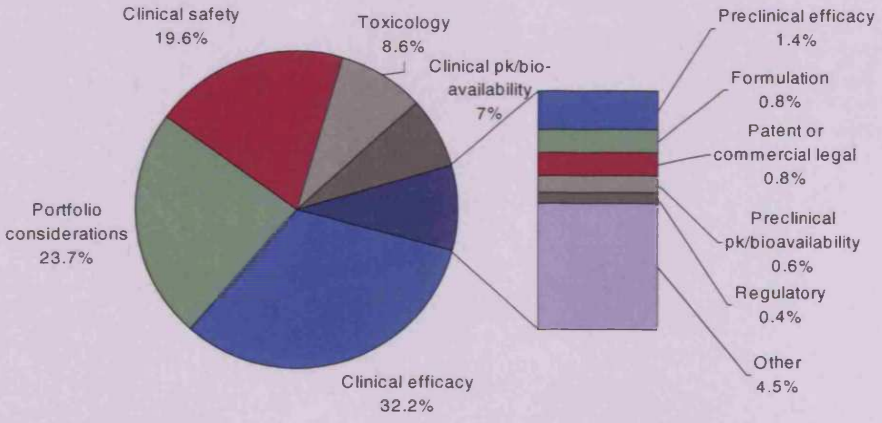
(n) is the number of NASs terminated per year included in the analysis. Statistical comparison of these Kaplan-Meier survival curves using a logrank model showed that there were no significant differences in time to termination between the three years (p>0.0.5).

launch (Phase III), thereby undertaking more work in Phase II? For NASs terminated in 2002, 95% of the decisions to terminate were made within 7.1 years after the administration of the first human dose, an improvement of more than half a year over both 1998 and 2002 (7.6 and 7.7 years, respectively), supporting the decreased number of terminations observed in later phases of the clinical development process (Figure 7.4).

Reasons for terminating further development activities

Information relating to the reason for termination was provided for 490 of the 519 NASs (94%) for which clinical development was terminated over the duration of this study (Figure 7.8). For these, 'Clinical Efficacy' (158 NASs, 32%), 'Portfolio Considerations' (116 NASs, 24%) and 'Clinical Safety' (96 NASs, 20%) were the three most frequently stated reasons for termination, followed by 'Toxicology' (42 NASs, 9%) and 'Clinical Pharmacokinetics/ bioavailability' (36 NASs, 7%). For ten NASs (2%) terminated during clinical development, the

Figure 7.8 Clinical termination reasons, 1998-2002

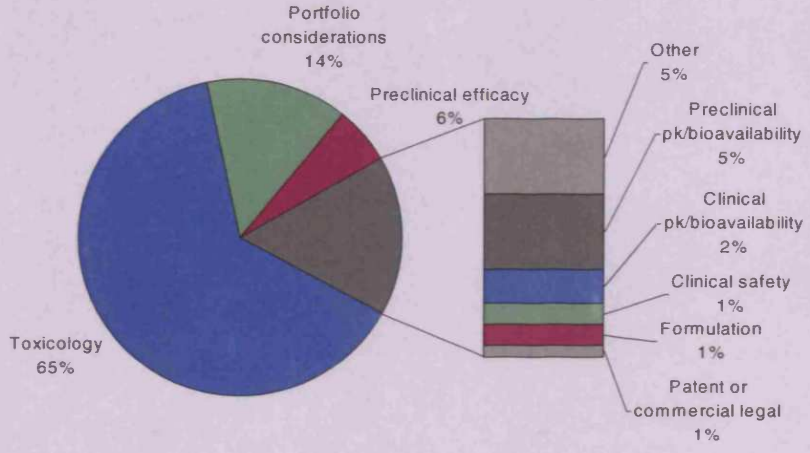


Breakdown by termination reason for 490 NASs terminated between 1998 and 2002 while in clinical development.

reason for termination was associated with preclinical characteristics ('Preclinical Efficacy' and 'Preclinical Pharmacokinetics (pk)/bioavailability'). This could be due to unfavourable outcomes of additional preclinical studies undertaken in parallel to clinical development, suggesting that the insufficient quality of the active substance could have been picked up prior to administration to humans. Only two of the 490 NASs (0.4%) were terminated for reasons associated with regulatory review.

Information on the reason for termination was provided for 135 of the 150 (90%) NASs terminated during preclinical development between 1999-2002 (Figure 7.9). Of these, two-thirds (98 NASs) were terminated for reasons related to the toxicological profile of the NAS. A further 19 NASs were terminated due to 'Portfolio Considerations' (14%) and for eight NASs the decision to abandon further development was based on concerns relating to insufficient preclinical

Figure 7.9 Preclinical termination reasons, 1999-2002

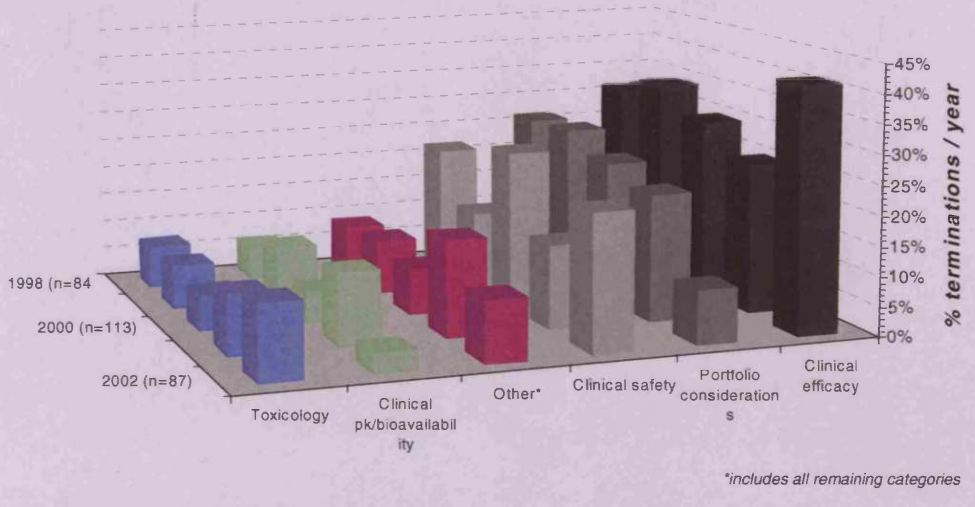


Breakdown by termination reason for 135 NASs terminated between 1999 and 2002 while in preclinical development.

efficacy (6%). For five NASs 'Clinical Safety' and 'Clinical Pharmacokinetics/ bioavailability' were quoted as the reason for terminating preclinical development. One possible explanation for this apparent contradiction in the data could be that the outcome of predictive preclinical studies led to sufficient concern relating pharmacokinetics/ bioavailability and safety in humans to warrant the decision to halt further development activities.

Changes over time from 1998 to 2002 for the five most frequently quoted reasons for termination are shown in Figure 7.10. Over this period of time, the frequency with which 'Toxicology' was quoted as the main reason for termination almost doubled, from 7% in 1998 (six NASs) to 13% (11 NASs) in 2002. The frequency for 'Clinical Efficacy' demonstrated a slight decline from 31% in 1998 (26 NASs) to 26% in 2001 (25 NASs). However, 'Clinical Efficacy' was cited as the reason for halting development for 36 NASs (41%) in 2002, ten percentage points higher than the frequency observed in 1998. 'Portfolio

Figure 7.10 Clinical termination reasons by year, 1998-2002

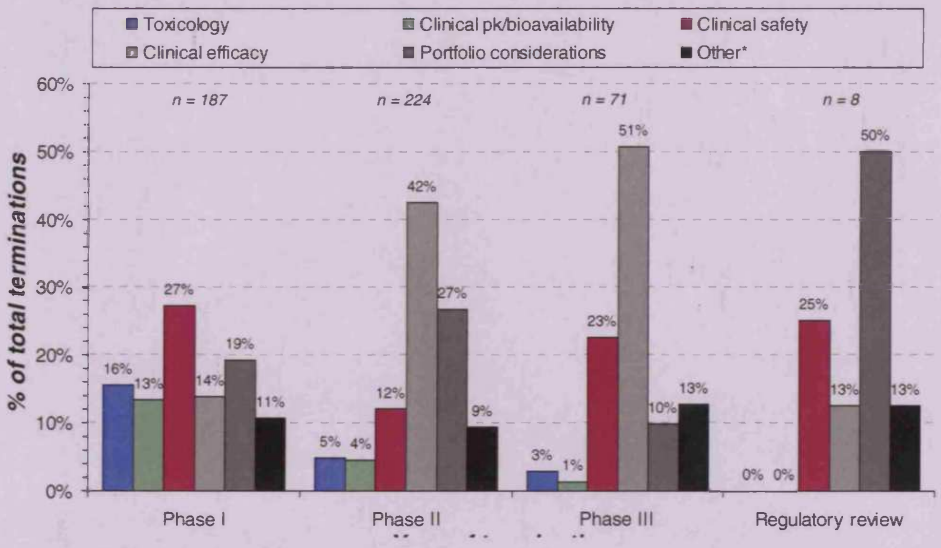


Statistical analysis of these data using a Chi-square test showed that there were no significant differences between the frequencies of the termination reasons over time (p>0.05).

considerations' was the fourth most cited reason for termination in 2002 (9%, eight NASs). This was in sharp contrast with the earlier years investigated in this study. In 1998 and 1999, this reason was the second most important reason, representing 26-27% of all terminations in those years (22 and 29 NASs, respectively). Annual fluctuations were observed in the proportion of NASs terminated due to clinical safety concerns. In 1998, 2000 and 2002 this reason was cited for more than 20% of terminations, whereas in 1999 and 2001 this reason accounted for 13-14% of development failures. The proportion of NASs terminated due to concerns in the area of clinical pk/ bioavailability also varied year on year, from a low of 3% (2001) to a high of 12% (2002).

A breakdown of the reasons for termination by phase is provided in Figure 7.11. In Phase I, 'Clinical Safety' is most frequently quoted as the reason for the decision to terminate development (27%, 51 NASs), followed by 'Portfolio Considerations' (19%, 36 NASs) and 'Toxicology' (16%, 29 NASs). In both Phase II and Phase III, the most frequently quoted reason for termination was 'Clinical Efficacy' (42% and 51%, respectively). In Phase II, the second most frequently quoted reason was 'Portfolio Considerations' (27%, 60 NASs) followed by 'Clinical Safety' (12%, 27 NASs). The reverse was observed for Phase III where 'Clinical Safety' was the second most frequently quoted reason (23%, 16 NASs), followed by 'Portfolio Considerations' (10%, seven NASs). For

Figure 7.11 Clinical termination reasons by phase, 1998-2002

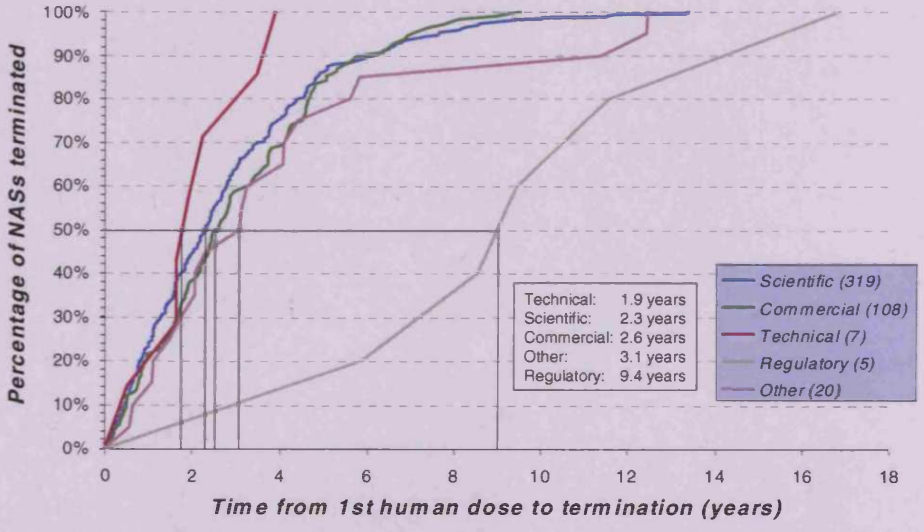


*n is the total number of terminations in each phase for which the reason of termination was known. * Includes all remaining categories.*

four of the eight NASs (50%) terminated during the regulatory review stage the reason quoted was 'Portfolio Considerations'. For two NASs terminated during this phase (25%) 'Clinical Safety' was quoted as the reason for termination.

The time to termination by termination reason is plotted in Figure 7.12 for those NASs for which all relevant information was provided (i.e. termination reason

Figure 7.12 Time from first human dose to termination by termination reason, 1998-2002

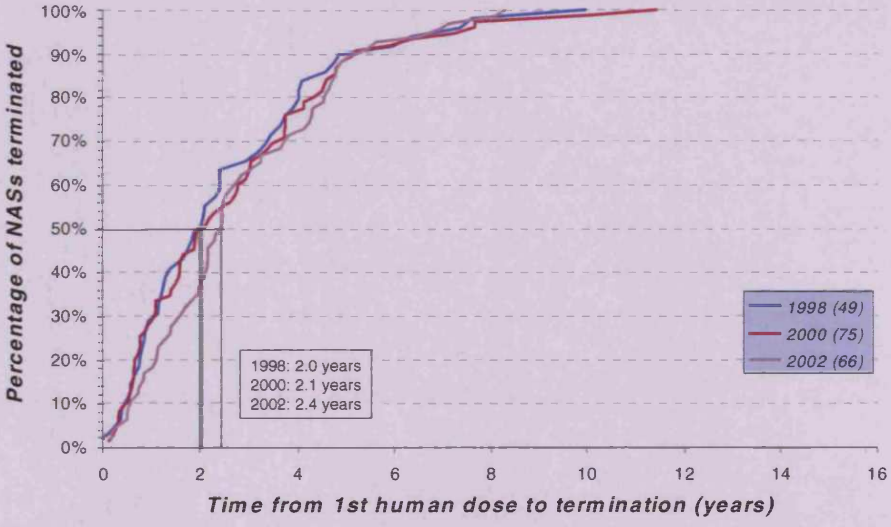


(n) is the number of NASs included in the analyses. Statistical comparison of these Kaplan-Meier survival curves using a logrank model showed that the time to termination for NASs terminated for regulatory reasons was significantly longer than that for NASs terminated for any other reason (p<0.0.1).

and date and the date of 'first human dose). The median time to termination for NASs that failed due to technical complications was 1.9 years, compared to 2.3 years for NASs terminated for scientific reasons and 2.6 years for NASs terminated for commercial reasons. Although it was not surprising that the median time to termination for those NASs terminated for regulatory issues (9.4years) was much longer than for other termination reasons, it should be noted that this is almost double the median time from 'first human dose' to 'first launch' for successful NASs (Table 7.6). No conclusions could be drawn with regards to the timing of termination for NASs terminated for regulatory or technical reasons, due to the low number of NASs terminated for these reasons (five and seven, respectively).

In Figure 7.13 the time to termination is shown for NASs terminated for scientific reasons in 1998, 2000 and 2002 by year in which the decision to halt development was taken. The observed increase in the median time to termination from 2.0 years in 1998 to 2.4 years in 2002 (15%) corresponded with the observed overall increase in time to termination (Figure 7.7).

Figure 7.13 Time from first human dose to termination over time for terminations for scientific reasons, 1998, 2000 and 2002

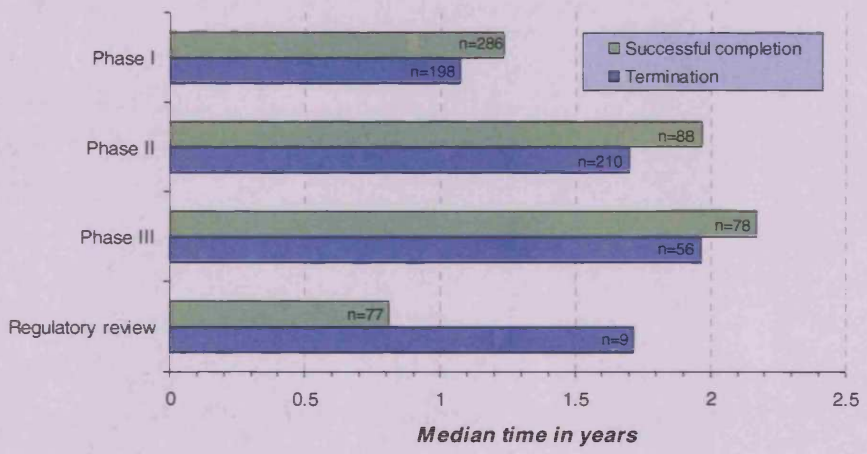


(n) is the number of NASs terminated per year included in the analysis. Statistical comparison of these Kaplan-Meier survival curves using a logrank model showed that there were no significant differences in time to termination between the three years (p>0.0.5).

In Figure 7.14, the median time from the start of each phase to successful completion of that phase (i.e. to the start of the next phase) is compared to the

median time from the start of each phase to termination, where termination took place in that phase. For all phases but the regulatory review stage, the median time to termination was slightly shorter than the time to the start of the next phase. This was not surprising, since the time for successful completion was measured as the time from the administration of the first dose in the first trial in that phase to the first administration of the first dose in the first trial in the next phase. As such, it included not only the time to the decision to progress; it also included any additional activities required to achieve the first human dose in the

Figure 7.14 Time to termination vs. time to successful completion by phase, 1998-2002

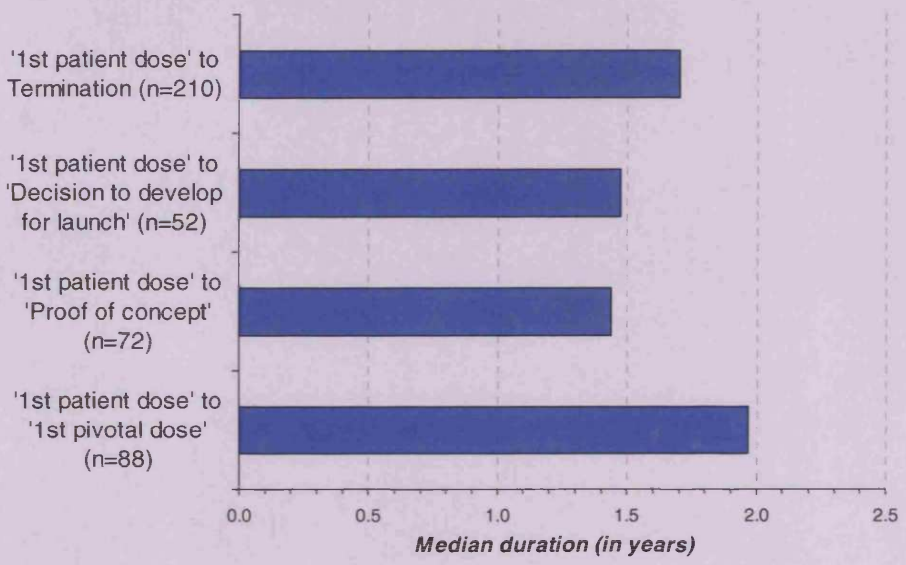


next phase, including study start-up and enrolment of the first patient. Between 1998 and 2002, all relevant information to calculate the duration from 'first human dose' to 'first patient dose was available for 286 NASs successfully completing Phase I. The median duration for completion of Phase I was 1.2 years, compared to a median time to termination of 1.1 years based on 198 NASs terminated in Phase I over the period of the study. For Phase II, the median duration for successful completion was calculated to be 2.0 years (based on 88 NASs), compared to a median of 1.7 years (based on 210 NASs) from the start of Phase II to termination in this phase. The median duration for successful completion of Phase III (2.2 years, based on 78 NASs) exceeded the time to termination in this phase by 2 months (2.0 years, based on 56 NASs).

The duration of Phase II is studied in more detail in Figure 7.15. In addition to the median time from the start of Phase II ('first patient dose') to termination and

to the start of the next phase ('first pivotal dose'), the time from 'first patient dose' to 'Decision to develop for launch' and to 'Proof of concept' is shown. The additional time to the beginning of Phase III compared to the time to the decision to terminate can be explained by activities required to prepare for the administration of the first patient dose in the first pivotal study ('first pivotal dose') once the decision to progress was made. More interesting are the slight differences observed for the median time to termination (1.7 years, based on

Figure 7.15 Duration of Phase II, 1998-2002

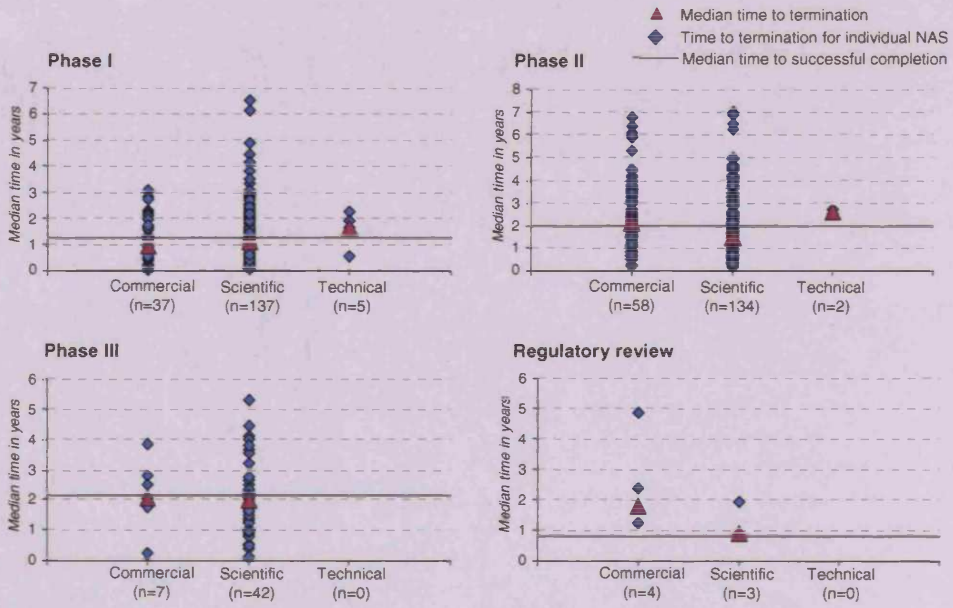


210 NASs) and the median time to 'Proof of concept' (1.4 years, based on 72 NASs) and 'Decision to develop for launch' (1.5 years, based on 52 NASs). One approach to termination that potentially could explain the observations made would be that in order to take the decision to progress to full development for launch, the clinical proof of concept has to be demonstrated and that a timeframe has been set within which this has to be demonstrated. If clinical proof of concept is demonstrated, the decision to progress to Phase III will be made shortly after achieving this milestone. However, if at the end of the set of time period the clinical proof of concept cannot be demonstrated, the decision will be made to abandon development for this NAS.

The time to termination within a phase by termination reason is shown in Figure 7.16. The duration in years from the start of the phase is presented for individual NASs as blue diamonds. The median time to termination for each

phase and termination reason is presented by a purple triangle, and the grey line represents the median time for successful completion of the phase (i.e. the time to the start of the next phase). For phase I, the median time to termination for both commercial and scientific reasons was slightly shorter than the median time for successful completion of that phase, however there was a wide range in the time to termination for individual NASs, with some NASs terminated for scientific reasons more than six years after the start of the phase. A similar pattern was observed for Phase II. For both Phases I and II the median time to termination for technical failure was only slightly longer than the median time to success. There were no terminations for technical reasons in Phase III or during

Figure 7.16 Time to termination by phase by termination reason, 1998-2002



Statistical comparison of the data for each phase using the Kruskal-Wallis test across all termination reasons included in the graphs shows that there is a significant difference in the time to termination in Phase II between NASs terminated for commercial reasons and NASs terminated for scientific reasons ($p<0.05$). For the remaining three phases, no significant differences could be demonstrated.

the regulatory review stage. For this last stage, the time to termination for each NAS exceeded the median time for successful completion. One potential explanation for this could be the process of regulatory review, which includes time for companies to address any questions or issues raised by the regulatory authority. Where difficulties arise that could lead to potential termination of the NAS at this late stage, companies will try everything possible to prevent this, thereby potentially lengthening the process.

Influence of compound characteristics on termination profile

An assessment was made of the influence of therapeutic area, origin, compound type and novelty of the pharmacological mode of action on time to termination and termination reason (Table 7.5). The time to termination, expressed as the time in years from the administration of the first human dose to the decision to terminate varied between therapeutic areas, although no significance could be demonstrated. The shortest duration was observed for 'Alimentary & Metabolism', where half of all terminations occurred within 1.5 years of achieving the milestone 'first human dose'. For NASs in development for oncology indications, this duration was the longest of the ten areas investigated (2.7 years).

Four of the ten therapeutic areas showed a termination reason profile similar to that of all terminated NASs, with 'Clinical Efficacy' being quoted as the most frequent reason for termination, followed by 'Portfolio Considerations' ('Respiratory', 'Cardiovascular', 'Cancer', 'Dermatological'). The two most frequently cited reasons for terminations for almost all therapeutic areas were a combination of the Top 3 reasons overall, 'Clinical Efficacy', 'Portfolio Considerations' and 'Clinical safety' (see Figure 7.8). Exceptions to this general observation were the therapeutic areas 'Musculoskeletal', 'Alimentary & Metabolism' and 'GU & Sex Hormones'. Although for both 'Alimentary & Metabolism' and 'GU & Sex hormones' 'Clinical Efficacy' was the most frequently cited reason, the second-most frequently cited reason was not in the overall Top 3. For 'Alimentary & Metabolism' the second-most frequently cited reason was 'Toxicology' and for 'GU & Sex hormones' this was 'Other'. Interestingly, more than half of the terminations for reasons grouped as 'Other' within the latter area were related to preclinical activities. NASs developed for Musculoskeletal indications were most frequently terminated for issues relating to 'Clinical Safety' (43%), followed by 'Toxicology' (20%).

Of all characteristics investigated, therapeutic area appeared to have the most influence on the reason for termination (Table 7.5). However, some additional differences were found between the categories for the other characteristics

Table 7.5 Proportion of terminations, time to termination and termination reason by active substance characteristic, 1998-2002

Characteristic	Median time to termination (yrs)	Top 2 termination reasons (% of terminations within category)
All NASs	2.4 yrs	Clinical efficacy (32%) Portfolio cons. (24%)
Therapeutic area		
Respiratory	2.1 yrs	Clinical efficacy (48%) Portfolio cons. (18%)
Nervous system	2.3 yrs	Clinical efficacy (38%) Clinical safety (23%)
Blood	2.3 yrs	Portfolio cons. (42%) Clinical safety (26%)
Cardiovascular	2.4 yrs	Clinical efficacy (31%) Portfolio cons. (25%)
GU & Sex hormones	2.3 yrs	Clinical efficacy (29%) Other (25%)
Cancer	2.7 yrs	Clinical efficacy (38%) Portfolio cons. (32%)
Dermatological	1.9 yrs	Clinical efficacy (42%) Portfolio cons. (25%)
Alimentary & Metabolism	1.5 yrs	Clinical efficacy (31%) Toxicology (24%)
Musculoskeletal	2.1 yrs	Clinical safety (43%) Toxicology (20%)
Anti-infectives	2.1 yrs	Portfolio cons. (37%) Clinical safety (21%)
Origin		
Self originated	2.1 yrs	Clinical efficacy (32%) Portfolio cons. (22%)
Licensed-in/acquired	2.5 yrs	Clinical efficacy (39%) Portfolio cons. (21%)
Compound type		
Chemical entity	2.2 yrs	Clinical efficacy (33%) Portfolio cons. (21%)
Biotech compound	2.7 yrs	Clinical efficacy (33%) Portfolio cons. (33%)
Novelty of mechanism of action		
Novel mode of action	2.2 yrs	Clinical efficacy (35%) Clinical safety (27%)
Established mode of action	2.4 yrs	Clinical efficacy (35%) Portfolio cons. (22%)

To allow statistical analysis of the time to termination, this data was plotted as Kaplan-Meier survival curves. Statistical comparison of these Kaplan-Meier survival curves using a logrank model showed that there were no significant differences in time to termination for any of the characteristics presented in the table ($p>0.0.5$). Statistical analysis of the termination reason data using a Chi-square model showed that there were no significant differences between the distributions of termination reasons for any of these characteristics. Using this model, no significant differences could be demonstrated for the less detailed breakdown between commercial and scientific termination reasons ($p>0.05$).

assessed (origin, compound type and novelty of mechanism of action). The termination reason profile for self-originated NASs was very similar to that of licensed-in or acquired NASs. Around two-third of NASs were terminated due to clinical efficacy issues (32% and 39%, respectively), with 'Portfolio Considerations' being quoted second most frequently as the reason for failure. Similar profiles were observed for the different compound types (chemical entities vs. biotech NASs) and when assessing the influence of the novelty of the pharmacological mode of action (novel vs. established). One exception was the slightly higher proportion of biotech NASs for which the decision to terminate was associated with portfolio considerations (33%).

The time to termination demonstrated slight differences for self-originated NASs compared to NASs that were licensed-in or acquired (Table 7.5). The decision to terminate appeared to be made slightly quicker for self-originated NASs than for NASs obtained through licensing or acquisition activities. For the first category, 50% of all terminations took place within 2.1 years of first human dose. This duration increased to 2.5 years for the latter category. When comparing the termination profile for chemical entities with that of biotech-derived NASs, it was observed that terminations generally took place within a shorter time frame for chemical entities (50% of terminations within 2.2 years of first human dose) compared to biotech NASs (50% of terminations within 2.7 years of first human dose). The time to termination for NASs with a novel mode of action and those with an established mode of action was reasonable similar. Fifty percent of NASs with a novel mechanism of action were terminated within 2.2 years of first human dose compared to 2.4 years for NASs with an established mode of action. None of the described differences were found to be significant.

Influence of company characteristics on termination profile

To assess the influence of company characteristics or different approaches companies can take towards termination, the 28 companies for which termination data were available for all five years 1998-2002, were grouped into cohorts. The four company characteristics that have been studied in this way are: 1) company size; 2) focus on early termination; 3) focus on obtaining clinical proof of concept before starting full development for launch and 4)

number of NASs taken into man. For each of these cohorts of companies, the termination profile has been assessed in terms of 1) the ratio of terminated NASs: NASs in active development; 2) the median time to termination and 3) the Top 3 termination reasons. In an attempt to assess the potential success of the different approaches to termination, total clinical development time, late stage clinical success rates, overall clinical success rates and the relative number of new product launches were assessed for each of the different company cohorts. The results of all analyses described are presented in Table 7.6. Further details of the criteria for the company cohorts and of the analyses are provided in Table 7.2 (page 197) and Table 7.3 (page 198), respectively.

Company size

To assess the potential influence of company size companies were grouped into two cohorts with companies spending more than or equal to US$ 1bn on the R&D of ethical pharmaceuticals in 2002 classified as "major" companies and companies whose ethical pharmaceutical R&D spend in 2002 was less than US$ 1bn classified as "other" companies. No differences were observed between the two cohorts in the top three termination reasons, although 'Portfolio considerations' was slightly more prevalent for "other" companies than for "major" companies (28% and 20% of terminations, respectively). However, "other" companies took significantly longer over the decision to terminate, with 50% of failures taking place within 2.6 years of administration of the first human dose, compared to 2.2 years for "major" companies. Small differences were observed in the overall clinical development time and success rates, none of which were found to be significant. Compared to "major" companies, the overall clinical development time, measured as the median time in years from 'first human dose' to 'first submission', for "other" companies was slightly shorter, combined with slightly higher success both from 'first human dose' and 'first pivotal dose' (Table 7.6).

There are many approaches that can be taken towards attrition and these can vary by company and by stage of the development process. There are two extremes in this: 1) terminate everything unless there is a valid reason to progress; and 2) progress everything unless there is a valid reason to terminate.

Table 7.6 Termination profile by company cohorts, 1998-2002

All companies (n=28)	519 NASs	2.4 yrs	Clinical efficacy (32%) Portfolio cons. (24%) Clinical safety (20%)	5.1 yrs (68)	56%	12%	0.5 NASs/$bn
Company size: *Annual R&D expenditure*							
"Major" (n=14)	401NASs	2.2 yrs	Clinical efficacy (33%) Portfolio cons. (20%) Clinical safety (19%)	5.2 yrs (53)	56%	12%	0.5 NASs/$bn
"Other" (n=14)	118 NASs	2.6 yrs	Clinical efficacy (29%) Portfolio cons. (28%) Clinical safety (21%)	4.9 yrs (15)	61%	14%	0.7 NASs/$bn
Transition from preclinical to clinical development: *Annual number of clinical candidates / R&D expenditure*							
1-2 NASs / US$ bn (n=7)	77 NASs	2.4 yrs	Portfolio cons. (29%) Clinical efficacy (27%) Clinical safety (20%)	5.2 yrs (17)	65%	24%	0.6 NASs/$bn
3 NASs / US$ bn (n=8)	189 NASs	2.6 yrs	Clinical efficacy (39%) Portfolio cons. (25%) Clinical safety (15%)	5.0 yrs (29)	53%	9%	0.6 NASs/$bn
4 NASs / US$ bn (n=6)	177 NASs	2.4 yrs	Clinical efficacy (32%) Clinical safety (23%) Portfolio cons. (14%)	6.6 yrs (15)	56%	11%	0.7 NASs/$bn
>4 NASs / US$ bn (n=7)	76 NASs	1.6 yrs	Clinical efficacy (25%) Portfolio cons. (25%) Clinical safety (22%)	3.0 yrs (7)	46%	11%	0.5 NASs/$bn

[1]Total number of NASs terminated 1998-2002. [2]Calculated as median time from 1st human dose to termination for NASs terminated 1998-2002. [3]Calculated as percentage of all NASs terminated by cohort of companies between 1998 and 2002. [4]Calculated as the median time from 1st human dose to 1st submission for NASs submitted 1998-2002. [5-7]See page 217. (n) is the number of companies. For more information see Table 7.2 and Table 7.3. Company size: Statistical comparison of the data using Mann-Whitney U-tests showed significant differences in time to termination (p<0.05). No significant differences between cohorts were demonstrated for clinical development time and success rates. Transition from preclinical to clinical development: Statistical comparison of the data using Chi-squared tests showed that success rates from 'first patient dose' to 'first pivotal dose' for the cohort '1-2 NASs / US$ bn' were significantly higher than for the cohorts '3 NASs / US$ bn' and '4NASs / US$ bn' (p<0.01). No significant differences were demonstrated for clinical development time and time to termination.

Table 7.6 (continued) **Termination profile by company cohorts, 1998-2002**

Transition from Phase I to Phase II: *Success rate from 'first human dose' to 'first patient dose'*							
High success rate (n=7)	86	2.8 yrs	Clinical efficacy (37%) Portfolio cons. (28%) Clinical safety (16%)	5.0 yrs (25)	48%	23%	0.7 NASs/$bn
Medium success rate (n=8)	157	2.4 yrs	Clinical efficacy (29%) Portfolio cons. (28%) Clinical safety (17%)	5.3 yrs (16)	68%	14%	0.6 NASs/$bn
Low success rate (n=8)	258	2.3 yrs	Clinical efficacy (33%) Clinical safety (22%) Portfolio cons. (15%)	5.4 yrs (22)	48%	8%	0.4 NASs/$bn
Transition from Phase II to Phase III: *Duration Phase II*							
"Fast" (n=6)	123 NASs	2.5 yrs	Clinical efficacy (33%) Portfolio cons. (22%) Clinical safety (19%)	5.6 yrs (16)	57%	10%	0.7 NASs/$bn
"Medium fast" (n=7)	177 NASs	2.4 yrs	Clinical efficacy (33%) Portfolio cons. (26%) Clinical safety (19%)	4.5 yrs (25)	57%	13%	0.5 NASs/$bn
"Slow" (n=6)	143 NASs	2.4 yrs	Clinical efficacy (30%) Clinical safety (23%) Portfolio cons. (15%)	7.0 yrs (15)	55%	15%	0.5 NASs/$bn

[4-7]See page 216. [5]Calculated as the probability of success from 1st pivotal dose to market. [6]Calculated as the probability of success from 1st human dose to market. [7]For each cohort the average annual number of NASs reaching the market between 1998 and 2002 was divided by the 2002 ethical pharmaceutical R&D expenditure. (n) is the number of companies. For more information see Table 7.2 and Table 7.3. Transition from Phase I to Phase II: Statistical comparison of the data using a Kruskal-Wallis test showed significant differences between the cohorts in time to termination. Further analysis using Mann-Whitney U-tests showed that the time to terminate for the cohort 'high success rate' was significantly longer than for the cohort 'low success rate' ($p<0.05$). Statistical comparison of success rates using Chi-square tests showed that success rates from 'first patient dose' to 'first pivotal dose' for the cohort 'high success rates' were significantly higher than for both other cohorts ($p<0.01$) and that success rates from 'first submission' to market for the cohort 'medium success rates' were significantly higher than for both other cohorts ($p<0.05$). No significant differences between cohorts were demonstrated for clinical development time (Mann-Whitney U-test). Transition from Phase II to Phase III: Statistical comparison of the data did not show significant differences between the three cohorts in time to termination, clinical development time and success rates.

In this study, different approaches to attrition were investigated for three different hurdles in the development process: 1) transition from preclinical to clinical development; 2) transition from Phase I to Phase II; and 3) transition from Phase II to Phase III.

Transition from preclinical to clinical development

The number of NASs taken into man relative to company size was used as a surrogate measure of how stringent the criteria were that companies apply when selecting a clinical candidate. It is postulated that companies taking a relatively low number of NASs in man will have applied more stringent criteria, terminating everything in preclinical development unless there is a reason to progress. Companies taking a higher number of NASs into man might be applying these stringent criteria later in the clinical development process. For each company, the average number of NASs passing the milestone 'first human dose' per year for the years 1998-2002 was divided by the ethical pharmaceutical R&D expenditure in 2002. Based on this relative number of NASs taken into man companies were grouped into four cohorts: a) companies taking 1-2 NASs per US$ bn into man; b) companies taking three NASs per US$ bn into man; c) companies taking four NASs per US$ bn into man and d) companies taking more than four NASs per US$ bn into man. An overview of the termination profiles for these cohorts of companies as well as overall clinical development times, success rates and the number of new product launches is provided in Table 7.6. The fastest median time to termination was observed for those companies taking the highest number of NASs into man per US$ bn (1.6 years), suggesting that stringent selection criteria were applied early in the clinical development process, e.g. at the end of Phase I. This cohort of companies also demonstrated the fastest overall development time (3.0 years) and the lowest late-stage success rates (46%), but not the lowest overall clinical success rates (11% compared to 9% for companies taking four NASs into man per US$ 1bn). The highest success rates from 'first human dose' to market was observed for those companies taking only 1-2 NASs into clinical development per US$ bn (24%), suggesting that it may be worthwhile to apply stringent screening during selection of candidates for clinical development. This was

mainly driven by the significantly higher success rates for this cohort of companies from 'first patient dose' to 'first pivotal dose'.

Interesting differences were observed between companies taking three NASs into man and those taking four NASs into man. The median clinical development time for the first cohort was shorter than that for the latter (5.0 years and 6.6 years, respectively). Both late stage success rates and overall clinical success rates were lower for companies taking three NASs into man (53% and 9%, respectively) than for companies taking four NASs into man (56% and 11%, respectively). Differences were also observed in the relative number of new product launches, with the cohort of companies taking the highest number of NASs into man launching the lowest relative number of new products, suggesting that taking more NASs into man does not necessarily translate into a higher output.

Transition from Phase I to Phase II

Success rates from 'first human dose' to 'first patient dose' were taken as a surrogate measure of the height of the hurdle placed at the end of Phase I, where high success rates were assumed to correlate to a low hurdle and low success rates to a high hurdle. For companies placing the lowest hurdle at the end of Phase I ('high success rates', 2.8 years), the median time to termination was significantly longer than for those placing the highest hurdle at the end of this phase ('low success rates'; 2.3 years). Only slight differences between the cohorts were observed in total clinical development times, ranging from 5.0 years for companies with the lowest hurdle to 5.4 years for companies with the highest hurdle in place. Interestingly, the cohort of companies with the highest success rates at the end of Phase I demonstrated significantly higher success rates from 'first patient dose' to 'first pivotal dose', suggesting that this cohort of companies have a second low hurdle in place at the end of Phase II, which might explain the low overall success from 'first human dose' to market (8%).

Transition from Phase II to Phase III

One strategy in preventing late stage termination is for companies to undertake more work in Phase II to achieve clinical proof of concept prior to making the

decision to progress to the later phases of the development process. In this study the duration for Phase II has been used as a surrogate measure for the amount of effort undertaken in this phase. Companies have been grouped into three cohorts. In total, 19 of the 28 companies could be allocated to one of the three cohorts, including only those companies for which the duration of Phase II could be calculated for two or more NASs completing Phase II between 1998 and 2002. The companies with the longest Phase II duration ("slow" companies) were also the companies for which the longest overall clinical development time was observed (7.0 years) However, the companies with the shortest Phase II duration ("fast" companies) were not the companies with the shortest overall clinical development time (5.6 years vs. 4.5 years for "medium fast" companies). The "medium fast" company cohort was the cohort with the highest overall success rate from 'first human dose' to market (15%). Although the lowest success rates from 'first human dose' to market were observed for "fast" companies, suggesting that speed may not be the overall driver for development, this cohort of companies did achieve the most launches relative to R&D expenditure. The termination reason profile for "slow" companies differed slightly from the overall industry ranking, with 'Portfolio Considerations' (15%) taking third place behind 'Clinical Safety' (23%, Table 7.6). None of the observed differences between "fast" companies, "medium fast" companies and "slow" companies were demonstrated to be significant.

DISCUSSION

As outlined in the introduction, studying past terminations could help in improving future drug development processes. In this study, data on clinical development failures for a cohort of 28 companies were investigated in detail. Additional information on NASs terminated during preclinical development was incorporated to enhance the understanding of the drivers for clinical termination. This cohort of companies, representing 76% of global ethical pharmaceutical R&D expenditure in 2002, reported the termination of 519 NASs in clinical development over the duration of this study, 1998-2002. An additional 150 NASs failed during preclinical development between 1999 and 2002.

Over the duration of the study, the number of NASs taken into clinical development per year fluctuated between 97 and 125 NASs. Similar fluctuations were observed for the output of the clinical development process, both in terms of successful NASs (those that made it to market) and in terms of NASs for which development was terminated. Despite these fluctuations, the number of NASs in development on the 31st December of each year remained remarkably constant around 450 NASs. The clinical pipeline size varied year on year by a maximum of only 3 NASs, compared to a range of over 25 NASs for those entering development as well as those failing. This suggests that one of the drivers behind a company's portfolio is capacity. If this is this the case, it will be of influence on the decision-making process and it should therefore be taken into account when studying past drug development failures.

Time to termination

Fifty percent of all clinical terminations took place within 2.4 years of the administration of the first human dose which is taken as the starting point for clinical development in this study. Within 4.6 years of the first human dose, an additional 30% of this cohort of 519 failures were terminated. The median time to termination increased by 16% over the duration of the study from 2.1 years in 1998 to 2.5 years in 2002. Over the same period, however, the time from first human dose to termination within which 95% of terminations took place decreased by 7%, from 7.6 years in 1998 to 7.1 years in 2002. This could be taken as an early sign that companies have started to get better at tackling late stage terminations earlier in the development process.

Considerable differences in the time to termination were observed between therapeutic areas which was not surprising considering the differences in success rates described in Chapter six. With a median time to termination of 1.5 years, the therapeutic area 'Alimentary & Metabolism' was found to be the area in which decisions were made quickest. The longest median time to termination was observed for NASs in development for oncology indications (2.7 years), which might be related to the relative complexity of demonstrating incremental improvements over existing clinical practices, which often involves multiple drug cocktails of cytotoxic chemotherapy agents (Booth *et al.*, 2003). Perhaps

surprisingly was the observation that the median time to termination for anti-infectives was only slightly shorter than that for all terminations (2.1 years vs. 2.4 years, respectively). Terminations in Phase I, resulting in relatively short termination times used to be typical for this therapeutic area (Parrish, 1989). Could it be that in recognising and addressing the issues typically associated with anti-infectives by developing preclinical studies with a higher predictive value of clinical pharmacokinetics, the industry has succeeded in terminating failures earlier, i.e. prior to administration to man?

The outcome of this study suggests that therapeutic area is not the only project characteristic influencing when development is terminated. The median time to termination was observed to be 0.4 years (19%) longer for licensed in or acquired NASs than for self-originated NASs. Despite the natural differences observed in success rates between NASs with a novel mode of action and those with an established mode of action (see Chapter six), the difference in the time to termination was only limited: 2.2 years for NASs with a novel mode of actions compared to 2.4 years for NASs with an established mode of actions. Chemical entities were observed to fail, in general, 0.5 years earlier than NASs that were derived through biotechnology. Relatively more biotech NASs were terminated for commercial reasons, which might explain the longer time to termination for this cohort of compounds. This might be related to the nature of biotechnology derived NASs, many of which are naturally occurring proteins and therefore less prone to trial and error than chemical entities, which was also reflected in the higher success rates for biotechnology NASs compared to chemical entities (Chapter six).

By far the majority of the termination decisions were made in early clinical development, in line with the observed median time to termination. Thirty-eight percent of failures took place in Phase I and a further 46% of NASs underwent attrition in Phase II. The remaining 16% of the 519 NASs terminated over the duration of the study failed during Phase III, or even after submission of the regulatory dossier. Over the duration of the study, a shift was observed in the phase distribution of development failures towards Phase II being the phase where most NASs undergo attrition. In 1998, more NASs failed during Phase I

than during Phase II. In later years this changed and in 2002 the majority of terminations took place in Phase II (53%) compared to 39% of NASs undergoing attrition in Phase I. Simultaneously, the proportion of NASs undergoing attrition in Phase III halved, from 18% of all terminations in 1998 to 9% in 2002. An even more pronounced decrease in attrition was observed for NASs undergoing regulatory review, with no terminations reported in this phase in 2002. This could suggest that over the duration of this study, companies have become more successful in screening out failures prior the NAS entering the more costly phase III. In addition, the observed decrease in the proportion of terminations in Phase I could mean that companies have also become more successful in obtaining information from preclinical studies to predict potential problems in early clinical development, killing off compounds prior to phase I where in the past these would have failed at a later stage.

Parrish (1989) studied development activities of seven UK-owned companies between 1964 and 1987 and found that over 60% of failures took place within 1 yr of first human dose and that 90% of termination decisions were made by the end of the 4^{th} year of clinical development. Two of the seven companies investigated by Parrish focused the majority of their activities on the development of anti-infectives and the influence of the specific requirements of this therapeutic area goes some way towards explaining the much longer time to termination observed in this study. A further possible explanation for the observed delay might be found in the overall increase in development times for the industry during the 1980s (DiMasi, 2001b). However, Parrish reported that 68% of all terminations took place in Phase I, and only 28% in Phase II/III of the development process, compared to 38% of terminations in Phase I and 60% in Phase II/III observed in this study. The differences in the phase distributions of development failures between Parrish's work and this study suggests that lengthening cycle times are not the sole driver for the observed increase in time to termination.

In a more recent study, DiMasi (2001a) concluded that pharmaceutical companies were making quicker decisions on research failures in the 1990s than in the 1980s. For investigational new drugs (INDs) filed in the early 1990s,

the median time to research abandonment decreased 20% relative to the early 1980s. This was measured as the time from IND filing to termination and for IND's filed between 1990 and 1992 reported by DiMasi this was 3.2 years. The different activities used as the start of clinical development (IND filing vs. first human dose) are most likely underlying the longer median time to termination reported by DiMasi. DiMasi (2001a) found that the proportion of terminations in Phase II remained constant during the 1980s and early 1990s with around half of all terminations taking place in this phase. Over the same period of time, an increase in the proportion of NASs terminated in Phase I was observed, with the proportion of NASs failing during late development decreasing.

Late stage terminations impact on the pharmaceutical industry not just in terms of increased R&D expenditure and in relation to the industry's R&D productivity (Drasdo, 2003). Late stage terminations also have an influence on other functions in the industry and on an organisation's culture. When an NAS fails late into Phase III or even during the regulator review, it will have implications for sales force plans as well as additional financial consequences as a result of manufacturing plant investments. Companies participating in Drasdo's survey indicated that following a late-stage termination, many organisations loose confidence in their decision-making systems and often become risk-averse. Externally, late-stage terminations could result in a negative perception of the organisation by physicians, investors and analysts. Apart from the knock-on effect on the stock-market performance of the organisation, this will also have an impact on company morale (Drasdo, 2003). In order to prevent late-stage terminations where possible, it is important to examine in detail why NASs have failed in the past to understand where efforts need to be focused trying to prevent late-stage terminations in the future.

Reason for termination

Information on the primary reason for termination was available for 490 of the 519 terminated NASs included in this study. Clinical efficacy was quoted as the main cause for development failures (32%), followed by 'portfolio considerations' (24%) and clinical safety (20%). Toxicology and clinical pk/bioavailability accounted for only 9% and 7% of terminations, respectively.

Not surprisingly, differences were observed in the termination reason profiles for different therapeutic areas. The two most frequently cited reasons for terminations for almost all therapeutic areas were a combination of the Top 3 reasons overall, 'Clinical Efficacy', 'Portfolio Considerations' and 'Clinical safety'. Exceptions to this general observation were the therapeutic areas 'Musculoskeletal', 'Alimentary & Metabolism' and 'GU & Sex Hormones'. Although for both 'Alimentary & Metabolism' and 'GU & Sex hormones' 'Clinical Efficacy' was the most frequently cited reason, for 'Alimentary & Metabolism' the second-most frequently cited reason was 'Toxicology' and for 'GU & Sex hormones' this was 'Other'. NASs developed for Musculoskeletal indications were most frequently terminated for issues relating to 'Clinical Safety' followed by 'Toxicology'. Out of the other project characteristics investigated (i.e. compound type, origin and novelty mode of action) differences in the termination reason profile were only observed for novelty of mode of action. Not surprisingly, clinical safety was less often a reason for termination for NASs with an established mode of action, where more information and experience already exists.

The prevalent reason for termination in Phase I was clinical safety. The fact that this was not pharmacokinetics/bioavailability, the primary objective for Phase I studies, suggests effective pre-screening prior to the administration of the first human dose. For 135 NASs terminated during preclinical development, pharmacokinetics accounted for less than 10% of failures, indicating that pharmacokinetic issues are being tackled even prior to preclinical development. Almost half of NASs undergoing attrition in Phase II did so for issues relating to clinical efficacy, with a further quarter of failures due to portfolio considerations. In Phase III, clinical efficacy was the reason for termination for the majority of NASs. Although portfolio considerations accounted for only 10% of failures in Phase III, surprisingly half of the eight NASs terminated during regulatory review were terminated for this reason, with a further 25% being terminated for safety concerns. Seven of the eight NASs that failed while under regulatory review were terminated prior to 2001, the year in which Baycol was withdrawn and the first speculations surfaced that the USA Food and Drug Administration (FDA) was becoming more safety conscious, sending more than twenty

products back with request for more data (Shimmings, 2002). It is therefore unlikely that the observations in this study can be related to the changing regulatory environment.

Over the duration of this study, a decline in the incidence of 'portfolio considerations' as the primary reason for termination was observed. In 1998, 'portfolio considerations' was the second-most frequently quoted reason for failure (26%). In 2002, however, 'portfolio considerations' had moved into fifth place, accounting for only nine percent of all terminations in that year. Over the same period of time, an increasing frequency was observed in toxicology related failures. This increase might at least partially be explained by the slight increase in the proportion of the pipeline in development for Alimentary & Metabolism indications observed over the same period of time in the study reported in Chapter five of this thesis. Toxicology was observed to be of relatively more importance as a reason for failure for Alimentary & Metabolism indications than in other therapeutic areas. Further investigation into the therapeutic areas for which the NASs failed for toxicological reasons will be required to assess with more certainty as to whether the increase in Alimentary & Metabolism NASs was driving the observed increase in toxicological failures. Another development that could have contributed to the increased prevalence of toxicology as a reason for drug development failure is the increased complexity of the molecular mechanism targeted and active substance investigated (Kola and Landis, 2004). However, neither this nor the increased focus on Alimentary & Metabolism indications can explain the decreasing frequency of portfolio considerations as a reason for termination. Clinical efficacy was quoted as the primary reason for pharmaceutical development failures throughout the period studied. This observation was supported by other studies on the subject of drug development failures, where clinical or human efficacy was consistently identified as one of the major reasons for termination (Parrish, 1989; DiMasi, 2001a; Drasdo, 2003; Kola and Landis 2004).

The goal of drug development is to develop a product with successful administration and manufacture (low technical risk), safety and efficacy (manageable medical risk), and satisfactory profit potential (acceptable

commercial risk). Actual or anticipated deficiencies in any of these areas should lead to termination of development (Lam, 2004a). DiMasi (2001a) concluded that failures for commercial reasons tend to occur later in the development process than failures for reasons related to safety and efficacy, which is confirmed by the outcome of this study. Technical failures were identified earliest in the process. Scientific failures, including those attributed to toxicology, efficacy or safety issues, were identified next, with the median time to termination being calculated as 2.3 years from 1st human dose. Commercial terminations occurred later in the process, with half of all termination decisions for commercial reasons taken within 2.6 years from 1st human dose. These observations can at least partially be explained by the general process of drug development. Technical risk, including formulation issues, can be assessed relatively early in the process and any potential issues can be investigated prior to clinical development or during the first clinical trials when bioavailability is assessed and dose-finding studies are undertaken. Slightly later in the process, clinical efficacy and safety will become the subject of clinical trials and more information will be gathered to either prove of disprove the theoretical concept of the drug treatment in development. The majority of the information required to assess technical and scientific risk can be obtained internally and is not dependent on external factors. This is not the case however for commercial risks, which are much more complex to assess. In the therapeutic target profile (TPP) information is provided on the target dosing and indications as well as on alternative treatments currently available. Although the first two topics are related to internal factors and can be controlled to a certain level by the company, the third factor is not only outside their control it is also difficult to pre-empt all developments in this area. An additional explanation for the later identification of commercial failures might also be that commercial risk assessment only starts to play a major role once technical and scientific risks have been addressed. Terminations for regulatory reasons occurred latest of all reasons specified, based on median time to termination, in line with the natural process of drug development where regulatory review is the last hurdle to be scaled in order to successfully achieve product launch.

Based on the outcome of this study, several areas have been identified where improvements might be made in order for companies to be able to identify failures earlier. A detailed discussion of these will be provided in Chapter eight.

Timing of the decision-making process

In view of the low success rates in Phase III as described in Chapter six and the impact of late-stage terminations, decision-making in Phase II of the development process was examined in more detail. As with all clinical phases, the median time to completion for Phase II exceeded the median time to failure. This was not surprising, since the time for successful completion was measured as the time from the administration of the first dose in the first trial in that phase to the first administration of the first dose in the first trial in the next phase. As such, it included not only the time to the decision to progress; it also included any additional activities required to achieve the first human dose in the next phase, including study start-up and enrolment of the first patient. Information on two additional milestones, 'decision to develop for full launch' and 'clinical proof of concept', was available for a subset of the data allowing a more detailed investigation of when the decision to progress is made in Phase II compared to the decision to terminate. Based on median cycle times from the start of Phase II, clinical proof of concept was reached only slightly earlier than the decision to develop for full launch (1.4 years and 1.5 years, respectively). The decision to terminate was taken slightly later in the process, around 1.7 years after the administration of the first patient dose (i.e. the start of Phase II). Although not supported by statistical analyses, the information does not contradict the theory that companies are focusing on obtaining proof of concept prior to progressing to full development for launch. One scenario that could describe the observations made involves companies putting a time limit on achieving clinical proof of concept. If the theoretical concept is proven with clinical data prior to this time limit, the decision to start Phase III is made almost immediately. If clinical proof of concept is not obtained within the time limit, which could be coupled to a set internal review point such as a meeting of the decision-making committee, further development will be abandoned. Data from Drasdo (2003) on the settings within which decisions to terminate are made suggest that the above scenario is not unlikely to occur within pharmaceutical companies. Seven

of the 17 companies included in Drasdo's study indicated that they combine event-based decision making with formal meetings at set points in the year. However, the current observations were made on median cycle times based on NASs for which at least one of the investigated milestones was available. For more solid conclusions to be drawn, a detailed investigation of individual NASs is required, taking into account only those NASs where all relevant milestones are available as well as the reason for termination. Only than can conclusions be drawn with regards to the timing of the decision-making process in Phase II with more confidence, taking into account the different processes that might be involved for scientific and commercial failures.

Chapter eight of this thesis will continue this discussion, including an assessment of the effects of different attrition strategies on R&D efficiency. It will correlate the outcome of this study with the outcome of the studies reported in Chapters 3-6 to evaluate the current status of pharmaceutical R&D efficiency and productivity.

SUMMARY

- In this study, data on clinical development failures between 1998 and 2002 from a cohort of 28 companies were investigated in detail.

- Of the 519 NASs terminated, 38% of terminations took place in Phase I, 46% in Phase II, 14% in Phase III and 2% during regulatory review. Half of all terminations took place within 2.4 years of the administration of the first human dose, which was taken as the starting point for clinical development in this study.

- 'Clinical Efficacy' was quoted most frequently as the primary reason for termination (32% of all terminations), followed by 'Portfolio considerations' (24%) and 'Clinical safety' (20%). The incidence of 'Portfolio considerations' as the primary reason for termination decreased from 26% of NASs terminated in 1998 to 9% of NASs terminated in 2002.

- The median time to termination was significantly longer for "other" companies (2.6 years) than for "major" companies (2.2 years). No significant differences were observed for the median time to termination by therapeutic area, compound type, origin and novelty of mode of action.

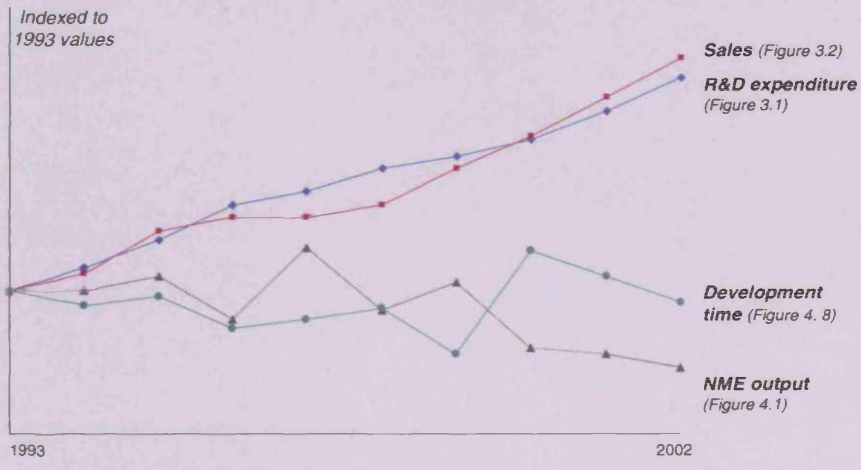
- The findings of this study suggest that companies are focussing on obtaining proof of concept prior to progressing to full development for launch.

CHAPTER EIGHT

GENERAL DISCUSSION

The main reason for undertaking this study was the observed decline in the number of new products reaching the market during the early and mid-1990s against a background of dramatically increasing R&D expenditure (MacFarlane, 1998) leading to wide spread speculation about the sustainability of the industry as it has existed over the past few decades (Brown and Allport, 2003; Malek and Kager, 2003; Arndt, 2004; Booth and Zemmel, 2004; Fraser, 2004; Tufts CSDD, 2004). The outcome of this study revealed that the gap between R&D investment and output continued to widen into the 21st century (Figure 8.1). Over the period 1993-2002, R&D expenditure increased with more than 75%, whereas the number of new molecular entities (NMEs) reaching the market declined by almost 25%. Some have suggested that any concern about the industry's productivity is exaggerated since the industry is still performing with

Figure 8.1 Trends in pharmaceutical sales, R&D expenditure, NME output and development times, 1993-2002



growth in global sales exceeding that of R&D expenditure over the ten-year period investigated (Walton, 2000). However, due to lengthy development times (~11 years) as well as the time from first launch to peak sales ('longevity', ~14 years), today's sales performance is an indicator of the strategy and processes as far back as 20-25 years ago (Schmid and Smith, 2004; Ansell, 2000). In order to get a better view on the industry's current performance, today's investment and strategies were investigated in this study.

Historically, R&D expenditure has been a relative consistent proportion of sales. However, the outcome of this study suggests that the proportion of sales

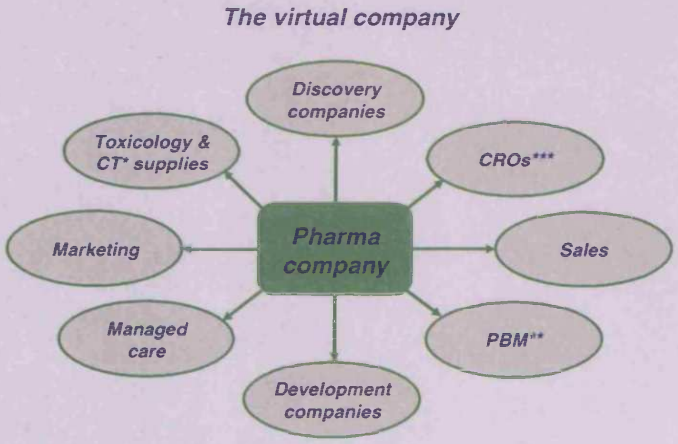
revenue that is re-invested in R&D has declined from 1998 to 2002; a trend that was most pronounced for "major" companies (i.e. those spending over US$ 1bn on ethical pharmaceutical R&D expenditure). As discussed in Chapter three, a potential driver for this could be that companies are reducing R&D expenditure in order to meet shareholders expectations of profit margins. If this development is the result of moving away from setting R&D budgets as a fixed percentage of sales in favour of basing it on the resources required to develop the current development pipeline and support ongoing discovery activities, then this could be a positive move towards improving productivity. However, if the percentage is merely diminished for the sake of increasing profitability, without improvements in efficiency, it could be a potential recipe for disaster.

In Chapter one it was indicated that through more extensive use of external resources, companies might be able to improve their efficiency. Partnerships, licensing and outsourcing can lower risk and volatility and at the same time provide access to resources, skills and expertise not available within the organisation itself (Grabowski, 2000; Gilbert *et al.*, 2003; Lam, 2004a). The outcome of this study indicated that companies are tentatively moving away from the more traditional business model of a fully integrated company, in which all activities from discovery through to marketing are undertaken by themselves, towards a model in which a company will take on more of a "network integrator" role, developing a number of external relationships with organisations dedicated to segments of the process or specific disease areas or technologies. For example, this can be done through alliances with academia and dedicated discovery organisations in research, or through the outsourcing of clinical trials and sales activities.

Ashton (2001), indicated that there were two approaches to the function of such an external network in relation to the in-house organisation. As a long-term strategy, companies can focus investment externally and develop external relationships in preference to incorporating new technologies in-house. Alternatively, an external network can be used as a short-term means of accessing and evaluating new technologies until companies are able to 'catch-up' and the technology is fully integrated into in-house R&D processes. Taking

the first option to its extreme could lead to the transformation into a virtual company: an organisation coordinating the activities of others to facilitate the R&D of new medicines, but that does not undertake any actual R&D activities itself (Figure 8.2; Cavalla, 2003). The outcome of this study indicated that pharmaceutical companies still allocate the majority of their R&D budget to in-house activities suggesting that participating companies are not as yet making this transition. Some companies are applying this long-term strategy to parts of their processes. For example, Wyeth has recently signed a ten-year contract with Accenture for the latter to take on all clinical data management services, thereby taking advantage of Accenture's expertise in managing large scale transaction processing centres (Lam, 2004b).

Figure 8.2 Graphical representation of a virtual company



*Source: E Mario (1995). *Clinical trial supplies; ** Pharmacy benefit manager; *** Contract Research Organisations.*

Outsourcing can be advantageous for an organisation for diverse reasons and can be used both as a short-term solution as well as more strategically (long term view). Outsourcing provides companies with the opportunity to reduce their critical mass to a base level below that of the maximum workload, taking up the services offered by contract research organisations (CROs) when more resources are required during 'peak times'. The complexity and priority of clinical trials is another driver behind companies' approaches to outsourcing. Some companies outsource more routine trials that are not on any critical path and do not require specific expertise, freeing up internal resources for the more complex and business critical trials and thereby keeping most of the risk in-

house. Other companies turn to service-providing organisations especially for their experience and the fact that they do not have a vested interest in the outcome of a trial. As such, they have no incentive to shape its outcome (Albert Grignolo in Lam, 2004a), something that internally can be an issue with questionable clinical data unintentionally being overlooked because there is such a drive to deliver positive results (Schmidt and Calantone, 1998; Christoph Hergersberg in Lam, 2004a).

When companies are under pressure to perform, line extension products can produce short term gain, since their development requires relatively less investment than the development of new molecular entities. The outcome of this study showed that the percentage of R&D investment in line extensions has stabilised over the last five years, following an initial increase in the mid-to late 1990s (van den Haak, 2002). Some R&D directors believe that life cycle management could deflect attention from innovative R&D (Lam, 2004b), although they recognise the importance of maximising revenue potential by optimising the in-market potential for given indications as well as developing existing products for additional indications (Anon, 2004r). The effort invested in this short term gain should always be balanced against the resource requirements for the development of new medicines (long term gain)

Similarly, the use of alliances, licensing and outsourcing should be applied strategically and balanced against in-house capabilities, taking into account the potential consequences of a high dependency on other companies and service providers. For example, many biotechnology companies started as dedicated drug discovery organisations, relying on pharmaceutical companies to take on development and marketing; a partnership that was beneficial for both parties involved. However, many biotechnology companies have now made the transition towards becoming more integrated, being able to undertake both research and development activities, often competing with the more traditional pharmaceutical companies. If the pharmaceutical companies would have been wholly reliant on biotech companies to obtain access to these types of technologies, this could have become problematic for the industry since it has proven to be a valuable source for potential new medicines. However,

pharmaceutical companies have been working towards integrating biotechnology in-house, frequently through acquisition of biotech companies, for example the acquisition of Centocor by Johnson & Johnson and the connection between Genentech and Roche (Johnson & Johnson, 1999; Roche, 2004).

Each organisation and each project is unique and requires tailor-made decisions as to the internal and external development options available, driven by scientific and technological complexity, priority, internal capability and company strategy. As such, the benefits of employing the above described "building blocks" in improving efficiency and revenue potential will differ per company. The outcome of this study indicates that companies are making selective use of alliances, outsourcing, licensing and life cycle management, suggesting that they employ these options strategically where relevant to their situation.

The cost of bringing a new medicine to market has increased considerably over the last three decades (Parexel, 2004), with recent estimates ranging from US$ 0.8bn (DiMasi *et al.*, 2003) to US$ 1.5bn (Gilbert *et al.*, 2003). An increased clinical workload has been suggested as one of the drivers for this upward trend. However, despite the industry's perception that the number of subjects in pivotal trials included in submission dossiers has increased (McAuslane and Anderson, 2003), there is no conclusive evidence of any such trend in recent years. Moreover, the latest data from CMR International demonstrates a decline in the median number of subjects per dossier between 1995 and 2003 (McAuslane and Anderson, 2003). Nonetheless, the outcome of the present study suggests that it is the cost per clinical candidate that is underlying the continuing increase in R&D expenditure, since no increase was observed in the number of new active substances (NASs) in development and the proportion of line extension expenditure has remained stable.

In relation to overall development time, the outcome of this study showed no significant changes between 1993 and 2002. However, it was found that "major" companies were significantly quicker in bringing new medicines to market than smaller companies – a gap that widened over the period studied (1993-2002)

due to "major" companies bringing products to market quicker and development times for new medicines launched by "other" companies lengthening. Could this be an indication that an economy of scale exists for the overall R&D process? It has been recognised that a larger size (in terms of R&D budget) can be advantageous in clinical development, marketing and distribution, but not necessarily in research (Ashton, 2001). The availability of more resources increases an organisation's flexibility and allows for short-term prioritisation of projects when issues or opportunities arise, without having to halt other projects in development. The larger volume of the pipeline also provides "major" companies with an increased opportunity for collective learning. For example, the regulatory department of larger companies will have more experience in composing submission dossiers and perhaps also better contacts with the regulatory authorities. However, the advantages of smaller organisations in research and early development have been recognised by "major" companies as illustrated by the organisational structures of Pfizer and GlaxoSmithKline. In 2001 GlaxoSmithKline announced the restructuring of its research function into a collection of biotechnology sites which compete with each other and external biotechnology companies to supply compounds into a centralised development organisation whereas Pfizer operates as a collection of medium-sized, fully integrated, semi-collaborative pharma sites (Schmid and Smith, 2004; Piling, 2001). It should be noted that the calculation of overall development time does not distinguish between self-originated compounds and those that were licensed-in. As such, the observed decrease in development times for "major" companies could partially be a reflection of successful licensing-in practices.

The improvements in development times for "major" companies could demonstrate that there has been an effect of the industry's effort to improve R&D efficiency, although other factors, such as increases in both R&D FTEs and expenditure will also have impacted on development times. The question remains however what the overall effect was on the performance of this cohort of companies. Responsible for over 60% of global pharmaceutical R&D expenditure, the 14 "major" companies only launched 41% of all new medicines reaching the market between 1993 and 2002. However, the number of new product introductions should not be the only parameter to judge performance

and it could be argued that "major" companies are developing bigger products in terms of peak sales values, as suggested by the fact that 42 of the 50 best-selling prescription drugs in 2003 were marketed by companies spending US$ 1bn or more on ethical pharmaceutical R&D in 2002 (Anon, 2004s).

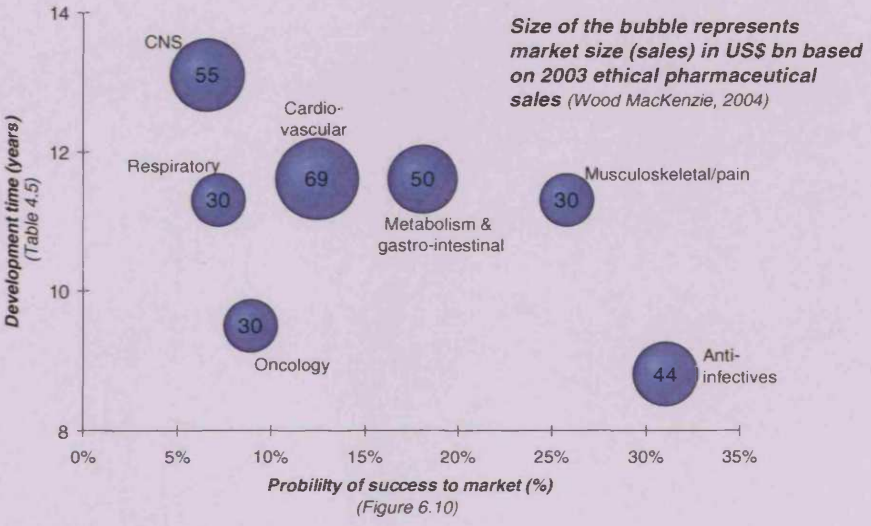
With clinical pipeline sizes and development times static, it could suggest that the main driver for the decline in output is to be found in attrition. Based on NASs entering clinical development during the 1980s, DiMasi (2001a) reported success rates to approval between 20-23%, declining to 17% for NASs entering clinical development in the early 1990s. Although slightly different inclusion criteria and methodology were applied in the present study, the outcome does support a continued decline in success rates during the 1990s, with only one in ten NASs expected to reach the market based on NASs entering clinical development between 1997 and 1999. However, the most recent success rates calculations demonstrated a minor improvement in late-stage success rates, which is suggested to continue based on the decreasing proportion of terminations in Phase III and the regulatory review stage.

Many reasons have been suggested for the declining success rates, including an increased focus on the development of treatments for chronic and more complex diseases, additional cost-effectiveness demonstration over and above existing safety and efficacy requirements, as well as a shift from a purely medically-driven decision-making process to also include commercial value as a criterion for project selection (Engel, 2000; De Visser, 2003; Anon, 2004a; Schmid and Smith, 2004). According to a recent White Paper from the USA Food and Drug Administration (FDA, 2004) one of the contributing factor is the fact that the applied sciences needed for product development have not kept pace with the tremendous advances that have been made in the basic sciences. The path to market even for successful candidates is long, costly and inefficient, due in a large part to the current reliance on cumbersome safety and efficacy assessment methods. The FDA specifies that there is an urgent need for a new 'product development toolkit' containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and efficacy, and new clinical evaluation techniques, to improve

predictability and efficiency along the critical path from laboratory concept to commercial product (FDA, 2004; Charles River Associates, 2004).

In this study, significant differences between therapeutic areas were demonstrated in clinical success rates and development times, as well as pipeline composition in terms of the proportion of biotechnology-derived, licensed-in NASs and novel NASs (Figure 8.3). Additionally, the potential market size differs per therapeutic area, with the three biggest areas being Cardiovascular, Central Nervous System (CNS) and Anti-infectives (US$ 69bn, US$ 55bn and US$ 44bn, respectively; Wood MacKenzie, 2004).

Figure 8.3 Therapeutic area differences



n = market size for each therapeutic area based on 2003 ethical pharmaceutical sales in US$ bn. For example, in 2003 global ethical pharmaceutical sales for CNS products amounted to US$ 55bn.

This variation is in part due to the intrinsic differences between therapeutic areas, requiring specialist skills and knowledge which are not easily transferable between areas. It could therefore be postulated that some of the benefits of company size is lost when this is spread over many therapeutic areas. One potential strategy that companies could apply to improve productivity would be focusing on a limited number of therapeutic areas, building expertise in these areas and either relying on an external network for development activities in other therapeutic areas, or by divesting potential candidates in other areas. This theory is supported by the fact that companies that have concentrated on a limited number of therapeutic areas have registered the greatest growth in

health-care revenue in 2002 (Truelove, 2003). Companies can use the differences between therapeutic areas to their benefit by balancing high risk, high return areas against areas with lower attrition rates. For example, the therapeutic area "Nervous System" has lower success rates and longer development times than any other therapeutic area, but its market size is such that it is still an attractive area for development, as illustrated by the high number of NASs in development for indications in this area. However, it is important to spread the risk by balancing these high risk projects with other projects with more predictability and lower risks, e.g. Anti-infectives.

Many pharmaceutical companies have indicated that they are looking to develop treatments that will meet unmet medical needs. With high barriers to market entry for medicines with an established mode of action and the potential synergies from novel medicines in combination with existing products, it seems therefore reasonable to expect an increased focus on the development of NASs with a novel mode of action. In this study, innovation has been investigated in terms of the novelty of the pharmacological mode of action during development as well as the proportion of new medicines that reached the market as the 1st or 2nd in their class. The outcome of this study does not reveal any such increase; rather it demonstrates a relatively stable situation over the ten years investigated (1993-2002) and any observed differences appear to be fluctuations around this constant proportion (one-third of new product launches), suggesting that the relationship between commercial value and innovation might not be as straightforward as was suggested. Historically, much of the industry's value creation has not come from first-in-class medicines against new targets, but from follow-on products that improve the efficacy or reduce the side-effects of existing compounds. The main reason for this is that follow-on products are able to differentiate themselves through improved clinical strategies, knowing the 'weaknesses' of the active substances that reached the market first (Booth and Zemmel, 2003). This value generation combined with the relative low risk of developing products based on an existing mode of action provides a logical argument in favour of the development of 'non-novel' active substances in addition to innovative medicines. However, in order to turn a follow-on product into a commercial success a large marketing effort is required,

resource for which is available within "major" companies, but not always in smaller organisations. This might explain the increased proportion of novel NASs in development by these companies. Innovation is still important to meet unmet medical needs, but the above demonstrates that value can be generated from developing follow-on compounds (Baker and Gill, 2005).

Since the introduction of the first product of biotechnology, Eli Lilly's Humulin (recombinant human insulin), in 1982 (Ashton, 2001), the expectations of this new technology were high with some believing that it would be able to make up the shortfall in the industry's new product output (Drews, 1998b). The outcome of this study demonstrates that biotechnology has contributed considerably to the industry's output during the 1990s but that this was not sufficient to counter the effect of the declining number of chemical entities reaching the market. Even more, in recent years, the contribution of biotechnology to the industry's output appears to have been reduced, with only 10-15% of new medicines introduced in 2002 and 2003 derived from biotechnology. This seemingly disappointing performance might partially be due to unrealistic expectations. Although delivering promising candidates, these still have to go through the same lengthy and costly development process. Pipeline data for the period 1998-2002, suggests that biotechnology will continue to make a contribution to the industry's output, albeit in a different format than in the last decade. It was found that companies are in-licensing biotech products at much later stages in the development process, leaving more of the development to the increasingly mature biotechnology industry.

The findings of this study show changes in pipeline distribution with relative more NASs in Phase I and fewer in Phase III in 2002 compared to 1998. Could this be due to decreasing quality of clinical candidates, or is it a reflection of a change in the industry's attitude towards project selection, identifying failures earlier to decrease the number of costly late-stage terminations? The observed decrease in the number of phase III terminations suggests the latter, with companies making the decision to terminate earlier.

According to Kola and Landis (2004), examination of the causes as to why compounds undergo attrition in the clinic is instructive and helps in the identification of strategies and tactics to reduce these rates and thereby improve efficiency of drug development. There are many approaches that can be taken to managing the risk in pharmaceutical R&D. It is a delicate balance between caution, cost-savings and the development of as many high-value products as possible. There are two extremes in this: (1) companies can terminate everything unless there is a valid reason to progress or (2) companies can progress everything unless there is a valid reason to terminate. The first approach would result in cost being kept at a minimum and only those compounds that have been proven to contain a real promise would be taken into development. However, with this approach the risk of terminating of a project that would have been successful is extremely large as well as that it would eliminate any 'chance' discovery. Late-stage surprises such as the blockbusters Prozac (fluoxetine) and Lipitor (atorvastatin) would not have been discovered if this approach was applied at all times (Lam, 2004a). The wrongful termination of successful projects is a much smaller issue with the second approach, but the downside of that approach is the high cost of investigating everything that has the slightest chance of making it to market.

The focus should be on correctly identifying failures as early as possible to maximise the cost-effectiveness of developing successful ethical pharmaceuticals. The key question throughout is what is the right balance between obtaining more information and the expenditure and resources required to do so. More, and more reliable information will become available with further development activities, enabling a better-informed decision to be made over the viability of the NAS. However, further development activities will require further allocation of resources, decreasing the efficiency of the R&D process. The two attitudes to project selection can be applied at every phase when the decision is to be made whether the active substance is technically, medically and commercially viable based on the evidence available at that moment in time. The approach taken can vary by company and by stage (Carbonell *et al.*, 2004). For example some companies might take everything into the clinic for which there is no reason to terminate, but will only progress

NASs from Phase I to Phase II if it has proven to be viable. Other companies might put this 'hurdle' later, e.g. at the end of Phase II, or earlier, e.g. at the end of preclinical development. It is unlikely for one company to apply one extreme throughout the development process. Thus the question becomes where a company should apply the most stringent selection criteria for continuing development.

The first hurdle investigated was one placed at the end of preclinical development. Companies were grouped into four cohorts based on the number of NASs taken into man, normalised by R&D expenditure to minimise the influence of company size. Interesting observations were made for the cohorts of companies based on the normalised number of NASs taken into man. The median time to termination was shortest for those companies taking the most NASs into man compared to their company size, supporting the theory that these companies place their major hurdle later in the process rather than at the end of preclinical development. The outcome of this study suggests that a high hurdle at the end of the preclinical stage could lead to improved efficiency. It could be argued that the high success rates to market (24%) for the cohort of companies taking the smallest number of NASs into clinical development is born out of necessity since there will only be a limited number of NASs in the pipeline. However, these NASs have to fulfil the same safety and efficacy requirements and therefore be of similar or better quality. The low number of terminations for this cohort of companies, as well as the cohort of companies taking the most NASs into clinical development, suggests that these cohorts mainly consist of smaller companies, potentially influencing the outcome of the analyses.

The second hurdle that was investigated was placed at the end of Phase I. Success rates from 1st human dose to first patient dose were taken as a surrogate marker of the attitude towards attrition at the end of Phase I. A negative correlation between the height of the hurdle at the end of Phase I and overall R&D efficiency is suggested by the outcome of these analyses. The cohort of companies with the highest success rates from 'first human dose' to 'first patient dose' (i.e. lowest hurdle) demonstrated the shortest development

times and higher overall success rates. These findings suggest that it might be beneficial to approach decision-making at the end of Phase I with the attitude to progress unless there is valid reason for termination has been identified.

The third hurdle investigated was the amount of effort that companies put into clinical Phase II, as a surrogate measure for requiring clinical proof of concept prior to progressing to late development. Based on the assumption that more effort would result in longer phase II cycle times, companies were grouped into three cohorts. The highest probability of success was observed for the cohort of "slow" companies. However, it was also for this cohort that the longest development times were demonstrated. For "medium fast" companies, overall success rates were only slightly lower (13% vs. 15%), whereas clinical cycle times were considerably shorter (4.5 yrs vs. 7.0 yrs), suggesting that there is an optimum in the duration, and by extrapolation the amount of effort, to be invested in Phase II. In other words, investing a reasonable amount of effort in Phase II prior to progressing through to Phase III is beneficial, but either too much or too little effort (i.e. duration) in Phase II decreases an organisations overall R&D efficiency.

In the past, the drive to speed up drug development has led to some companies undertaking Phase II and III studies in parallel. Although this will have had advantages for the duration of clinical development, it does mean that costly Phase III studies are initiated with less information available to make a well informed decision about the scientific, technical and commercial viability of the project, potentially resulting in unnecessary late-stage terminations. It might be better to focus on overall productivity improvement taking into account cost, cycle times and success rates. Part of this effort to improve productivity is the undertaking of more intensive and constructive Phase II trials, focused on obtaining clinical proof of concept prior to making the decision about progressing to full development for launch. Although this increases the workload, duration and cost of Phase II, the outcome of this study suggests that it increases late-stage success rates, which will improve return on R&D investment and bring treatments to patients sooner (FDA, 2004).

Throughout this discussion it has become apparent that decision-making plays a key role in improving pharmaceutical R&D productivity; not only decisions regarding the selections of projects for development, but also in relation to how development will be undertaken (e.g. in-house vs. externally). Historically, the common situation would be for the R&D director to make the majority of such decisions. However, it has been recognised that better results can be obtained through the use of more sophisticated processes involving all relevant functions (research, development, regulatory and marketing). By involving all parties in the design of a target therapeutic profile (TTP) early on, in which clear requirements for go/no go decisions are specified in terms of safety, efficacy and commercial value, all R&D activities can be focused towards meeting these criteria and clear and objective decision-making is facilitated (Vose, 2001).

Based on the outcome of this study, several areas have been identified where improvements might be made in order for companies to be able to identify failures earlier and which affect the decision-making process. With the majority of drug development failures attributed to concerns around clinical efficacy it seems obvious to suggest an increased effort towards obtaining proof of efficacy earlier in the process; for example through the application of translational medicine or by undertaking human Phase 0 studies, i.e. early assessment of drug metabolism in humans through the administration of micro-doses (Lappin and Garner, 2003; Mankoff *et al.*, 2004). Additionally, this might be achieved through the development of better animal, *in vitro* or *in silico* models to predict clinical efficacy or to undertake trials focusing on demonstrating clinical efficacy earlier in the clinical development process (FDA, 2004; Kola and Landis, 2004). However, some critics have indicated that the many late-stage terminations due to efficiency issues might have been averted by the addition of more dose-response studies in Phase III (Temple, 2004), although this would add substantially to the already expensive process of drug development.

The traditional clinical development process consists of three phases (Spilker, 1994):

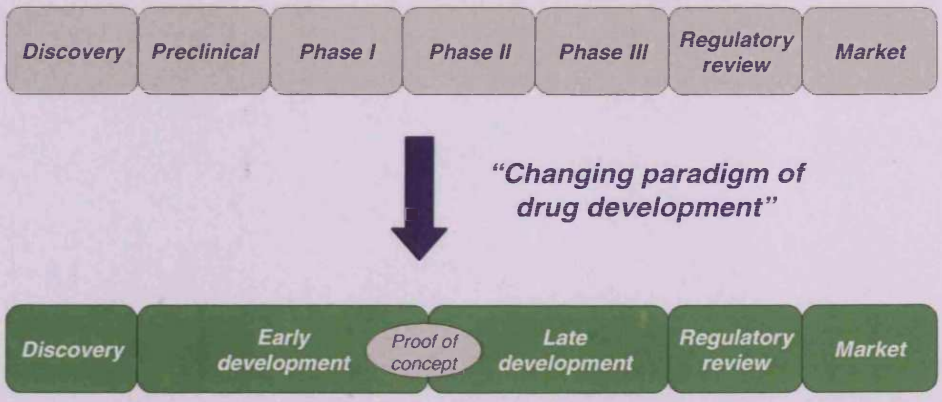
- Phase I in which initial safety trials are undertaken, usually conducted in

healthy volunteers;

- Phase II, in which clinical trials are undertaken to evaluate efficacy (and safety) in the intended patient population;
- Phase III, in which large scale clinical trials are undertaken in the intended patient population to generate further evidence of safety and efficacy, including comparative safety and efficacy.

In this model, most issues regarding clinical efficacy do not come to light until late into Phase III, the most costly of all clinical phases (Sculthorpe and Ogg, 2003). Late stage development failures, and the associated impact on cost, R&D productivity, organisational culture and external perceptions of the organisation (Drasdo, 2003), have led to a shift in the drug development paradigm, with companies moving away from the traditional three-phase model to a model consisting of two stages: early and late development, with clinical proof of concept marking the transition point between the two stages (Figure 8.4). The idea behind this two-stage model is to obtain clinical proof of concept both in terms of efficacy and safety as well as generating evidence for commercial viability, in the first phase (early development) prior to starting activities for the full development for launch, including the large safety and efficacy trials that traditionally were part of Phase III (Vose, 2001; Anon, 2003e). The main difference between the traditional Phase III trials and clinical trials during late development can be found in the focus of the studies.

Figure 8.4 Changing drug development paradigm



Traditional Phase III trials are undertaken to prove the active substance's efficacy and safety, whereas late-development trials ('confirmatory studies')

focus on obtaining large-scale confirmation of clinical efficacy and safety data already identified on a smaller scale during early development ('exploratory development'). Key to preventing late-stage terminations is approaching drug development as a risk management exercise (Lam, 2004a) by identifying the potential risks associated with the specific characteristics of the NASs in development as well as the intended indication early on, based on previous experiences. The identified risk areas should then be used to design a development programme for that specific project. For example if there are concerns around bioavailability based on earlier failures of similar types of compounds for this reason, the question of bioavailability should be addressed much earlier than in clinical trials (Kola and Landis, 2004, De Visser, 2003). This could be done in several ways, such as by extending existing preclinical studies or by developing and undertaking specific cell-studies to identify whether there is sufficient reason to believe that bioavailability will not be a limiting step for the development of this NAS. As with all measures put in place to identify failures earlier, the advantages and disadvantages of the precaution will need to be balanced against the advantages and disadvantages of the more traditional approach. For example, the cost of designing and undertaking additional preclinical studies may outweigh the projected cost of failure during clinical development.

A second area where improvements can be made relates to commercial failures. As observed in this study as well as by DiMasi (2001a), commercial reasons tend to occur later in the development process than technical or scientific reasons. The complexity surrounding commercial failures becomes apparent when listing the factors that are to be taken into account. Information is required on the scientific profile of the product in development as well as on currently available treatments for the intended indication and patient population. Additionally, information is required on products currently in development by other organisations and the impact this might have on the potential commercial value of your product. Both internal and external factors can change during the development lifetime of a product when more, and more reliable, information becomes available. However, this level of complexity does not mean that there is nothing companies can do to try and pre-empt late-stage commercial failures.

Alignment of research, development and marketing functions much earlier in the development process is one of the actions that can be taken. Tufts CSDD (2001) reports that senior industry executives have suggested that marketing and sales groups should join the product development team two to three years before product launch, whereas Kola and Landis (2004) suggest that all three functions should be involved from as early as discovery onwards. Involving marketing and sales groups earlier will not only have the obvious benefit that risks and issues specifically related to sales and marketing will be taken into account at an earlier stage, it also results in the involvement of individuals in the decision making process who have been less involved in the very early stages of discovery and development and who will therefore have less of a personal 'relationship' with the product, thereby facilitating a more rational approach to decision-making (Lam, 2004a).

STUDY LIMITATIONS

The finite time available for each of the studies that have contributed to this thesis has obviously imposed limits to what has been possible to achieve. Naturally, given additional time, the findings of each study could be expanded. Some suggestions towards this are given below.

The main criticism of the studies reported in this thesis is the under representation of small companies in the data sets. Therefore when utilising the data to investigate company strategy it should be taken into account that the data sets are mainly based on data from large and medium-sized companies and that the incentives, and thus their strategies, could be different for smaller companies. Similarly, Japanese companies were less represented in the data sets in favour of USA and European companies (based on location of corporate headquarters). However, for each of the studies, the cohort of participating companies represents the majority of global pharmaceutical R&D expenditure. As such, the actions of participating companies will shape developments in pharmaceutical R&D and are therefore representative of the pharmaceutical industry for the purpose of investigating industry trends.

In this thesis, the influence of characteristics such as therapeutic area and compound type on company and industry performance has mainly been assessed in isolation. The relationship between the different characteristics have not always been assessed, leaving questions unaddressed such as '*to what extent is the higher proportion of licensed-in compounds in biotech driving the higher success rates for this type of compound compared to chemical entities*?' and '*Did the relatively high proportion of biotech NASs in the therapeutic area 'Alimentary & Metabolism' contribute to the rise in success rates in this area?*'. However, the investigation of the influence of single characteristics provides insights into the complexity of pharmaceutical R&D and enables companies to translate the industry trends into performance metrics relevant for their portfolio.

As part of the study of pharmaceutical R&D expenditure and sales (Chapter three) an assessment was made of company's vulnerability to loss of income from patent expiration due to generic competition. There are several limitations to this assessment. First of all, it does not take into account pipeline activities, such as line extensions or promising new late-stage projects currently in development. Secondly, it takes a snapshot of the situation as it was in 2002. In this fast moving industry, today's picture could be completely different from the one examined in this study. The third factor to be aware of is that it is a relative rather than an absolute assessment. Despite these limitations, it is believed that this model is of value to companies in assessing their relative vulnerability to loss of income due to generic competition, providing an early warning sign if their income is becoming too dependent on a limited number of products or on older products.

A weakness of the study of the global ethical pharmaceutical development pipeline is the limited availability of information on the novelty of the mode of action of NASs in development. Based on the different levels of complexity in obtaining confirmation of novel or established mode of actions it was deduced that the data might be slightly skewed towards NASs with an established mode of action. However, it is unlikely that this has changed over time, enabling the

use of the available data to examine trends over time with reasonable confidence.

The future output predictions reported in the study of clinical success rates and their consequences (Chapter six) were based on current R&D practices only, and do not take into account any increase in the number of NASs in development resulting from in-licensing activities. The future output predicted by this model has already been shown to be reasonably accurate in the short term. For 2003, the model predicted that the 34 participating companies would launch a total of 17 NASs. A recent study by Read and Sculthorpe (2004) found that of the 26 NASs reaching the market in 2003, 18 NASs were marketed by this cohort of companies. It should be noted that with increasing time between the year for which the prediction is made and the year in which the prediction was made, the accuracy of the model is likely to decline, since there will be more opportunity for changes in any of the three parameters used to predict future output. Although it is unlikely that R&D practices will remain constant over time, it is believed that with this model predictions can be made as to what the future output might be if no changes are made. Furthermore, it enables an early assessment of the impact that any proposed changes might have in terms of the number of NASs reaching the market, assisting pharmaceutical companies in setting targets and deciding on company strategy.

The simulated future output predictions described in this study relate to theoretical situations, in which only one or two parameters have been changed at a time. These situations are unlikely to happen in real life, since a change to one of the parameters will usually have an effect on the other two, e.g. increasing the number of NASs in development might lead to an increase in cycle times due to capacity restrictions. However, it is believed that the approach taken in this study provides valuable insight into the extent to which the three metrics (success rates, cycle times and pipeline size) might impact on future output enabling companies to focus their efforts in improving output where this is likely to have the most effect.

One of the main criticisms of the study of clinical development failures (Chapter seven) related to the reasons behind termination decisions. The decision to advance or halt the development of pharmaceutical products is a complex process and is rarely clear cut (Lam, 2004a). Although the information that can be derived from investigating the primary reason for termination, as undertaken in this study, will support general observations and conclusions in this area, this approach could be perceived as a simplification of the truth. The current study does not allow full insight into situations where a combination of factors contributes to the decision to terminate, for example in a situation where clinical efficacy can only be proven for a smaller patient population than specified in the original therapeutic target profile. The smaller patient population might have implications for the predicted economic value of the active substance to such an extent that further development of the NAS is no longer commercially viable.

The study of clinical development failures (Chapter seven) included an assessment of the relationship between attrition and R&D efficiency. To enable the analysis of different approaches that companies can take without compromising the confidentiality of the data, companies were grouped into cohorts. These cohorts were based on single observations over a five-year period and did not allow for any changes over time in companies' approaches to be taken into account. Furthermore, the different time frames for each of the metrics investigated do not allow conclusions to be drawn from comparing across metrics. For example overall clinical success rates cannot directly be translated into the number of NASs required for launch, since different time periods are used in each analysis. However, it is possible to compare one metric across the different company cohorts. Further investigation is recommended to determine the validity of the assumptions made and to support any detailed interpretation of the data. Although it is arguable whether the single data points used as criteria for the company cohorts accurately reflect the complexity of the decision-making process under investigation, the outcome provides an insight into what relationships might exist between attrition and efficiency and can be used as a basis for discussion and further exploration of this subject.

The outcome of this unique study should be taken as a fascinating first endeavour to unearth the complex relationship between attrition and R&D efficiency and the actions that companies can undertake to influence this to their benefit. The outcome of this and other parts of the thesis is intended to fuel discussions within the industry as well as with external stakeholders, leading to a greater understanding of the risks and issues involved in drug development and ultimately to a higher degree of control over pharmaceutical R&D efficiency and productivity.

FURTHER STUDY DEVELOPMENT

Given that the topic of pharmaceutical R&D productivity is likely to remain a key issue for the foreseeable future it would be advantageous and beneficial to annually repeat the surveys used in this thesis to continue to monitor the industry's R&D performance. Indeed, 2003 data has already been collected for each of the studies and the survey of the global ethical pharmaceutical development pipeline has recently been sent out to initiate collection of 2004 data. It is suggested that the content of each of the surveys is continuously monitored against industry developments to ensure that the data collected continues to be a relevant reflection of industry's R&D practices.

To be able to investigate all aspects of R&D productivity, it is recommended to add two more dimensions to the studies included in this thesis. Firstly, data on the actual resources ($ and full-time equivalents (FTEs)) per new active substance would provide more detailed insight into the input side of the efficiency equation than the current expenditure data can provide. Secondly, data on the commercial value, either estimated or actual, would complete the information required to accurately assess R&D productivity, taking into account both the quality and the quantity of the output produced per unit of input. It is recommended that an initial investigation into the current availability of these types of data is undertaken to identify the most appropriate and cost-effective way to obtaining this information.

Furthermore, the relationship between metrics should be investigated in more

detail. A start has been made in studying the relationship between the duration of clinical phases and success rates, which can be extended to include pipeline size and composition as well as cost and value measures recommended to be collected above. Similarly, it is suggested to investigate the relative influence of characteristics such as therapeutic area, compound type and origin on company and industry performance through factor analysis, which can be used to study the patterns of relationship among many dependent variables (Darlington, 2005). In addition, a number of further developments for each study are as follows:

For the study of pharmaceutical R&D expenditure and sales (Chapter three) it is suggested to investigate to what extent companies are utilising alliances, outsourcing and life cycle management to increase productivity. In this study, expenditure patterns were investigated for each of these three options in isolation. Investigating the combined expenditure patterns for individual companies could provide insight into their overall strategic direction. Additionally, effort should be made to improve the participation of companies across years to enhance the consistency of the data enabling trend analyses on a larger population.

It is recommended that the scope of the study of NMEs launched onto the world market (Chapter four) and that of the global ethical pharmaceutical development pipeline (Chapter five) be extended to include major line extension activities. The definition of line extension projects and products and other inclusion criteria should be developed in collaboration with the industry to ensure that they are realistic and clear descriptions of today's practices against which consistent and high quality data should be provided. Furthermore, for the study of pipeline activities effort should be made to obtain more complete data on the novelty of the mode of action by entering into dialogue with participating companies to identify the reasons for low data provision and collaborate with them to address these reasons.

In the study of success rates (Chapter six) a model was presented to estimate future output based on recent current industry success rates, cycle times and pipeline volume, which does not take into account the impact of characteristics

such as therapeutic area, origin, compound type or novelty of mechanism of action. Since it has been demonstrated that these characteristics influence both success rates and cycle times (Hadfield, 2002, DiMasi *et al.*, 2004), and the profile of the development pipeline is not static, it is suggested that splitting the pipeline based on these characteristics and applying success rates and cycle times specific for each cohort of NASs (e.g. self-originated chemical entities with a novel mode of action in development for nervous system indications) would lead to better estimates of future output. However, there may be insufficient data to allow for all possible combinations. Using factor analysis, the characteristics with the biggest impact on success rates and cycle times can be identified, and subsequently used to cohort the NASs in development. The improvement of the model through the use of metrics corrected for compound characteristics was supported by delegates from the 34 participating companies to whom this model was presented (Van den Haak, 2002).

The current model allows for the prediction of output in terms of the number of new product launches only, irrespective of R&D investment or commercial value. However, it is hoped that the above suggested study of these aspects of drug development will provide sufficient insight as to how these relate to the metrics success rates, cycle times and pipeline volume, allowing for the model to be extended to enable the prediction of output in terms of both quantity and quality per unit input, in other words the assessment of productivity.

As discussed, the outcome of the study of clinical development failures (Chapter seven) is representative of large to medium-sized pharmaceutical companies. The impact of company size within this group was demonstrated in this study, in particular with regards to the time to termination. It would be interesting to extend this research to smaller companies, where late stage failures are suggested to have an even higher impact. In order to obtain a better and more detailed understanding of the complex matrix of factors contributing to attrition in pharmaceutical R&D, the current study could be expanded by collecting multiple reasons for terminations and their relative contribution to the overall decision to terminate. This will provide a more detailed insight into the decision-making process underlying attrition. Participating companies should be

asked to identify their attrition strategy at different decision points in the R&D process for this information to be used to extend the assessment of the relationship between attrition strategy and R&D efficiency. It is hoped that this will provide insight into the effectiveness of different strategies by identifying the differences between what companies set out to achieve and their actual performance. Furthermore this information can be used to investigate the validity of the assumptions made and to support any detailed interpretation of the data.

CONCLUSION

Despite the increase in global pharmaceutical sales, the ever-widening gap between R&D investment and the number of new product launches continues to be a cause for concern. The time lag between the undertaking of R&D and the return on investment, due to the lengthy development times and longevity characteristic of the pharmaceutical industry, means that global sales is not an indicator of today's R&D performance, but that from over a decade ago. The findings in this thesis illustrate that the industry is aware of the seriousness of the situation and is collectively seeking to increase its R&D productivity. The impetus on speeding up development during the mid 1990s has led to a reduction in overall development times for "major" companies. However, success rates continued to decline suggesting that focussing all efforts on only one parameter will not lead to the desired overall increase in R&D productivity.

The findings in this thesis indicate that the industry's output is not predicted to improve in the next four to five years. However, these predictions are based on current industry practices and there are signs that these are changing, with companies moving away from the fully integrated company model by building up external networks which will provide them access to resources and skills not available in-house. Small improvements in late stage success rates and the increasing number of NASs in preclinical development suggest that the industry's efforts to improve productivity are starting to produce results. However, it will take time for this to be translated into an improvement in the industry's output, the measure most frequently used to assess the industry's

performance. Therefore it is important for the industry to manage the expectations of its stakeholders and to supply them with clear and objective information on temporary indicators of efficiency and productivity as provided in this thesis.

This thesis is unique in reporting on five dimensions of pharmaceutical R&D productivity, i.e. pipeline, success rates, time, investment and output, investigated through longitudinal studies based on consistent definitions and criteria, enabling the examination of the influence of industry developments in recent years, as well as supporting statistical analysis of the impact of compound and company characteristics. Focusing on identifying the relationship between strategy and performance, the outcomes of these studies provide unique insights into the dynamics of R&D productivity. The findings presented are intended to stimulate discussions within the industry as well as with external stakeholders, leading to a greater understanding of the risks and issues involved in drug development, and ultimately to a higher degree of control over pharmaceutical R&D efficiency and productivity.

REFERENCES

Accel Team (2004). Employee motivation, the organizational environment and productivity. Available at www.accel-team.com

Anon (1997). Glossary of Terms. In *Statlets™ User Guide*, NWP Associates, Inc. Available at http://www.mrs.umn.edu/~sungurea/statlets/usermanual/glossary.htm

Anon (1999a). Interpreting Friedman's test, in *The Prism Guide to Interpreting Statistical Results*. Available at www.graphpad.com/articles/interpret/ANOVA/Friedmans.htm

Anon (1999b). Top 50 companies ranked by research & development expenses. *MedAdNews*, Vol 18, No. 9

Anon (2000a). *Guidelines for planning effective surveys*. Statistical Services Centre and The University of Reading. Released March 2000 (ref: 628)

Anon (2000b). Top 50 companies ranked by research & development expenses. *MedAdNews*, Vol. 19, No.9

Anon (2001a). *Approaches to the analysis of survey data*. Statistical Services Centre and The University of Reading. Released March 2001

Anon (2001b). Top 50 companies ranked by research & development expenses. *MedAdNews*, vol 20, No. 9

Anon (2002). Top 50 companies ranked by health-care R&D expenditure. *MedAdNews*, vol 21, no 9

Anon (2003a). FDA sees drug discovery technology, mergers cutting down on NDAs. *"The Pink Sheet"*, 10th March 2003, p27

Anon (2003b). Hyperdictionairy. Available at www.hyperdictionary.com

Anon (2003c). Top 50 companies ranked by health-care R&D expenditure. *MedAdNews*, vol 22, no. 9

Anon (2003d). Biotech blasts back in 2003. Published on 19th December 2003. Available at www.Inpharma.com

Anon (2003e). Early proof of mechanism findings would boost R&D productivity, Exec says. *"The Pink Sheet"*, 21st April 2003, p23

Anon (2004a). Tufts gives its answer to industry's R&D crisis. Published on 9th January 2004. Available at www.Inpharma.com

Anon (2004b). Merck sees change to "repatriate cash to US; GSK wants to ship out. "*The Pink Sheet*', 9th August 2004, p30-31

Anon (2004c). Bayer now in "exclusive talks" for Roche OTC? Published 29th June 2004. Available at www.pharmatimes.com

Anon (2004d). Bayer buys Roche OTC for €2.4Bn. 19th July 2004. Available at www.pharmatimes.com

Anon (2004e). Survival analysis. Newcastle University, School of Mathematics & Statistics. Available at www.mas.ncl.ac.uk/~njnsm/medfac/docs/surv.pdf

Anon (2004f). *Drug sales hit $500 billion*. 17th March 2004. Available at www.pharmatimes.com

Anon (2004g). *Lilly disappoints with '04 forecast.* 6th January 2004. Available at www.pharmatimes.com

Anon (2004h). *GSK revenues drop on generic Paxil.* 29th April 2004. Available at www.pharmatimes.com

Anon (2004i). *B-MS agrees Teva Paraplatin deal.* 28th April 2004. Available at www.pharmatimes.com

Anon (2004j). *Losses continue to widen at SP.* 23rd April 2004. Available at www.pharmatimes.com

Anon (2004k). *Profits down at Merck.* 23rd April 2004. Available at www.pharmatimes.com

Anon (2004l). *Schering ups guidance on strong Q2.* 22nd July 2004. Available at www.pharmatimes.com

Anon (2004m). Top 50 companies ranked by Healthcare revenue. *MedAdNews*, Vol. 23, No. 9, p12-13

Anon (2004n). *Roche sees 12 blockbusters.* 5th May 2004. Available at www.pharmatimes.com

Anon (2004o). *Merck reassures over the future performance.* 28th April 2004. Available at www.pharmatimes.com

Anon (2004p). *Strong Q1 expected from Novartis.* 21st April 2004. Available at www.pharmatimes.com

Anon (2004q). Pfizer's new benchmark for new era: 7% annual growth is sustainable. "*The Pink Sheet*", 6th December 2004, p3-4

Anon (2004r). *Interview with Thomas Ebeling, Head of the Pharmaceuticals Division, Novartis.* 23rd January, 2004. Available from www.pharmatimes.com

Anon (2004s). 200 best-selling prescription drugs. *MedAdNews*, Vol. 23, No. 5, p62-64

Anon (2005). *B-MS to divest certain OTC products?* 5th January 2005. Available at www.pharmatimes.com

Ansell, J (2000). More Mileage than Meets the Eye: Revealing True Product Potential and its impact. *Spectrum Life Sciences*, 4, pp1-16

Ansell, J (2003). Quantifying New Product Need: Productivity Targets Considered at Company Level. *Spectrum*, 8, pp1-14

Arlington, S (1999). *Industry Trends - Pharma 2005.* Available at www.PharmaPortal.com

Arndt, M (2004). *Pharmaceuticals: For Drugmakers, There's No Panacea.* www.businessweek.com.

Ashton, GA (2001). *The impact of biotechnology on pharmaceutical R&D.* PhD Thesis, Cardiff University

Ashton, GA, Lobo, IL, Griffiths, SA and McAsulane, JAN (1998). Activities of the international pharmaceutical industry in 1997: Pharmaceutical investment and output. CMR International report, CMR98-104R2

Baker, A and Gill, J (2005). Rethinking innovation in Pharmaceutical R&D

Banerjee, PK, Myers, SD, Baker, A, Andersen, M and Bichet, S (2001). *High performance drug discovery*. Accenture Executive Briefing

Bautier, P (2004). *Euro-zone and EU25 annual inflation down to 2.2%.* Euro-indicators, Eurostat news release 152/2004. Available at http://europe.eu.int/comm/eurostat

Becker, LA (2004). *Crosstabs: measures for ordinal data.* Psychology department, University of Colorado, Colorado Springs, USA. Available at http://web.uccs.edu/lbecker/SPSS/ctabs2.htm

Beynon, K (2000). Feeling confident in the countdown to patent expiry. *Scrip Magazine*, January 2000, p31-33

Bienz-Tadmor, B, DiCerbo, PA, Tadmor, G and Lasagna, L (1992). Biopharmaceuticals and conventional drugs: clinical success rates. *Bio/Technology* 1992 May;10(5):521-5

Bilyard, KG and Hennessy, M (1994). Assessing uncertainty and risk in new product development. *Journal of biotechnology in healthcare*, vol 1, no. 4, p333-340

Booth, BL and Zemmel, R (2003). Quest for the best. *Nature Reviews Drug Discovery*, Vol 3, p838-841

Booth, BL and Zemmel, R (2004). Prospects for productivity. *Nature Reviews Drug Discovery*, vol 3, p451-456

Booth, BL, Glassman, R and Ma, P (2003). Oncology's trials. *Nature Reviews Drug Discovery*, Vol. 2, p609-610

Booth, BL, Lennon, DJ and McCafferty, EJ (2004). Improving the pharma research pipeline. *The McKinsey Quarterly*, August 2004. Available from www.mckinseyquarterly.com

Bowden, M (2001). *Accelerating patient recruitment with an integrated approach.* Available at www.healthdec.com/downloads/patient_recruitment_US

Brown, TJ and Allport, S (2003). A titanic struggle to survive. *Scrip Magazine*, November 2003, p18-19

Capdeville, R, Buchdunger, E, Zimmermann, J and Matter, A (2002). Gleevec (ST1571, Imatinib) a rationally developed, targeted anti-cancer drug. *Nature Review Drug Discovery*, vol 1, No. 7, pp493-5-3

Carbonell, P, Escudero, AIR and Aleman, JLM (2004). Technology newness and impact of go/no-go criteria on new product success. *Marketing Letters*, 15:2-3, p81-97

Carmines, EG and Zeller, RA (1991). *Reliability and validity assessment.* Newbury Park: Sage Publications, in Palmquist, M (Ed.) (2004). Reliability and Validity. Writing@CSU: Writing Guides. Available at http://writing.colostate.edu/references/research/relval

Cavalla, D (2003). The extended pharmaceutical enterprise. *DDT*, vol. 8, No 6, pp267-274

Charles River Associates (2004). *Innovation in the pharmaceutical sector.* A

study undertaken for the European Commission by Charles River Associates. Published 8th November 2004

CMR International (2002a). *Forum 13: Performance Metrics in Pharmaceutical R&D and Clinical development.* CMR International meeting report, 8-10 October 2002, the Royal Berkshire, Ascot, Berkshire, UK

CMR International (2002b). *Forum 12: Performance Metrics in Clinical Development.* CMR International meeting report, 30 May 2002, Merrill Lynch Training and Conference Center, Plainsboro', NJ, USA

CMR International (2003). *Global R&D Performance Metrics Programme Questionnaire 2004.* CMR International Questionnaire, CMR03-223Q

CMR International (2004a). *2004 R&D Factbook.* CMR International publication

CMR International (2004b). *Performance Metrics in Global Pharmaceutical R&D, 2004 Executive Briefing.* CMR International CMR04-223EB

CMR International (2004c). *2004 Annual Global R&D Performance Metrics Strategy Workshop.* CMR International Workshop summary report, June 17th & 18th 2004, Lansdowne resort, VA, USA

Crichton, N (2000a). Mann-Whitney test. *Journal of Clinical Nursing*, 9, p583. Available at http://www.blackwellpublishing.com/specialarticles/jcn_9_583.pdf

Crichton, N (2000b). Wilcoxon Signed Rank Test. *Journal of Clinical Nursing*, 9, p584. Available at http://www.blackwellpublishing.com/specialarticles/jcn_9_584.pdf

Darlington, RB (2005). Factor analysis. Psychology Department, Cornell University, Ithaca, NY, USA. Available at http://comp9.psych.cornell.edu/Darington/factor.htm. Accessed on 14th February 2005

Davis, J (1994). New chemical entities for unmet medical needs. *Scrip Magazine,* January 1994, p42-43

Davis, J (1995). Therapeutic advances in the NCEs of 1994. *Scrip Magazine*, January 1995, issue 31; p42-43

Davis, J (1996). NCEs - fewer but better? NCEs in 1995. *Scrip Magazine*, January 1996, p54-55

Davis, J (1997). Bumper crop of NCEs. *Scrip Magazine*, January 1997, issue 53; p64-65

Davis, J (1998). A good year for new launches. *Scrip Magazine*, January 1998 Issue 64; p60-61

De Visser, S (2003). *A question based approach to drug development.* PhD thesis, Universiteit Leiden, The Netherlands

DeLamarter, JF and Fumero, S (2001). Wither innovation and profits. *Current Drug Discovery*, 1-8 Nov

Diem, KG (2002a). *Choosing a data collection method for survey research.* Fact Sheet FS996. The State University of New Jersey Rutgers Cooperative Extension, New Jersey Agricultural Experiment Station

Diem, KG (2002b). *A step-by-step guide to developing questionnaires and survey procedures for program evaluations and research.* Fact Sheet FS995. The State University of New Jersey Rutgers Cooperative Extension, New Jersey Agricultural Experiment Station

DiMasi, JA (1995). Success rates for new drugs entering clinical testing in the United States. *Clinical Pharmacology and Therapeutics* 1995 Jul;58(1):1-14

DiMasi, JA (2001a). Risks in new drug development: approval success rates for investigational drugs. *Clinical Pharmacology & Therapeutics*, volume 69, number 5, 297-307

DiMasi, JA (2001b). New drug development in the United States from 1963 to 1999. *Clinical Pharmacology & Therapeutics*, vol. 69, No. 5, p286-296

DiMasi, JA (2002). The value of improving the productivity of the drug development process. *Pharmacoeconomics*, 20 suppl. 3:1-10

DiMasi, JA, Grabowski, HG and Vernon, J (1995a). R&D costs, innovative output and firm size in the pharmaceutical industry. *Int J Econ Bus*, 2:201-19

DiMasi, JA, Grabowski, HG and Vernon, J (2004). R&D costs and returns by therapeutic category. *Drug Information Journal*, Vol. 38, pp 211-223 (665)

DiMasi, JA, Hansen, RW and Grabowski, HG (2003). The price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics*, 22: 151-185

DiMasi, JA, Hansen, RW, Grabowski, HG and Lasagna, L (1991). Cost of innovation in the pharmaceutical industry. *J Health Econ*, 10:107-42

DiMasi, JA, Hansen, RW, Grabowski, HG and Lasagna, L (1995b). Research and development costs for new drugs by therapeutic category: a study of the US pharmaceutical industry. *Pharmacoeconomics*, 7: 152-69

Doogan, D (2003). *Improving Success Rates (an Industry Perspective).* Presentation given on 15th September 2003

Drasdo, A (2003). *Late stage terminations 2002.* Presentation given at the 13th Benchmarking Forum organised by CMR International, June 2003, UK

Drews, J (1995). *The impact of cost containment on pharmaceutical research and development.* CMR Annual Lecture, CMR International, Surrey, UK

Drews, J (1998a). Innovation Deficit Revisited: Reflections on the Productivity of Pharmaceutical R&D. *DDT*, Vol. 3, No 11, p491-494

Drews, J (1998b) (870) in Ashton, GA (2001). *The impact of biotechnology on pharmaceutical R&D.* PhD Thesis, Cardiff University

Drews, J and Ryser, S (1996). Innovative Deficit in the Pharmaceutical Industry. *Drug Information Journal*, Vol 30 p97-107

Dyer, G (2002). Testing times for the pharmaceutical industry. *Financial Times*, 14th February 2002

Easton V and McColl J (2001). *STEPS statistics glossary v1.1.* Available at: http://www.cas.lancs.ac.uk/glossary_v1.1/

Engel, S (1999). The pipeline is full.... *R&D directions*, June 1999

Engel, S (2000). Where the value and strength lie. *PharmaBusiness*, June 2000

Engel, S (2001). Fundamentally sound. *MedAdNews*, September 2001

FDA (2003). *Overview of PDUFA.* Office of Planning, FDA. Available at www.fda.gov/oc/pdufa/report2002/2002-overview.html

FDA (2004). *Innovation or Stagnation: Challenge and opportunity on the critical path to new medical products.* FDA White Paper. Available from www.fda.goc/oc/initiatives/criticalpath/whitepaper.html

Firn, D (2002). EMEA to slash spending. *Financial times*, 7th October 2002

Fleming, E and Ma, P (2002). Drug life-cycle technologies. *Nature Reviews Drug Discovery*, volume 1, p751-752

Fletcher, L (2000). Re-engineering the Pharmaceutical Industry. *Pharmaceutical Business News*, 16th August 2000, p9-10

Fraser, A (2004). *Treating the poor health of the industry.* 29th September 2004. Available from open.IMSHealth.com

FTC (2000). *FTC order clears way for $90 billion merger of Pfizer Inc. and Warner-Lambert Company.* Released 19th June 2000 by the Federal Trade Commission, USA. Available at www.tftc.gov/opa/2000/06/pfizer.htm

Fumero, S (2002). *The role of partnership & collaboration in R&D productivity.* Presentation, February 2002

Getz, KA and De Bruin, A (2000). Breaking the development speed barrier: assessing successful practices of the fastest drug development companies. *Drug Information Journal*, Vol.34, p725-736

Gilbert, J, Henske, P and Singh, A (2003). Rebuilding Big Pharma's business model. *In Vivo – the business and medicine report*, 20 (10)

Giorgianni, SJ, Plese, NK and Pereira, C (1997). Fundamental changes in the pharmaceutical research and development environment. *The Pfizer Journal*, Vol. 1, Issue 1, pp17-26

Goldstein and Zedeck (1985). *Standards for Educational and Psychological Testing.* In: Burns WC (1996). *Chapter 5: Fair employment strategies in human resource management.* (Eds) Barrett RS, published by Quorum Books, Westport, Connecticut, 1996. ISBN: 0-89930-986-0

Gosse, ME and Manocchia, M (1996) in Ashton, G. (2001). Growing pains for biopharmaceuticals. *Nature Biotechnology*, Vol 19, p307-311

GPEC (2004). *U.S. Inflation Rates.* Greater Phoenix Economic Council Information Center, available from www.gpec.org

Grabowski, H (2000). *R&D Returns and the Changing Market Structure in Pharmaceuticals.* Presentation given on 16th October 2000

Grabowski, H, Vernon, J and DiMasi, JA (2002). Returns on research and development for 1990s new drug introductions. *Pharmacoeconomics*, 20, suppl 3, pp11-29

Hadfield, SG (2002). *Key metrics across therapeutic areas.* Presented at Forum

13: Performance Metrics in Pharmaceutical R&D and Clinical Development 8-10 October, 2002

Horrobin, D (2000). *Innovation in the Pharmaceutical Industry*. Available at www.pharmaceuticals2000.com

Humphreys, A (2000). Buy or Bust. *MedAdNews*, July 2000

Hunter, K (2004). *Spending more and more on R&D but getting less*. Available at www.inpharm.com, 1st April 2004

Hynes, CL, Russell, SN, McAuslane, JAN, Lumley, CEL. and Walker, SR (1997). World-*wide Pharmaceutical R&D expenditure 1986-1997*. CMR International Report, CMR97-81R

Johnson & Johnson (1999). *Johnson & Johnson announces completion of merger with Centocor, Inc.* Press release 6th October 1999. Available at www.jnj.com

Jung, J (2002). *Creating breakthrough innovation during a pharmaceutical merger or acquisition*. IBM Institute for Business Value

Karpinski, A (2004). *Psychology: Statistics and data analysis II. Chapter 10: One-Factor Repeated Measures ANOVA*. Available at http://astro.temple.edu/~andykarp/psych524/10_Repeated1.pdf

King, J and Engel, S (2004). Areas of interest. *R&D Directions*, Vol 10, no.6

Kola, I and Landis, J (2004). Can the pahrmaceutical industry reduce attrition rates? *Nature Review Drug Discovery*, Volume 3, p711-715

Lacetera, N and Orsenigo, L (2001). *Political regimes, technological regimes and innovation in the evolution of the pharmaceutical industry in the USA and in Europe*. Paper for Conference on Evolutionary Economics, John Hopkins University, Baltimore, 30th & 31st March, 2001

Lam, MD (2004a). *Knowing when to pull on your experimental drug (how to succeed by failing faster)*. Available at www.pharmexec.com

Lam, MD (2004b). How to win friends, influence people and make NMEs. *Pharmaceutical Executive*, August 2004, p49-56

Lappin, G and Garner, RC (2003). Big physics, small doses: the use of AMS and PET in human microdosing of development drugs. *Nature Reviews Drug Discovery*, Volume 2, p233-240

Lindon, JC (2003). Biomarkers: present concepts and future promise. *Preclinica*, Vol 1 No 5, p221

Liu, B (2000). Keeping his eye on the ball; interview with Jan Leschly. *Financial times*, 2nd November 2000

Lloyd, I (2002). R&D revolution remains just around the corner. *Scrip Magazine*, February 2002, p72-73

Lloyd, I (2003). A little jam today, but more tomorrow? *Scrip Magazine*, February 2003, p60-61

Lloyd, I (2004). The R&D revolution remains elusive. *Scrip Magazine*, Feb 2004, pp52-53

MacFarlane, FG (1998). *The impact of changes in the healthcare environment on pharmaceutical R&D*. PhD Thesis, Cardiff University

MacFarlane, FG, Griffiths, SA, Luscombe, DK and Walker, SR (1997). *World-wide pharmaceutical R&D expenditure: Can the growth continue?* Int. J Pharm Med., 1997;11:193-199

MacInnes, R, Karia, R, Lumley, CE and Walker, SR (1992). *Novel medicines launched on to a twenty country market (1970-89)*. CMR International Report

Malek, J and Kager, P (2003). In the eye of the storm. *Pharmaceutical Executive*, April 2003, p44-50

Malone, E (2002). Pharma tunes into biotech. *Scrip Magazine*, February 2002, p48-49

Mankoff, ST, Brander, C, Ferrone, S and Marincola, FM (2004). Lost in translation: obstacles to translational medicine. *Journal of Translational Medicine*, 2:14

Mario, E (1995). *The virtual company*. FT Conference

Matheson, D and Matheson, J (1998). *The smart organization*. Harvard Business School Press, Boston, Massachusetts, USA

McAuslane, JAN and Anderson, C (2003). *The changing regulatory environment: reality and perception*. CMR International Report, CMR03-221R

McCarthy, N (2001). *Maximizing product lifecycles*. Available at www.imshealth.com, published on 3rd October 2001

McNamara C (1999). Overview of basic methods to collect information. Available at www.http:mapnp.org/library/research

Middleton, S (2004). Barriers to innovation in the development of new medicines in Europe and possible solutions to address these barriers. *EFPIA position paper*, November 2004)

Palmquist, M (Ed.) (2004). *Reliability and Validity*. Writing@CSU: Writing Guides. Available at http://writing.colostate.edu/references/research/relval

Parexel (2002). *Parexel's Pharmaceutical R&D Statistical Sourcebook 2002/2003*. Parexel International

Parexel (2004). *Parexel's Pharmaceutical R&D Statistical Sourcebook 2004/2005*. Parexel International

Parrish, JA (1989). *Investigation of trends and changes in the status of innovation during clinical development (1964-1987)*, Chapter three of *Assessment of innovative performance in the UK pharmaceutical industry*, MPhil thesis Cardiff University

Pilling, D (2001). GlaxoSmithKline: Big pharma think small. *Financial times*, 1st April, 2001

PJB (2005). *PharmaProjects*. PJB Publicications, London, UK. More information on http://www.pjbpubs.com/pharmaprojects/index.htm

Powell, S (2004). *Streamlined research*. Published 21st January 2004. Available at www.pharmafocus.com

Read, K and Sculthorpe, P (2004). New Medicine Launches 2003: a complete guide to new molecular entities (NMEs) launched world-wide. *CMR International Publication*

Roche (2004). *Roche Annual Report 2003*. Available from www.roche.com

Schmid, EF and Smith, DA (2004). Is pharmaceutical R&D just a game of chance or can strategy make a difference? *DDT* vol 9, No.1. p18-26

Schmidt, JB and Calantone, RJ (1998). Are really new product development projects harder to shut down? *J Prod Innov Manag*, 15:111-113

Schulz, A (2004). *Life after Vioxx - $2.5 billion up for grabs?* Published on 11th October 2004. Available at www.detail-direct.com

Sculthorpe, P and Ogg, M (2003). *Resources in pharmaceutical development: 2002 project report*. CMR International Report, CMR03-208R

Sellers, LJ (2003). Fourth Annual Pharm Exec 50. *Pharmaceutical Executive Special Report*, May 2003

Sheck, L, Cox, C, Davis, HT, Trimble, AG, Wardell, WM and Hansen R (1984). Success rates in the United States drug development system. *Clinical Pharmacology and Therapeutics* Nov;36(5):574-83

Shimmings, A (1999). Quality not quantity counts. *Scrip Magazine*, January 1999 Issue 75; p62-63

Shimmings, A (2000). Fierce marketing but fewer new products. *Scrip Magazine*, February 2000, p68-69

Shimmings, A (2002). Stumbling blocks at every stage. *Scrip Magazine*, February 2002, p65-67

Southgate, J (2001). A bumper year for launches bucks the downward trend. *Scrip Magazine*, February 2001, p80-81

Southgate, J (2002). Quality beats quantity. *Scrip Magazine*, February 2002, p70-71

Spilker, B (1994). *Multinational pharmaceutical companies: principles and practices*. 2nd edition, Raven Press, New York, USA

Steven, SE (2002). Focused portfolio measures to support decision making throughout the pipeline. *Drug Information Journal* vol. 36, p623-630

Temple, B (2004). Personal communication

Thomas, KE, McAuslane, JAN, Parkinson, C, Walker, SR and Luscombe, DK (1998). A study of trends in pharmaceutical regulatory approval times for nine major markets in the 1990s. *Drug Information Journal*, vol. 32, p787-801

Tranter, D (1999). Preparing for the new millennium. *DDT*, vol. 4, no 1, p1-2

Trochim, WMK (2002a). *Plus and minus of survey methods. Research Methods Knowledge Base*. Available at www.http://trochim.human.cornell.edu

Trochim, WMK (2002b). *Types of surveys*. Available at www.http://trochim.

human.cornell.edu

Truelove, C (2003). Business model in need of revision. *MedAdNews*, September 2003

Truelove, C (2004). On the defensive. *MedAdNews*, September 2004, p4-10

Tufts CSDD (1999). Clinical development times for new drugs drop 18%, reversing 12-yr trend. *Tufts Center for the Study of Drug Development Impact Report*, volume 1

Tufts CSDD (2001). *Pharmaceutical firms making quicker decisions on compounds in R&D.* Tufts Center for the Study of Drug Development, Impact Report, volume 3, Number 3, p1-4

Tufts CSDD (2003). *Outlook 2003.* Tufts Center for the Study of Drug Development

Tufts CSDD (2004). *Outlook 2004.* Tufts Center for the Study of Drug Development.

Van Brunt, J (2000) in Ashton, G. (2001). Growing pains for biopharmaceuticals. *Nature Biotechnology*, Vol 19, p307-311

van den Haak, MA (2002). *The current status of health of Pharma R&D: how best to measure productivity?* Presented at Forum 13: Performance Metrics in Pharmaceutical R&D and Clinical Development 8-10 October, 2002

Van den Haak, MA (2004). *Bespoke Success Rates Analyses commissioned by Pfizer.* CMR International ENQ04-0058

van den Haak, MA, Berry, DL and Lumley, CE (2004). *Industry Success Rates 2004 – including a Focus on Decision Outcomes.* CMR International, CMR04-234R

van den Haak, MA, Ellis, CE, Whittaker, JY, Palachandran, J and Isherwood, G (2003a). *Global Clinical Performane Metrics incorporating 2000-2002 company analyses.* CMR International, CMR02-192R

van den Haak, MA, Ellis, CE, Whittaker, JY, Palachandran, J and Isherwood, G (2003b). *Performance metrics in global pharmaceutical R&D. Incorporating 2000-2002 company analyses.* CMR International, CMR02-191R

Van Houwelingen, JC, Stijnen, Th and Van Strik, R (1995). *Inleiding tot de medische statistiek.* Second edition, Wetenschappelijke Uitgeverij Bunge, Utrecht, The Netherlands. ISBN 90 6348 009 1

Vose, CW (2001). Proof of concept - support to effective GO / NO GO decisions for development candidates. *Clinical Research Focus*, 12(4)

Walker, SR (2004). *Possible reasons for declining output / submission.* Presentation

Walonick, DS (1997). *Survival statistics.* StatPac, Inc., Bloomington, MN, USA. ISBN 0-918733-11-1

Walton, J (2000). *An Investors View on Mergers, Acquisitions, and Allicances.* Presented at Office of Health Economics Conference

WHO (2002). *Guidelines for ATC classifications and DDD assignment.* WHO Collaboration Centre for Drug Statistics Methodology. ISBN 82-90312-38-5

Wood MacKenzie (2004). *Therapeutic area overview.* Wood MacKenzie Executive's guide 2004

PUBLICATIONS

Ogg, MS, van den Haak, MA and Halliday, RG (2001). *Challenging Issues for the Future of the Pharmaceutical Industry.* CMR International Report CMR01-153R

Ogg, MS, van den Haak, MA and Halliday, RG (2001). *Challenging Issues for the Future of the Pharmaceutical Industry – Executive Briefing.* CMR International Executive Briefing CMR01-153R

Van den Haak, MA (2001). *Fewer New Launches in 2000.* CMR News Vol. 19(1): 10-14

Van den Haak, MA and Ashton, GA (2001). *Industry Success Rates 2001.* CMR International Report CMR01-165R

Van den Haak, MA, Berry, DL and Lumley, CE (2004). *Industry success rates 2004.* CMR International Report CMR04-234R

Van den Haak, MA and Kermani, F (2002). *Drug development 2001: a Complete Guide to New Drug Launches Worldwide.* CMR International Publication

Van den Haak, MA, Lumley CE and McAuslane, JAN (2003). *Pharmaceutical Investment and Output survey 2001: Annual Report.* CMR International Report, CMR02-171AR

Van den Haak, MA and McAuslane, JAN (2002). *The Global Ethical Development Pipeline 2001. Pharmaceutical Investment and Output survey: Data Report II.* CMR International Report, CMR02-171RB

Van den Haak, MA and McAuslane, JAN (2002). *The Global Ethical Development Pipeline 2001. Pharmaceutical Investment and Output survey: Executive Briefing.* CMR International Report, CMR02-171ESB

Van den Haak, MA, Sculthorpe, PD and McAuslane, JAN (2002) *New Active Substance Activities 2001: Submission, Authorisation and Marketing: Data Report III.* CMR International Report, CMR02-171RC

Van den Haak, MA, Sculthorpe, PD and McAuslane, JAN (2002) *New Active Substance Activities 2001: Submission, Authorisation and Marketing: Executive Briefing.* CMR International Report, CMR02-171ESC

Van den Haak, MA, Vounatsos, FG and McAuslane, JAN (2002). *International Pharmaceutical R&D expenditure and Sales 2001. Pharmaceutical Investment and Output survey: Data Report I.* CMR International Report, CMR02-171RA

Van den Haak, MA, Palachandran, J and Benjamin, GA (2003). *Performance Metrics in Global Pharmaceutical R&D: Company specific review 2002.* CMR International Report, CMR03-204R

Poster presentations

Van den Haak, MA, Salek, S and Walker, S (2002*). New Product Launches: What will the Future Bring?* Presented at the 38th Annual DIA Meeting, June 16-20, 2002. The New Lakeside Center at McCormick Place, Chicago, IL, USA

Van den Haak, MA, Salek, S and Walker, S (2003). *Drug Development Failures: What can be learned from them?* Presented at the 39th Annual DIA Meeting, June 15-19, 2003. Henry B. Gonzalez Convention Center, San Antonio, TX, USA

Van den Haak, MA, Salek, S and Walker, S (2005*). How do 'go/no go' decisions influence R&D efficiency?* Presented at the 17th Annual Euro DIA Meeting, to be held March 7-9, 2005, Lisboa Congress Centre, Lisbon, Portugal (2nd Prize)

Oral presentations

Van den Haak, MA (2000). *Activities of the international pharmaceutical industry in 1999.* Presented at the UK R&D Finance Forum, 16th November 2000, AstraZeneca, Macclesfield, UK

Van den Haak, MA (2001) *Challenging issues for the future of the pharmaceutical industry.* Presented at the UK R&D Finance Forum, November 2001, Lilly Research Centre, Erl Wood, Windlesham, Surrey, UK

Van den Haak, MA (2002*). The current status of health of pharma R&D: how best to measure productivity?* Presented at the workshop Performance Metrics in Pharmaceutical R&D and Clinical Development – Forum 13. 8th-10th October 2002, Royal Berkshire Hotel, Berkshire, UK

Van den Haak, MA (2005). *Industry metrics for clinical development: what are the trends and do they provide indicators of clinical productivity?* Presented at the 17th Annual Euro DIA Meeting, to be held March 7-9, 2005, Lisboa Congress Centre, Lisbon, Portugal

Van den Haak, MA (2005). *Measuring productivity and efficiency in R&D: Which performance metrics are required?* Presented at the 17th Annual Euro DIA Meeting, to be held March 7-9, 2005, Lisboa Congress Centre, Lisbon, Portugal

APPENDIX I

QUESTIONNAIRE:

INTERNATIONAL PHARMACEUTICAL R&D EXPENDITURE AND SALES (2001-2002E)

Objective and outcome

This questionnaire collects **key R&D expenditure, staff & sales data** for the financial year 2001 with estimates for 2002. This survey is unique in gathering information relating only to **ethical pharmaceutical activities.** Companies supplying data will be provided free of charge with a Data Report containing aggregated analyses of the data. Additionally, participating companies are entitled to the Annual Report on Pharmaceutical Investment and Output, which combines the data collected in this questionnaire with data on the Global Development Pipeline and data on New Active Substance Activities.

Background

CMR International Ltd. collects confidential data annually from the leading pharmaceutical companies describing their pharmaceutical R&D expenditure, global sales, clinical development pipeline, and new active substances launched on to the major pharmaceutical markets. Over 60 companies, including the leading companies by R&D expenditure, the leading biotech companies, the leading Japanese companies and all additional members of CMR International's Institute for Regulatory Sciences are being invited to provide information relating to their activities in these areas during 2001, with estimates for 2002.

Confidentiality

All information from individual companies will be kept strictly confidential and no information which would identify an individual company or person will be reported, or details made available to any third party. CMR International Ltd. has over 20 years experience in handling confidential information. Confidence in this experience and integrity is demonstrated by the continuing and growing support for CMR surveys.

Data to be included

Please provide details (in national currency, without adjusting for inflation) of R&D expenditure, staff, and global sales for **ethical (prescription only) pharmaceuticals** in the financial year 2001, with estimates for 2002, using the definitions provided. Please include as much information as possible for all wholly-owned company groups.

Definitions

Ethical pharmaceuticals	*Any medicinal chemicals, biologicals, products of biotechnology or in vivo diagnostics which are intended for the cure, alleviation, treatment, prevention or diagnosis of diseases of humans and are, or will be, available as 'prescription-only medicines'.*
New active substance (NAS)	*A new active substance (NAS) is a chemical, biological or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans.* *The term NAS also includes:* *an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available;* *a biological substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process;* *a radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available*

Definitions (continued)

Line extension	*NASs that are already marketed but are being further developed for new indications, formulations, dosages, routes of administration, or novel drug delivery systems.*
R&D expenditure	*The total expenditure on all research and development activities relating to ethical pharmaceuticals. This includes salaries and all other personnel-related costs, costs related to consumable materials and supplies, and an appropriate share of overheads to cover administration, depreciation, space charges, rent, etc. The cost of R&D conducted by means of grants or contracts to other companies or institutions, and proportional costs for joint ventures should be included. This definition excludes capital R&D expenditure.*
Capital R&D expenditure	*The total expenditure on equipment, land or buildings substantially devoted to pharmaceutical research and development activities relating to ethical pharmaceuticals.*
Global sales	*The income from sales of ethical pharmaceuticals. This includes finished products, bulk sales and royalties from licensed-out ethical pharmaceuticals.*
Commercial Outsourcing	*Amount of R&D expenditure allocated as contracts to external commercial organisations (e.g., for clinical trials, toxicology, formulation development, etc). NB: This does not include expenditure on joint ventures, e.g., with biotech companies, or expenditure on contracts to sister companies which are part of your company's legal entity.*
Academic Outsourcing	*Amount of R&D expenditure allocated as research contracts to academia/external research institutes, etc.*
Alliances	*Amount of R&D expenditure allocated to alliances, including expenditure relating to work conducted in-house as part of formal alliance agreements, and management and negotiation costs, as well as payments made to alliance partners (including milestone payments, but not royalty payments). Alliances must involve shared technical, development or commercial risk and reward to all alliance partners. NB: This does not include expenditure on in-licensed projects and outsourcing or "fee for service" contracts.*
Discovery research	*All basic research, synthesis and screening (including biological and pharmacological screening) and ADME (absorption, distribution, metabolism and excretion) studies.*
Non-clinical research	*All pharmaceutical & chemical development, toxicological, safety and associated kinetic tests in animals.*
Total clinical research	*All clinical studies in volunteers and patients, pre- and post-marketing, but not Phase IV clinical trials solely to support marketing.*
Post-marketing clinical evaluation	*All Phase IV clinical trials for new indications, formulations, dosage and further routes of administration, but not Phase IV clinical trials solely to support marketing.*

Section 1 General Information

Currency used for data: ..... **End of your company's financial year:** .....

Units in which data is provided (e.g. millions): .....

Company groups for which data is included: .....

Company groups for which you have been unable to include data: .....

Section 2 Headline figures and geographical breakdown

2.1) Please provide data relating to **ethical pharmaceuticals** for the financial year 2001, and estimates for 2002.

	2001	*2002e*
a) R&D expenditure on **ethical pharmaceuticals**		
b) Capital R&D expenditure relating to **ethical pharmaceuticals**		
c) Global sales of **ethical pharmaceuticals**		
d) R&D headcount		

2.2) Please provide the geographical breakdown for the relevant **2001** figures, relating to **ethical pharmaceuticals**, as provided in question 2.1.

	Europe	*USA*	*Japan*	*Rest of World*
a) R&D expenditure	%	%	%	%
b) Capital R&D expenditure	%	%	%	%
c) Global sales	%	%	%	%
d) R&D headcount	%	%	%	%

Section 3 – R&D expenditure: Outsourcing and Alliances

3.1) Please provide data relating to **ethical pharmaceuticals** for the financial year 2001, and estimates for 2002, using the definitions provided on page 3.

	Total		*Commercial*[1)]		*Academic*[1)]	
Outsourcing	*2001*	*2002e*	*2001*	*2002e*	*2001*	*2002e*
Total amount of R&D expenditure allocated as contracts to **external contracts** (outsourcing)						
Amount allocated to outsourcing as contracts in **discovery and non-clinical research**						
Amount of R&D expenditure allocated to outsourcing as contracts in **pre- and post-marketing clinical development including regulatory activities**						

1) please enter N/A in the columns for commercial and academic outsourcing when this breakdown is not available

3.2) Please provide data relating to **ethical pharmaceuticals** for the financial year 2001, and estimates for 2002, using the definitions provided on page 3.

Alliances	*2001*	*2002e*
a) Total amount of R&D expenditure allocated **alliances.**		
b) Amount allocated to alliances in **discovery and non-clinical research**		
c) Amount of R&D expenditure allocated to alliances in **pre- and post-marketing clinical development including regulatory activities**		

Section 4 - R&D expenditure by function and product type

4.1) Please enter the percentage of your R&D expenditure in 2001 (as provided in question 2.1a) in the following categories, using the definitions provided on page 2. If a further breakdown of total clinical research into Phase I, Phase II and III and post-marketing clinical evaluation is not available, please leave these fields blank.

Function	% of R&D expenditure
Discovery research	%
Non-clinical research	%
Total clinical research	%
Phase I	%
Phase II and III	%
Post-marketing clinical evaluation	%
Regulatory (all expenditure relating to regulatory affairs or activity)	%
Other research (any activity not covered above)	%

4.2) Please indicate the percentage of your R&D expenditure in 2001 (as provided in question 2.1a) which was allocated to researching and developing the following product types. This should include R&D expenditure required to launch an NAS in a country for the first time. Please also provide information on costs related to line extensions, etc.

Product type	% of R&D expenditure
NASs	%
Line extensions *(e.g., new formulations, indications, routes of administration, novel drug delivery systems)*	%
Other (*please specify, e.g., contraceptives, hormonal preparations, etc.)*	%
TOTAL	**100 %**

Section 5 - Pharmaceutical R&D expenditure by therapeutic area

5.1) Please enter the percentage of your company's R&D expenditure in 2001 (as provided in question 2.1a) allocated to the following therapeutic areas. A more detailed breakdown of the therapeutic areas can be found on page 5.

	%
Alimentary and metabolism	%
Blood	%
Cardiovascular	%
Dermatologicals	%
GU / Sex hormones	%

	%
Hormones	%
Antiinfectives	%
Cancer	%
Musculoskeletal	%
Nervous system	%

	%
Respiratory	%
Sensory	%
Various	%

Section 6 – Sales: Top 3 products and recently launched products

6.1) Please indicate the proportion of ethical (prescription only) pharmaceutical sales in 2001 (as provided in question 2.1c) attributable to your company's "top 3" products.

	Generic name	% of sales
Percentage of global sales in 2001 attributable to "top 3" ethical (prescription only) pharmaceutical products (please provide generic name for each of the three products, and the percentage of global sales attributable to each)	1)	%
	2)	%
	3)	%
	TOTAL	%

6.2) Please indicate the proportion of ethical (prescription only) pharmaceutical sales in 2001 (as provided in question 2.1c) attributable to products first marketed in the last 5 years.

Percentage of global sales in 2001 attributable to ethical pharmaceuticals marketed for the first time ever between 01-Jan-97 and 31-Dec-01	..... %

Classification of therapeutic areas

Alimentary and metabolism
Antacids, drugs for treatment of peptic ulcer and flatulence
Antispasmodic and anticholinergic agents and propulsives
Antidiarrheals, intestinal anti-inflammatory/antiinfective
Antiobesity preparations, excl. diet products
Other alimentary and metabolism products
Drugs used in diabetes
Blood
Antithrombotic agents
Antihaemorrhagics
Antianaemic preparations
Other haematological agents
Cardiovascular
Cardiac therapy
Antihypertensives
Serum lipid reducing agents
Renal failure
Septic shock
Dermatologicals
Antifungals for dermatological use
Emmollients and protectives
Preparations for the treatment of wounds and ulcers
Antipsoriatics
Antibiotics and chemotherapeutics for dermatological use
Corticosteroids, dermatological preparations
Anti-acne preparations
Other dermatological preparations
GU/Sex hormones
Other gynaecologicals
Sex hormones and modulators of the genital system
Urologicals
Hormones
Pituitary, hypothalamic hormones and analogues
Calcium homeostasis

Antiinfectives
Antibacterials for systemic use
Antimycotics for systemic use
Anti-HIV
Antivirals for systemic use
Anticancer
Antineoplastic agents
Endocrine therapy
Adjunct therapy to cancer
Immunosuppressive agents
Musculo-skeletal
Anti-inflammatory and antirheumatic products
Drugs for treatment of bone diseases
Nervous system
Analgesics
Antiepileptics
Drugs for the treatment of Parkinson's disease
Psycholeptics
Psychoanaleptics
Other nervous system drugs
Alzheimer's Disease
Stroke
Respiratory
Nasal preparations
Asthma
Antihistamines for systemic use
Other respiratory system products
Sensory
Ophthalmologicals
Various
Contrast media
Diagnostic radiopharmaceuticals

APPENDIX II

QUESTIONNAIRE:

INTERNATIONAL PHARMACEUTICAL R&D EXPENDITURE AND SALES (2002-2003E)

Objective and outcome

This questionnaire collects **key R&D expenditure, staff & sales data** for the financial year 2002 with estimates for 2003. This survey is unique in gathering information relating only to **ethical pharmaceutical activities.** Companies supplying data will be provided free of charge with aggregated analyses of the data.

Background

CMR International Ltd. collects confidential data annually from the leading pharmaceutical companies describing their pharmaceutical R&D expenditure & global sales. Over 40 companies, including the leading companies by R&D expenditure, the leading biotech companies, the leading Japanese companies and all additional members of CMR International's Institute for Regulatory Sciences are being invited to provide information relating to their activities in these areas.

Confidentiality

All information from individual companies will be kept strictly confidential and no information which would identify an individual company or person will be reported, or details made available to any third party. CMR International Ltd. has over 20 years experience in handling confidential information. Confidence in this experience and integrity is demonstrated by the continuing and growing support for CMR surveys.

Data to be included

Please provide details (in national currency, without adjusting for inflation) of R&D expenditure, staff, and global sales for ethical (prescription only) pharmaceuticals in the financial year 2002, with estimates for 2003, using the definitions provided in each section of the questionnaire.

Section 1 General information

Please provide all financial data in your own currency. This will be converted to US$ using OECD (Organisation for Economic Co-operation and Development) mean exchange rates.

1a. Please specify the currency in which you are providing data: .....

1b. Please state the units in which you are providing data (e.g. millions): .....

Section 2 Headline figures and geographical breakdown

2.1 Please provide data relating to **ethical pharmaceuticals** for the financial year 2002, and estimates for 2003.

	2002	*2003e*
R&D expenditure on **ethical (prescription only) pharmaceuticals**		
Capital R&D expenditure relating to **ethical (prescription only) pharmaceuticals**		
Global sales of **ethical (prescription only) pharmaceuticals**		
R&D FTEs		

2.2 Please provide the geographical breakdown for the relevant **2002** figures, relating to **ethical pharmaceuticals**, as provided in question 2.1.

	Europe	*USA*	*Japan*	*Rest of World*
R&D expenditure	%	%	%	%
Capital R&D expenditure	%	%	%	%
Global sales	%	%	%	%
R&D FTEs	%	%	%	%

Definitions (Section 2)

R&D expenditure	The total expenditure on all research and development activities relating to ethical pharmaceuticals. This includes salaries and all other personnel-related costs, costs related to consumable materials and supplies, and an appropriate share of overheads to cover administration, depreciation, space charges, rent, etc. The cost of R&D conducted by means of grants or contracts to other companies or institutions, and proportional costs for joint ventures should be included. This definition excludes capital R&D expenditure.
Ethical pharmaceuticals	Any medicinal chemicals, biologicals, products of biotechnology or in vivo diagnostics which are intended for the cure, alleviation, treatment, prevention or diagnosis of diseases of humans and are, or will be, available as 'prescription-only medicines'.
Capital R&D expenditure	The total expenditure on equipment, land or buildings substantially devoted to pharmaceutical research and development activities relating to ethical pharmaceuticals.
Global sales	The income from sales of ethical pharmaceuticals. This includes finished products, bulk sales and royalties from licensed-out ethical pharmaceuticals.
FTE	Someone employed by the company to work full-time in R&D. (Someone working part-time would be a fraction of an FTE, for example someone employed to work 3 days a week would be 0.6 FTE.) Where contractors are included in the internal salaries or operations expenditure they should be included as FTEs. Where contractors are treated as external costs they should be excluded here.

Section 3 – R&D expenditure: Alliances

3. Please provide data relating to **ethical pharmaceuticals** for the financial year 2002, and estimates for 2003 using the definitions provided.

	2002	*2003e*
d) Total amount of R&D expenditure allocated to **alliances.**		

e) Amount allocated to alliances in **discovery research**		
f) Amount allocated to alliances in **non-clinical research**		
g) Amount of R&D expenditure allocated to alliances in **pre- and post-marketing clinical development including regulatory activities**		

Definitions (Section 3)

Ethical pharmaceuticals	Any medicinal chemicals, biologicals, products of biotechnology or in vivo diagnostics which are intended for the cure, alleviation, treatment, prevention or diagnosis of diseases of humans and are, or will be, available as 'prescription-only medicines'.
R&D expenditure	The total expenditure on all research and development activities relating to ethical pharmaceuticals. This includes salaries and all other personnel-related costs, costs related to consumable materials and supplies, and an appropriate share of overheads to cover administration, depreciation, space charges, rent, etc. The cost of R&D conducted by means of grants or contracts to other companies or institutions, and proportional costs for joint ventures should be included. This definition excludes capital R&D expenditure.
Alliances	Amount of R&D expenditure allocated to alliances, including expenditure relating to work conducted in-house as part of formal alliance agreements, and management and negotiation costs, as well as payments made to alliance partners (including milestone payments, but not royalty payments). Alliances must involve shared technical, development or commercial risk and reward to all alliance partners. NB: This does not include expenditure on in-licensed projects and outsourcing or "fee for service" contracts.

Section 4 - R&D expenditure by function

In the table below, please indicate for each of the following functions

4a. How many people (FTEs) did you have in each function during 2002?

4b. What were your external costs (in your own currency) for each functions during 2002?

Function	Number of FTEs	External costs
Discovery research		
Chemistry, Manufacturing and Controls (CMC)		
Non clinical safety evaluation		
Clinical research		
Regulatory		
Miscellaneous		
Total		

Definitions (section 4)

FTE	Someone employed by the company to work full-time in R&D. (Someone working part-time would be a fraction of an FTE, for example someone employed to work 3 days a week would be 0.6 FTE.) Where contractors are included in the internal salaries or operations expenditure they should be included as FTEs. Where contractors are treated as external costs they should be excluded here.
External costs	Should include: all costs paid to external project-specific service providers (Contract Research Organisations (CRO's), contractors, investigators etc), clinical grants, research grants, and project-specific support services.
Discovery research	All basic research, synthesis and screening (including biological and pharmacological screening) and ADME (absorption, distribution, metabolism and excretion) studies.
Non-clinical safety evaluation	Toxicological, safety and associated kinetic tests in animals.
Chemistry, Manufacturing and Controls (CMC)	All pharmaceutical & chemical development, including, but not limited to, process research and development for drug substance and drug product, formulation, scale-up, technology transfer; analytical assessment, clinical supplies and compilation of technical regulatory dossier.
Clinical research	All clinical studies in volunteers and patients, pre- and post-marketing.
Regulatory	All R&D expenditure relating to regulatory activities.
Miscellaneous	Should include but not be limited to: Project management, R&D management, R&D IT, library and information services, administrative support.

Section 5 – R&D expenditure by stage of development

In the table below, please indicate for each of the following stages of development

5a. How many people (FTEs) did you have in each stage during 2002?

5b. What were your external costs (in your own currency) for each stage during 2002?

Stage	Discovery stage of development	Early Development	Late Development	Submission & launch programme	Further activities	Total
No. of FTEs						
External spend						

Definitions (section 5)

FTE	Someone employed by the company to work full-time in R&D. (Someone working part-time would be a fraction of an FTE, for example someone employed to work 3 days a week would be 0.6 FTE.) Where contractors are included in the internal salaries or operations expenditure they should be included as FTEs. Where contractors are treated as external costs they should be excluded here.
External costs	Should include: all costs paid to external project-specific service providers (Contract Research Organisations (CRO's), contractors, investigators etc), clinical grants and research grants. Project specific support services.
Discovery stage of development	All activities occurring prior to First dose in first toxicity study required for first dose to human.
Early Development	Starts with the first dose in first toxicity study, and ends with a decision to develop for launch. The date of the first dose in first toxicity study required for first dose to human is a key milestone indicating that the pre-clinical programme is now active. The decision to develop for launch results in decision to conduct the large-scale clinical safety and efficacy studies necessary to support registration. For many companies this will be the most important decision in financial terms since it represents a major commitment of resources.
Late Development	Starts with a decision to develop for launch, and ends with the submission of the first registration dossier. The decision to develop for launch results in decision to conduct the large-scale clinical safety and efficacy studies necessary to support registration. For many companies this will be the most important decision in financial terms since it represents a major commitment of resources. The date of the submission of the first registration dossier does not have to be to one of the 8 core markets and can involve submissions made to multiple countries.
Submission & launch programme	All activities between the submission of the first registration dossier and launch in last core market (the 8 core markets are: Canada, France, Germany, Italy, Japan, Spain, UK and USA).
Further Activities	Includes, but not limited to, line extensions, aftercare, launch in non-core markets and general support activities.

Section 6 – R&D expenditure by type of product

6) Please indicate the percentage of your R&D expenditure in 2002 (as provided in question 2.1a) which was allocated to researching and developing the following product types. This should include R&D expenditure required to launch an NAS in a country for the first time. Please also provide information on costs related to line extensions, etc.

NASs		Line Extensions (e.g. new formulations, indications, routes of administration, novel drug delivery systems	Other (please specify, e.g., contraceptives, hormonal preparations, etc.)	Total
Biotech	non-biotech			
				100%

Definitions (section 6)

New active substance (NAS)	A new active substance (NAS) is a chemical, biological or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans. The term NAS also includes: an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available; a biological substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process; a radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available
Biotech products:	A naturally occurring or modified polypeptide, protein, DNA or RNA product (produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals or transgenic plants), for therapeutic, prophylactic or in vivo diagnostic use in humans. The only vaccines included are recombinant vaccines.
Line extension	NASs that are already marketed but are being further developed for new indications, formulations, dosages, routes of administration, or novel drug delivery systems.

Section 7 - Pharmaceutical R&D expenditure by therapeutic area

7) Please enter the percentage of your company's R&D expenditure in 2002 (as provided in question 2.1a) allocated to the following therapeutic areas.

	%
Alimentary and metabolism	%
Blood	%
Cardiovascular	%
Dermatologicals	%
GU / Sex hormones	%

	%
Hormones	%
Antiinfectives	%
Cancer	%
Musculoskeletal	%
Nervous system	%

	%
Respiratory	%
Sensory	%
Various (ATC)	%
Miscellaneous*	%

**Please include in Miscellaneous all expenditure that cannot be attributed to any of the above categories*

Classification of therapeutic areas

Alimentary and metabolism
Antacids, drugs for treatment of peptic ulcer and
Antispasmodic and anticholinergic agents and
Antiemetics and antinauseants
Bile and liver therapy
Antidiarrheals, intestinal anti-inflammatory/antiinfective
Antiobesity preparations, excl. diet products
Digestives, incl enzymes
Appetite stimulants
Drugs used in diabetes
Other alimentary and metabolism products
Blood
Antithrombotic agents
Antihaemorrhagics
Antianaemic preparations
Blood substitutes and perfusion systems
Other haematological agents
Cardiovascular
Cardiac therapy
Antihypertensives
Diuretics
Vasoprotectives
Serum lipid reducing agents
Renal failure
Septic shock
Dermatologicals
Antifungals for dermatological use
Emollients and protectives
Preparations for the treatment of wounds and ulcers
Antipruritics including antihistamines and anaesthetics
Antipsoriatics
Antibiotics and chemotherapeutics for dermatological use
Corticosteroids, dermatological preparations
Anti-acne preparations
Other dermatological preparations
GU/Sex hormones
Sex hormones and modulators of the genital system
Urologicals
Other gynaecologicals
Hormones
Pituitary, hypothalamic hormones and analogues
Thyroid therapy
Calcium homeostasis
Antiinfectives
HIV

Antiinfectives *(continued)*
Antibacterials for systemic use
Antimycotics for systemic use
Vaccines
Antiprotozoals
Antihelmintics
Antivirals for systemic use
Anticancer
Antineoplastic agents
Endocrine therapy
Adjunct therapy to cancer
Immunomodulators
Non-cancer immunomodulators
Immunosuppressives (for transplant)
Musculo-skeletal
Anti-inflammatory and antirheumatic products
Muscle relaxants
Antigout preparations
Drugs for treatment of bone diseases
Osteoporosis
Other drugs for disorder of the musculo-skeletal system
Nervous system
Analgesics
Anaesthetics
Antiepileptics
Drugs for the treatment of Parkinson's disease
Multiple Sclerosis
Psycholeptics
Psychoanaleptics
Neurodegenerative diseases
Stroke
Other nervous system drugs
Respiratory
Asthma
Allergic rhinitis
Antihistamines for systemic use
COPD
Other respiratory system products
Sensory
Ophthalmologicals
Otological preparations
Various
Contrast media
Diagnostic radiopharmaceuticals
Therapeutic radiopharmaceuticals

Section 8 – Sales: Top 3 products and recently launched products

8.1) Please indicate the proportion of ethical (prescription only) pharmaceutical sales in 2002 (as provided in question 2.1c) attributable to your company's "top 3" products.

	Generic name	% of sales
Percentage of global sales in 2002 attributable to "top 3" ethical (prescription only) pharmaceutical products (please provide generic name for each of the three products, and the percentage of global sales attributable to each)	1)	%
	2)	%
	3)	%
	TOTAL	%

8.2) Please indicate the proportion of ethical (prescription only) pharmaceutical sales in 2002 (as provided in question 2.1c) attributable to products first marketed in the last 5 years.

Percentage of global sales in 2002 attributable to ethical pharmaceuticals marketed for the first time ever between 01-Jan-98 and 31-Dec-02	..... %

Definitions (section 8)

Ethical pharmaceuticals	Any medicinal chemicals, biologicals, products of biotechnology or in vivo diagnostics which are intended for the cure, alleviation, treatment, prevention or diagnosis of diseases of humans and are, or will be, available as 'prescription-only medicines'.
Global sales	The income from sales of ethical pharmaceuticals. This includes finished products, bulk sales and royalties from licensed-out ethical pharmaceuticals.

APPENDIX III

QUESTIONNAIRE:

NEW ACTIVE SUBSTANCE ACTIVITY: SUBMISSION, AUTHORISATION, AND MARKETING (2001)

Background

CMR International collects confidential data annually from the leading pharmaceutical companies describing their pharmaceutical R&D expenditure, global sales, clinical development pipeline, and new active substances launched on to the major pharmaceutical markets. Over 60 companies, including the leading companies by R&D expenditure, the leading biotech companies, the leading Japanese companies and all additional members of CMR International's Institute for Regulatory Sciences are being invited to provide information relating to their activities in these areas during 2001, with estimates for 2002.

Objective and outcome

CMR International has maintained an International Marketed Medicines Database (IMMED), with details on the development of medicines first marketed since 1970, for more than a decade. This has allowed us to report to the industry on trends such as drug development times, regulatory review times, the annual numbers of NASs first launched etc. To allow us to continue to provide companies with up-to-date data, this questionnaire is designed to collect data on your company's regulatory and marketing activities in all major markets during the calendar year 2001 with estimates for 2002. We are also tracking first ever launches in 2001 on a global basis.

Companies supplying data will be provided free of charge with a Data Report containing aggregated analyses of the data. Additionally, participating companies are entitled to the Annual Report on Pharmaceutical Investment and Output, which combines the data collected in this questionnaire with data on International Pharmaceutical R&D Expenditure and Sales and the Global Development Pipeline.

Confidentiality

All information from individual companies will be kept strictly confidential and no information which would identify an individual company or person will be reported, or details made available to any third party. CMR International has over 20 years experience in handling confidential information. Confidence in this experience and integrity is demonstrated by the continuing and growing support for CMR surveys.

Data to be included

Please provide information relating to your company's regulatory and marketing activity during 2001. This should include details of any co-marketed products or licensed-in NASs in the following markets:

1) *For major markets* (Australia, Canada, Japan, Switzerland, the USA and the EU, including Norway and Iceland)

a. All NAS submissions made within the listed markets in 2001;
b. All NAS marketing authorisations granted in the listed markets in 2001;
c. All NASs marketed within the listed markets in 2001;

2) *For any market*

d. Details of all NASs launched on *any* world market for the first time in 2001;
e. Overview of marketing activity for line extensions during 2001;
f. Estimate of NASs which your company will launch on the world market for the first time in 2002

EU Procedures

Since June 2000, Norway and Iceland are included in the Mutual Recognition and the Centralised procedures of the EU. When providing data for NASs going through either one of these procedures, please specify whether Norway (N) and Iceland (ICE) are included.

Section A: NAS regulatory submissions during 2001
(01-Jan-01 to 31-Dec-01 inclusive)

N.B. please do not include information relating to submissions for new formulations, dosages, etc. in markets where the NAS already has approval.

If submitted in Australia, Canada, Japan, Switzerland, USA, or the EU**, enter data below.

DETAILS OF YOUR COMPANY'S SUBMISSIONS IN MAJOR MARKETS IN 2001

- Please enter, on separate lines, the generic name of the NAS, the country (put "EU" if the centralised procedure was used), and the dates of submissions. To aid completion we have provided data from our IMMED database for confirmation. The only dates entered are those provided by your own company or published by regulatory authorities.
- Please indicate if the submission relates to a NAS for which there is a co-marketing agreement in a given country by putting Yes or No (Y/N) in the column headed "Co-Marketed" and annotate your entry with the name of the co-marketing company for that country.
- For submissions to countries within the EU please indicate the relevant route, i.e. "Centralised", "Mutual Recognition" (in which case please show if this entry relates to the reference member state ("RMS") or concerned member state ("CMS")) or "National". *For centralised procedure please specify whether Norway and Iceland are included (e.g. EU+N/ICE or EU).*
- Please indicate if the submission was electronic [enter (1)], partially electronic (2) or paper-based (3) – *see definitions*

Generic Name	*Country*	*Submission Date` (dd-mm-yy)*	*Co-Marketed? Y/N*	*European Union Only Centralised / Mutual Recognition (RMS or CMS) / National*	*Method of Submission*

***EU states in 2001: (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, the UK).*

Section B: NAS regulatory marketing authorisations during 2001
(01-Jan-01 to 31-Dec-01 inclusive)

N.B. please do not include information relating to authorisations for new formulations, dosages, etc. in markets where the NAS already has approval.

If approved in Australia, Canada, Japan, Switzerland, USA, or the EU** enter data below.

DETAILS OF MARKETING AUTHORISATIONS IN MAJOR MARKETS IN 2001

- Please enter, on separate lines, the generic name of the NAS, the country (put "EU" if the centralised procedure was used), and the dates of approvals. To aid completion we have provided data from our IMMED database for confirmation. The only dates entered are those provided by your own company or published by regulatory authorities.
- Please show if the approval relates to a NAS for which there is a co-marketing agreement in a given country by putting Yes or No (Y/N) in the column headed "Co-Marketed" and annotate your entry with the name of the co-marketing company for that country.
- For approvals in countries within the EU please indicate the relevant route, i.e. "Centralised", "Mutual Recognition" (in which case please show if this entry relates to the reference member state ("RMS") or concerned member state ("CMS")) or "National". *For centralised procedure please specify whether Norway and Iceland are included (e.g. EU+N/ICE or EU).*

				European Union Only
Generic Name	*Country*	*Approval Date (dd-mm-yy)*	*Co-Marketed? Y/N*	*Centralised / Mutual Recognition (RMS or CMS) / National*

*** EU states in 2001: (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, the UK).*

Section C: NAS marketing activity in the defined major world markets during 2001 (01-Jan-01 to 31-Dec-01 inclusive)

N.B. please do not include information relating to launches for new formulations, dosages, etc. in markets where the NAS already has approval.

If launched in Australia, Canada, Japan, Norway, Switzerland, USA, or the EU** enter data below. If the launch related to a first ever world launch then please also complete section D.

DETAILS OF LAUNCHES BY YOUR COMPANY IN MAJOR MARKETS IN 2000

- Please enter, on separate lines, the generic name of the NAS, the brand name of the NAS, the country, and the dates of launches. To aid completion we have provided data from our IMMED database for confirmation. The only dates entered are those provided by your own company or published by regulatory authorities.
- Please show if the launch relates to a NAS for which there is a co-marketing agreement in a given country by putting Yes or No (Y/N) in the column headed "Co-Marketed" and annotate your entry with the name of the co-marketing company for that country.

			Marketing Activity	
Generic Name	*Brand Name*	*Co-Marketed? Y/N*	*Country*	*Marketing Date (dd-mm-yy)*

*** EU states in 2000: (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, the UK).*

Section D: Details of all NASs launched on any world market for the first time in 2001 by your company

DID YOU LAUNCH ANY NASS ON ANY WORLD MARKET FOR THE FIRST TIME IN 2001? YES/NO

A list of NASs which we believe your company first launched in any country of the world in 2001 is provided below. Please complete or amend as appropriate referring to definitions on pages 8 and 9. Please enter all dates in the following format: dd-mm-yy.

Generic Name						
Biotech Product		Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
Originating company						
First synthesis/isolation	*Date*					
	Country					
Patent priority filing	*Date*					
	Country					
First world marketing	*Date*					
	Country					

Section E: Line Extension Products launched onto the world market for the first time in 2001 by your company

DID YOU LAUNCH ANY LINE EXTENSION PRODUCTS ON ANY WORLD MARKET FOR THE FIRST TIME IN 2001? YES/NO

Please provide details regarding the active substance and line extension type for all Line Extension Products launched onto the world market for the first time in 2001. **Please complete the following table using the definitions provided on pages 8 and 9.**

- For Product Identifier, please provide the brand name of the Line Extension Product with any additional description to allow unique identification of the product (e.g. brand name + dosage).
- For Active Substance, please provide the generic name of the active substance
- For Line Extension Type choose from *New Combination* (1), *New Formulation* (2), *New Route of Administration* (3), *New Indication* (4), *New Patient Population* (5), *New Dosage Strength* (6), *New Dosing Schedule* (7), *Combination of options given* (8), or *Other* (9).
- When *Combination* (8) or *Other* (9) has been selected for Line Extension Type, please provide additional specifications in the last column.

Product Identifier	*Active Substance*	*Line Extension Type*	*Specify Other / combinations*

Section F: Estimate of NASs which your company will launch on the world market for the first time in 2002

Please provide the following information on NASs that your company has already launched or is hoping to launch onto the world market for the first time in 2002.

Generic name	*Biotech product*	*Therapeutic area*
	Yes/No	
	Yes/No	
	Yes/No	
	Yes/No	

Definitions

New active substance (NAS)	*A new active substance (NAS) is a chemical, biological or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a **'prescription only medicine'**, to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans.* ***The term NAS also includes:*** • *an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available;* • *a biological substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process;* • *a radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.*
Line extension	*Chemical, biological or radiopharmaceutical substance that **has been previously available** for therapeutic use in humans and is destined to be made available as a 'prescription only' medicine, to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of disease in humans and for which both* • *clinical work (clinical trials and/or bioequivalence studies) additional to that conducted for the original product and;* • *a regulatory submission for approval to market are required.* ***This definition includes**:* • *new combinations of marketed active substances* • *new pharmaceutical formulations* • *new routes of administration* • *new indications* • *new patient populations* • *changes in dosage strengths* • *changes in dosing schedule* ***This definition excludes:*** • *Changes to manufacturing and control methods;* • *Changes to container and packaging* • *Changes to labelling other than those relating to new indications, formulations, dosage schedules and strengths patient population or route of administration*

Definitions (continued)

Biotech product	*A naturally occurring or modified polypeptide, protein, DNA or RNA product (produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals or transgenic plants) for therapeutic, prophylactic or in vivo diagnostic use in humans. The only vaccines included are recombinant vaccines.*
Brand name	*The accepted trade name of the NAS in each country.*
Electronic submission	*The provision of information to a regulatory agency on electronic media or by e-mail, either completely electronic (i.e. whole dossier available electronically) or partially electronic (i.e. part of the dossier available electronically).*
First synthesis	*The first synthesis or isolation of the NAS. Alternatively, for biotech NASs the first cloning or compound code assignment, if deemed more appropriate.*
First world marketing	*First launch of the NAS on any country i.e. goes on sale for the first time.*
Generic name	*The accepted name (or company code if unassigned) of the NAS.*
Marketing	*First launch of an NAS in a given country in the listed markets.*
Originating company	*Parent company responsible for first synthesising or isolating the NAS.*
Patent priority	*The date of the first ever patent application for the NAS with a patent office.*
Regulatory marketing authorisation	*The first marketing authorisation granted by the relevant national authority of each country in the listed markets, or by the European Commission through the Centralised procedure.*
Regulatory submission	*The first application for a marketing authorisation submitted to each country in the listed markets either by national application, or through the EU Centralised or Mutual Recognition procedures. For the EU Mutual Recognition procedure, where the country in question is a concerned member state (CMS) then the start date of the Mutual Recognition procedure should be used.*
Therapeutic area	*E.g. cardiovascular, nervous system, gastrointestinal, antiinfective etc.*

APPENDIX IV

QUESTIONNAIRE:

NEW MOLECULAR ENTITIES LAUNCHED ONTO THE WORLD MARKET (2000)

New Active Substances First Launched in 2000

Did your company introduce any NASs onto the world market for the first time during 2000?

Yes ❑ No ❑

If no, please sign this form below and return.

If yes, please provide the following details for each NAS first marketed in 2000 by your company. If more than one NAS was launched by your company in 2000, please make copies of this form as required.

Generic name _____

Brand name _____

Marketing company _____

Co-marketed Yes ❑ No ❑

Co-marketing company _____

Pharmacological class _____

First indication _____

Date of first world launch _____

Country of first launch _____

Please indicate important features of this compound, such as its pharmacological novelty, novel route of administration etc., that you would like us to consider including in our article.

.....
.....
.....
.....
.....
.....
.....
.....

This information has been provided by: .....

Position: ..... Date: .....

APPENDIX V

NEW MOLECULAR ENTITIES LAUNCHED ONTO THE WORLD MARKET (1998-2002)

NMEs included in the lists of new medicine launches 1998-2002 are new chemical entities (NCEs), new biological entities (NBEs) and new products of biotechnology which have not been previously available for therapeutic use in mane and are destined to be made available as a 'prescription only medicine', to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in man. Vaccines, new salts, pro-drugs, metabolites and esters of existing compounds and certain biological compounds (e.g. antigens) are not classified as NMEs. Combination products are excluded unless one or more of the constituents of the combination product has not bee previously available. Marketing companies are presented according to the company grouping at the time of first launch.

Table V.1 New medicine launches 1998

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
New Molecular Entities (NMEs)				
ACTONEL (risedronate)	Procter & Gamble/ Hoechst Marion Roussel	Bisphosphonate for Paget's disease of bone	August	USA
ACUTECT (technetium Tc 99m apcitide)	Diatide/ Nycomed Amersham	Scintigraphic imaging of acute venous thrombosis	October	USA
AGGRASTAT (tirofiban)	Merck & Co	Platelet IIbIIIa receptor antagonist for unstable angina	May	USA
ARAVA (leflunomide)	Hoechst Marion Roussel	Pyrimidine synthesis inhibitor for active rheumatoid arthritis	September	USA
AZOPT (brinzolamide)	Alcon	Carbonic anhydrase inhibitor for elevated intraocular hypertension or open-angle glaucoma.	June	USA
CLEACTOR **(Bt)** (monteplase)	Eisai	Plasminogen activator agonist for coronary thrombosis accompanying acute myocardial infarction	June	Japan
COMPTAN/ COMTESS (entacapone)	Orion/ Novartis	Catechol-O-methyltransferase inhibitor for Parkinson's disease	October	Sweden
CORLOPAM (fenoldopam)	Neurex	Dopamine D1 agonist for in-hospital, short-term management of severe hypertension	January	USA
DIASTABOL (miglitol)	Sanofi	Alpha glucosidase inhibitor for non-insulin dependent diabetes mellitus	May	Germany
ENBREL **(Bt)** (etanercept)	Immunex/ Wyeth Ayerst	Soluble tumour necrosis factor receptor for rheumatoid arthritis	November	USA
EVISTA (raloxifene)	Eli Lilly	Selective oestrogen receptor modulator for prevention of osteoporosis	January	USA
GASMOTIN (mosapride)	Dainippon	$5HT_4$ agonist for chronic gastritis	October	Japan
HERCEPTIN **(Bt)** (trastuzumab)	Genentech	Humanised monoclonal antibody for metastatic breast cancer	October	USA
INTEGRILIN (eptifibatide)	COR Therapeutics/ Schering Plough	Platelet IIbIIIa receptor antagonist for acute coronary syndrome and patients undergoing percutaneous coronary intervention	June	USA
MAXALT (rizatriptan)	Merck & Co	$5HT_{1D}$ agonist for treatment of migraine attacks	July	USA
MERIDIA (sibutramine)	Knoll	Serotonin and noradrenaline reuptake inhibitor for obesity	February	USA
MICARDIS (telmisartan)	Boehringer Ingelheim	Angiotensin II receptor antagonist for hypertension	November	USA
MIZOLLEN (mizolastine)	Synthelabo	Histamine H_1 antagonist for the symptomatic relief of seasonal allergic rhino conjunctivitis and urticaria	January	Germany
NEUMEGA **(Bt)** (oprelvekin)	Genetics Institute	Recombinant interleukin 11 for prevention of severe chemotherapy-induced thrombocytopenia	January	USA
PLAVIX (clopidogrel)	Bristol Myers Squibb/ Sanofi	ADP receptor antagonist for vascular ischemic events	March	USA

Table v.1 (continued) New medicine launches 1998

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
New Molecular Entities (NMEs)				
PRANDIN (repaglinide)	Novo Nordisk/ Schering Plough	Carbonyl methyl-benzoic acid derivative for type II diabetes	April	USA
PRIFTIN (rifapentine)	Hoechst Marion Roussel	Member of rifamycin class of antibiotics for pulmonary tuberculosis	October	USA
REGRANEX **(Bt)** (becaplermin)	Ortho-McNeil	Platelet-derived growth factor for the treatment of diabetic skin ulcers	February	USA
REMICADE **(Bt)** (infliximab)	Centocor	Tumour necrosis factor alpha inhibitor for Crohn's disease	October	USA
RENAGEL (severlamer hydrochloride)	GelTex/ Genzyme	Polymeric phosphate binder for the reduction of serum phosphorus in patients with end stage renal disease	November	USA
Revasc **(Bt)** (desirudin)	Aventis/ Novartis	Thrombin inhibitor for unstable angina and deep vein thrombosis	September	Germany
SIMULECT **(Bt)** (basiliximab)	Novartis	Monoclonal antibody for the prevention of acute rejection of transplanted kidneys	April	Switzerland
SUCRAID (sacrosidase)	Orphan Medical	Oral replacement therapy of genetically determined sucrase deficiency	July	USA
SUSTIVA (efavirenz)	DuPont	Non-nucleoside reverse transcriptase inhibitor for HIV infection	September	USA
SYNAGIS **(Bt)** (palivizumab)	MedImmune/ Abbott	Humanized monoclonal antibody for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children	September	USA
THYROGEN **(Bt)** (thyrotropin alpha)	Genzyme/ Knoll	Recombinant human thyroid stimulating hormone for use as an adjunctive diagnostic tool for serum thyroglobulin testing in the follow-up of patients with well-differentiated thyroid cancer	December	USA
TROVAN (trovafloxacin/ alatrovafloxacin)	Pfizer	DNA topisomerase ATP hydrolysing inhibitor for bacterial infections	January	USA
VIAGRA (sildenafil)	Pfizer	Cyclic GMP phosphodiesterase inhibitor for erectile dysfunction	May	USA
VITRAVENE (fomivirsen)	Isis Pharmaceuticals /Ciba Vision	Protein synthesis inhibitor for AIDS-related cytomegalovirus retinitis	November	USA
WINCEF (cefoselis)	Fujisawa	Cell wall synthesis inhibitor for gram-negative and -positive infections	September	Japan
XENICAL (orlistat)	Roche	Lipase clearing factor inhibitor for obesity	June	New Zealand
ZEMPLAR (paricalcitol)	Abbott	Synthetic vitamin D analogue for secondary hyperparathyroidism associated with chronic renal failure	May	USA

***(Bt)** Product of biotechnology*

Table V.2 New medicine launches 1999

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
New Molecular Entities (NMEs)				
ACTOS (pioglitazone)	Takeda / Lilly	Thiazolidinedione that sensitizes receptors, known as PPAR-gamma receptors, to the effects of insulin	August	USA
ADELE (colforsin daropate)	Nippon Kayaku	Inotropic, vasodilatory and adenylate cyclase activator activity for treatment of heart failure	March*	Japan
AGENERASE (amprenavir)	Glaxo Wellcome	HIV protease inhibitor	April	USA
AVALOX (moxifloxacin)	Bayer	A broad spectrum fluoroquinolone antibiotic active against both Gramnegative and -positive bacteria	September	Germany
AVANDIA (rosiglitazone)	SmithKline Beecham / Bristol-Myers Squibb	Thiazolidinedione that sensitizes receptors, known as PPAR-gamma receptors, to the effects of insulin	June	USA
AVISHOT (naftopidil)	Nippon Organon	Antihypertensive with alpha-adrenoceptor, calcium channel and 5-HT antagonist properties	April*	Japan

Table v.2 (continued) New medicine launches 1999

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
CELEBREX (celecoxib)	Searle / Pfizer	Selective inhibitor of cyclooxygenase-2 (COX-2) for treatment of symptoms of arthritis	February	USA
CETROTIDE (cetrorelix)	Asta Medica	A gonadotrophin-releasing hormone antagonist for prevention of premature ovulation in ovarian stimulation	May	Germany/ UK
CHOLEBINE (colestilan)	Mitsubishi-Tokyo / Yamanouchi	A non-absorbable bile acid sequestrant resin preparation with LDL-lowering activity	July	Japan
FASTIC/STARSIS (nateglinide)	Hoechst Marion Roussel / Yamanouchi	An orally active insulinotropic agent, with rapid onset and short duration of action	August	Japan
GADOVIST (gadobutrol)	Schering AG	A diagnostic imaging agent	January	Switzerland
HECTOROL (doxercalciferol)	Bone Care International	A synthetic vitamin D pro-hormone for use in secondary hyperparathyroidism	October	USA
IMPLANON (etonogestrel)	Organon	A female contraceptive	September	Netherlands
NEOTECT (technetium Tc 99m depreotide)	Diatide/ Nycomed Amersham	Imaging of suspected malignant tumours in the lung	September	USA
PANRETIN (alitretinoin)	Ligand Pharma-ceuticals	Retinoic acid receptor (RAR) and retinoid X receptor (RXR) pan-agonist for AIDS-related Kaposi's sarcoma	February	USA
RAPAMUNE (sirolimus)	Wyeth-Ayerst	A cytostatic immunosuppressant antibiotic for use in the prevention of transplant rejection	September	USA
RAPLON (rapacuronium bromide)	Organon	Neuromuscular blocking agents for use as muscle relaxant in general surgery	October	USA
RELENZA (zanamivir)	Glaxo Wellcome	Inhibits viral neuraminadase, an essential component in the replication of both type A and B influenza viruses	May	Australia
RIAMET (lumefantrine + artemether)	Novartis	An antimalarial for use in prophylaxis and treatment of infection	March	Switzerland
SHINBIT (nifekalant hydrochloride)	Mitsui	A class III antiarryhythmic agent for the treatment of serious ventricular arrhythmias	September	Japan
SUNPLA (SKI-2053R)	SK Pharma	An alkylating anticancer agent	December	South Korea
SONATA (zaleplon)	Wyeth-Ayerst	Interacts with the GABABenzodiazepine receptor-chloride channel macromolecular complex for the treatment of insomnia	May	Sweden
SYNERCID (quinupristin / dalfopristin)	Rhone-Poulenc Rorer	A semi-synthetic streptogramin antibiotic for treatment of nosocomial pneumonia, skin and soft-tissue infections and infections due to Enterococcus faecium	September	UK
TAMIFLU (oseltamivir)	Roche	Inhibits viral neuraminadase, an essential component in the replication of both type A and B influenza viruses.	October	Switzerland
TEQUIN (gatifloxacin)	Bristol-Myers Squibb	A broad spectrum fluoroquinolone antimicrobial with activity against Gram-negative, Gram-positive and some anaerobic organisms. Also active against chlamydia and mycoplasma.	December	USA / Mexico
TEMODAL (temozolomide)	Schering-Plough	Alkylating agent in new class of compounds called imidazotetrazines for refractory anaplastic astrocytoma	September	Various
TERANASE (lomerizine hydrochloride)	Pharmacia Upjohn	Antimigraine calcium antagonist	September	Japan
VALSTAR (valrubicin)	Anthra	DNA antagonist for bladder cancer	March	USA
VIOXX (rofecoxib)	Merck & Co	Selective inhibitor of cyclooxygenase-2 (COX-2) for treatment of symptoms of arthritis	February	Mexico
ZIAGEN (abacavir sulphate)	Glaxo Wellcome	Nucleoside reverse transcriptase inhibitor for HIV infection	January	USA
VISUDYNE (verteporfin)	Novartis	Radical formation agonist for treatment of wet-age related macular degeneration	December	Switzerland

Table v.2 (continued) New medicine launches 1999

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
Biologicals				
BEROMUN (tasonermin)	Boehringer Ingelheim	Recombinant human tumour necrosis factor alpha used as an adjunct to tumour removal surgery to prevent/delay amputation	September	Germany
Forcaltonin (calcitonin)	Unigene/ Strakan	A recombinant calcitonin stimulant for Paget's disease and hypercalcaemia of malignancy	October	UK
Glucagons	Eli Lilly	A recombinant glucagon for hypoglycaemia type 1 diabetes and diagnostic aid	March	USA
INFASURF (calfactant)	Forest	A calf lung surfactant for the prophylaxis and treatment of neonatal respiratory distress syndrome (RDS)	October*	USA
INSUMAN (recombinant human insulin)	Hoechst Marion Roussel	Recombinant human insulin for use in Type I and II diabetes	June	Germany
NOVORAPID (insulin aspart)	Novo Nordisk	An insulin analogue for treating Type I and Type II diabetes	September	UK
ONTAK (denileukin diftitox)	Ligand Pharma-ceuticals	Cytotoxic fusion protein designed to direct cytocidal action of diphtheria toxin to cells which express the IL-2 receptor	February	USA
REFACTO (moroctocog alfa)	Wyeth-Ayerst	A recombinant factor VIII for the treatment of Haemophilia A	April	Germany
SOLINASE (pamiteplase)	Yamanouchi	Modified tissue plasminogen activator for coronary thrombosis accompanying acute myocardial infarction	February	Japan
STEMGEN (ancestim)	Amgen	A recombinant stem cell factor for the treatment of certain types of anaemia, bone marrow failure and as a radio / chemoprotective agent	October	Canada

Table V.3 New medicine launches 2000

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
New Molecular Entities (NMEs)				
ALMOGRAN (almotriptan)	Almirall-Prodesfarma	Highly selective 5-HT1B/1D-agonist with rapid onset and consistent efficacy for the rapid relief of migraine attacks	September	Spain
ANGIOMAX **(B)** (bivalirudin)	The Medicines company	Intravenous direct thrombin inhibitor for use as an anticoagulant in patients undergoing percutaneous transluminal coronary angioplasty (PTCA)	July	New Zealand
ANTAGON (ganirelix)	NV Organon	Convenient GnRH antagonist for effective prevention of premature LH surges in Controlled Ovarian Hyperstimulation (COH) in the treatment of infertility	May	USA
AROMASIN (exemestane)	Pharmacia	Irreversible steroidal aromatase inactivator for the treatment of postmenopausal hormonal-sensitive advanced breast cancer	January	Germany
BAYNAS (ramatroban)	Bayer	Thromboxane A2 antagonist for the treatment of allergic rhinitis	May	Japan
DaTSCAN (ioflupane 123I)	Nycomed Amersham	First objective test to help differentiate essential tremor from Parkinsonism syndromes by detecting loss of functional dopaminergic neuron terminals in the striatum	September	EU
CEREDIST **(B)** (taltirelin)	Tanabe Seiyaku	Orally active thyrotropin releasing hormone (TRH) derivative for the treatment of spinocerebellar degeneration	September	Japan
DIOTUL (dosmalfate)	Faes	Gastroprotective drug for the prevention and treatment of NSAID-induced gastropathy	May	Spain
EVOXAC (cevimeline)	Daiichi / Snow Brand	Muscarine M1-agonist indicated for the treatment of dry mouth associated with Sjögren's syndrome	March	USA
KALETRA (lopinavir+ritonavir)	Abbott	HIV protease inhibitor with a high genetic barrier	September	USA
KEPPRA (levetiracetam)	UCB Pharma	Orally-active acetylcholine agonist for the treatment of epilepsy	April	USA
LANTUS/OPTISULIN **(B)** (insulin glargine)	Aventis	Long-acting analogue of human insulin indicated for glucose control in diabetes	June	Germany
LEVULAN (5-aminolevulic acid)	Schering AG	Topical photodynamic therapy for multiple actinic keratoses of the face and scalp	September	USA

Table v.3 (continued) **New medicine launches 2000**

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
LOTRONEX (alosetron)	Glaxo Wellcome	5-HT3-antagonist for the treatment of irritable bowel syndrome where diarrhoea is the predominant symptom	March	USA
MYLOTARG **(B)** (gemtuzumab ozogamicin)	Wyeth-Ayerst	Conjugate composed of an anti-CD33+ humanised antibody, a linker and a potent anti-neoplastic antibiotic, calicheamicin for the treatment of relapsed acute myeloid leukaemia	June	USA
OptiMARK (gadoversetamide)	Mallinckrodt	Diagnostic contrast medium for magnetic resonance imaging of brain, spine and liver lesions	March	USA
OXAROL (maxacalcitol)	Chugai	Vitamin D receptor derivative for the treatment of sec. hyperparathyroidism in hemodialysis patients	September	Japan
PRECEDEX (dexmedetomidine)	Abbott	α2-adrenoreceptor agonist for use in initially intubated and mechanically ventilated post-operative intensive care patients as an injectable sedative with analgesic properties with no respiratory depression	March	USA
SIMDAX (levosimendan)	Orion Pharma	Calcium sensitiser for the treatment of acute heart failure	October	Sweden
STOGAR (lafutidine)	UCB Pharma / Taiho	A potent and long-acting second generation histamine H2-receptor antagonist with a unique gastroprotective action	April	Japan
TALION (bepotastine besilate)	Tanabe Seiyaku	Non-sedative histamine H1-antagonist for the treatment of allergic rhinitis, lacking anti-CH/5-HT effects	October	Japan
TARGRETIN (bexarotene)	Ligand Pharma-ceuticals	Selective retinoid X receptor agonist for the treatment of all stages of cutaneous T-cell lymphoma	January	USA
TIKOSYN (dofetilide)	Pfizer	Potassium channel antagonist for the prevention of atrial flutter and atrial fibrillation	January	USA
TNKase **(B)** (tenecteplase)	Genentech	Plasminogen activator agonist to be used as a trombolytic in the treatment of myocardial infarction	June	USA
TRACTOTILE (atosiban)	Ferring	Injectable uterine-specific oxytocin antagonist with negligible systemic activity to be used as a labour inhibitor for pre-term labour	April	Austria/ Denmark/ Sweden
TRISENOX (arsenic trioxide)	Cell Therapeutics	Apoptosis agonist for the treatment of Acute Promyelocytic Leukaemia (APL)	September	USA
WELCHOL (colesevelam)	Sankyo	Non-absorbed lipid-lowering polymer used for the treatment of hypercholesterolaemia by binding bile acids in the intestine, impeding their reabsorption	September	USA
YASMIN **(B)** (drosperinone ethinylestradiol)	Schering AG	Female contraceptive combining ethinylestradiol with the new progestomimetic drosperinone, a progesterone agonist with antimineralocorticoid and antiandrogenic activity	November	Germany
ZEFNART (liranaftate)	Thorii Pharma-ceutical Co	Sqaulene epoxidase inhibiting antifungal for the topical treatment of dermatological infections including trichophytosis	August	Japan
ZELDOX (ziprasidone)	Pfizer	Atypical antipsychotic D2/5-HT2-antagonist for the treatment of schizophrenia	September	Sweden
ZOMETA (zoledronate)	Novartis	Biphosphonate antiosteoporotic agent acting as an osteoclast bone resorption inhibitor for the treatment of tumour-induced hypercalcaemia (TIH)	October	Canada
ZYVOX (linezolid)	Pharmacia	Oxazolidinon protein synthesis, active against all gram-positive bacteria, for the treatment hospital acquired pneumonia, community acquired pneumonia, skin and soft tissue infections and vancomycin-resistant enterococcal infections (VRE)	April	USA
Other products launched in 2000 (not classified as NMEs)				
Artecef 50 and 150 (artemotil)	ARTECEF BV	Agent against infection by Protozoa	May	The Netherlands
CHIROCAINE (levobupivacaine)	Purdue Pharma	Sodium channel antagonist indicated for local or regional anaesthesia in surgery and obstetrics, and post-operative pain management	March	USA
LEVOMET (l-dopa-methylester)	Chiesi	Oral levodopa prodrug with a more rapid onset of clinical activity for the adjunctive treatment of motor fluctuations in Parkinsonian patients	February	Italy
NEXIUM (esomeprazole)	AstraZeneca	First proton pump inhibitor (PPI) to be developed as an isomer, for the treatment of peptic ulcers and gastrooesophageal reflux disease (GORD)	September	Sweden

Table v.3 (continued) New medicine launches 2000

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
REMINYL (galantamine hydrobormide)	Janssen-Cilag /Shire	Selective, competitive and reversible AchE-inhibitor which also enhances the intrinsic action of acetylcholine on nicotinic receptors for the treatment of Alzheimer's disease	September	UK
VIRAFERONPEG/ PEGINTRON **(B)** (peginterferon α-2b)	Schering Plough	Pegylated, long-acting interferon alpha 2b for the treatment of hepatitis C	June	Germany/ UK

***(B)** biologicals, including products of biotechnology*

Table V.4 New medicine launches 2001

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
New Molecular Entities (NMEs)				
ANACT C **(B)** (activated protein C)	Teijin Co.	Active form of protein C for the treatment of disseminated intravascular coagulation.	January	Japan
ARANESP **(Bt)** (darbepoetin alfa)	Amgen	Long-acting recombinant erythropoietic protein for the treatment of anaemia associated with chronic renal failure (CRF).	June	Germany/the Netherlands
CAMPATH **(B)** (alemtuzumab)	Berlex Laboratories (Schering AG)	Humanized monoclonal antibody treatment for patients with B-cell chronic lymphatic leukemia (B-CLL) who have been treated with alkylating agents and have failed fludarabine therapy.	May	USA
CANCIDAS (caspofungin acetate)	Merck & Co	The first of a new class of antifungals, the echinocandins, which inhibit fungal cell wall systhesis. It is indicated for the treatment of invasive aspergillosis in patients who are refractory to or intolerant of other treatments.	February	USA
CLENAL (fudosteine)	Mitsubishi Pharma Corporation	Mucoregulator for the treatment of Chronic Obstructive Pulmonary Disease (COPD).	December	Japan
CroFab **(Bt)** (Crotalidae Polyvalent Immune Fab Ovine)	Savage Laboratories	Ovine polyclonal antibody-based product used for the treatment of minimal or moderate North American crotalid envenomation.	January	USA
EASYEF **(Bt)** (epidermal growth factor)	Daewoong Pharma-ceuticals	Recombinant human epidermal growth factor (EGF) used in the treatment of diabetic foot ulcers.	September	South Korea
FASTURTEC **(Bt)** (rasburicase)	Sanofi-Synthélabo	Recombinant urate oxidase enzyme used as a detoxifying agent for the treatment and prophylaxis of acute hyperuricaemia.	May	UK
FIBLAST **(Bt)** (trafermin)	Kaken	Recombinant human basic fibroblast growth factor indicated for the treatment of intractable skin ulcers.	June	Japan
FULSTAN (falecalcitriol)	Kissei Pharma-ceuticals	Vitamin D analogue for the treatment of secondary hyperparathyroidism due to chronic renal failure (CRF).	August	Japan
GLEEVEC/GLIVEC (imatinib/mesylate)	Novartis Pharma AG	Tyrosine kinase inhibitor for the treatment of chronic myeloid leukemia.	May	USA
KETEK/LEVVIAX (telithromycin)	Aventis	The first of a new class of antibiotics, the ketolides, indicated for the treatment of respiratory infections (community acquired pneumonia (CAP), acute sinusitis, exacerbations of chronic bronchitis and tonsilitis/pharangitis.	October	Germany
KINERET **(Bt)** (anakinra)	Amgen	Recombinant non-glycosylated interleukin-1 receptor antagonist for the treatment of rheumatoid arthritis.	November	USA
LULLAN (perospirone hydrochloride)	Sumitomo	Atypical serotonin-dopamine antagonist (SDA) for the treatment of positive and negative schizophrenic symptoms.	February	Japan
LUMIGAN (bimatoprost)	Allergan	Selective prostamide for the reduction of elevated intraocular pressure (IOP).	April	USA
LUVERIS (Bt) (lutropin alfa)	Serono	First pure recombinant human luteinising hormone for the treatment of female infertility.	May	Italy
METVIX (methyl aminolevulinate)	PhotoCure ASA	Photodynamic therapeutic agent for the treatment of basal cell carcinoma and actinic keratosis. Applied as a cream and activated by a proprietary light source, CureLight.	October	Sweden

Table v.4 (continued) New medicine launches 2001

First Brand Name (Generic Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
MYOBLOC **(B)** (botulinum toxin B)	Elan	Non-A botulinum toxin for longer acting relief of cervical dystonia. In the EU it is launched as NeuroBloc.	January	USA
NATRECOR **(Bt)** (nesiritidine citrate)	Scios Inc.	Recombinant form of human B-type natriuretic peptide for the treatment of acute congestive heart failure.	August	USA
OP-1 Implant **(Bt)** (osteogenic protein 1)	Stryker	Alternative to autograft in recalcitrant long bone non-unions where use of autograft is unfeasible and alternative treatments have failed.	May	Australia
OVIDREL **(Bt)** (choriogonadotropin alfa)	Serono	Recombinant human chorionic gonadotrophin used in infertility treatment.	April	USA
RADICUT (edaravone)	Mitsubishi Pharma Corporation	Neuroprotectant (free radical scavenger) in the treatment of acute-stage cerebral infarction.	June	Japan
RELPAX (eletriptan)	Pfizer	5-HT1B/1D receptor agonist for the treatment of migraine.	May	Australia
RESOVIST (ferucarbotran)	Schering AG	Liver-specific magnetic resonance imaging contrast agent.	September	Sweden
TOTELLE SEKVENS (trimegestone +17β-estradiol)	Wyeth Pharmaceutica ls	Combination product of the new progestomimetic trimegestone with 17β-estradiol used for the treatment of vasomotor symptoms and for the prevention of osteoporosis with endometrial protection.	March	Sweden
TRACLEER (bosentan)	Actelion	Oral sulfonamide-based endothelin-A and –B receptor antagonist indicated for the treatment of pulmonary arterial hypertension.	December	USA
TRAVATAN (travoprost ophthalmic solution)	Alcon	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.	March	USA
VIREAD (tenofovir disoproxil fumarate)	Gilead Sciences, Inc.	Nucleotide analogue reverse transcriptase inhibitor for the treatment of HIV infection for use in combination with other antiretrovirals.	November	USA
XIGRIS **(Bt)** (drotrecogin alfa)	Eli Lilly	Recombinant human activated protein C reducing mortality in adult patients with sepsis associated with acute organ dysfunction.	November	USA
ZELMAC (tegaserod maleate)	Novartis Pharma AG	Partial 5-HT4 receptor agonist for the treatment of irritable bowel syndrome (IBS).	July	Mexico
ZOFENIL/BIFRI (zofenopril)	Menarini	Angiotensin-converting enzyme (ACE) inhibitor indicated for the treatment of mild to moderate essential hypertension.	January	Italy
Other products launched in 2001 (not classified as NMEs)				
NEOCLARITYN (desloratadine)	Schering-Plough	This anti-histamine is the active metabolite of loratadine (Claritine) and is used for the treatment of seasonal allergic rhinitis.	January	Germany
PEGASYS **(Bt)** (peginterferon alfa-2a)	Roche	Pegylated interferon alfa-2a for the treatment of chronic hepatitis C.	September	Switzerland
VALCYTE (valganciclovir)	Roche	Oral prodrug derivative of ganciclovir for the treatment of AIDS related cytomegalovirus (CMV) retinitis.	June	USA
XYZAL (levocetirizine)	UCB Pharma Ltd	Isolated potent eutomer of cetirizine (Zyrtec) for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.	February	Germany

***(B)** Biological; **(Bt)** Product of biotechnology*

Table V.5 New medicine launches 2002

Generic Name (First Brand Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
New Molecular Entities (NMEs)				
Adefovir dipivoxil (Hepsera)	Gilead Science	A nucleotide analogue that blocks the replication of the hepatitis B virus. Used in the treatment of treatment of chronic hepatitis B.	September	USA

Table v.5 (continued) New medicine launches 2002

Generic Name (First Brand Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
Amrubicin hydrochloride (Calsed)	Sumitomo	An anthracycline antibiotic used in the treatment of non-small and small cell lung cancer>	December	Japan
Aripiprazole (Abilify)	Bristol-Myers Squibb / Otsuka	An antipsychotic quinoline derivative that stabilises dopamine/seratonin systems. Used in the treatment of schizophrenia.	November	USA
Balofloxacin (Baloxin)	Choongwae	A fluoroquinoline antibiotic.	September	South Korea
Digoxin Antibody (Digifab) **(B)**	Protherics	A sheep-derived polyclonal antibody. Used for the treatment of digoxin toxicity.	February	USA
Dutasteride (Avodart)	GlaxoSmith-Kline	An inhibitor of type 1 & 2 5-Alpha-reductase. Used in the treatment of benign prostatic hyperplasia.	November	USA
Ertapenem sodium (Invanz)	Merck & Co	A long acting carbapenem antibiotic. Used in the treatment of bacterial infections.	February	USA
Etoricoxib (Arcoxia)	Merck & Co	A COX-2 inhibitor. Used for the relief of pain associated with osteo and rheumatoid arthritis.	January	Mexico
Ezetimibe (Ezetrol)	Schering-Plough / Merck & Co	A hypolipaemic, used to inhibit the absorption of cholesterol into the blood.	November	Germany
Fondaparinux sodium (Arixtra)	Sanofi-Synthelabo & Organon	A pentasaccharide that inhibits activated Factor X. Used in the prophylaxis of deep vein thrombosis.	February	USA
Frovatriptan succinate (Migard)	Elan / UCB	A 5-HT receptor agonist. Used in the treatment of migraine.	June	USA
Fulvestrant (Faslodex)	AstraZeneca	An oestrogen antagonist. Used as an anti-cancer agent in the treatment of hormone receptor-positive metastatic breast cancer.	May	USA
Gefitinib (Iressa)	AstraZeneca	An epidermal growth factor receptor. Used as an anti-cancer agent. Targets cell surface receptors and intracellular signal transduction pathways.	August	Japan
Ibritumomab tiuxetan (Zevalin) **(Bt)**	IDEC	A targeted injectable radiation therapy. Used in the treatment of relapsed or refractory low grade, follicular, or transformed B-cell non-Hodgkin's lymphoma (NHL).	March	USA
Landiolol hydro-chloride (Onoact)	Ono	An ultra short acting b-blocker. Used in the treatment of operation-related tachycardia.	September	Japan
Micafungin (Mipamine)	Fujisawa	A fungal 1,3-b-glucan synthase inhibitor. Used as a antifungal agent.	December	Japan
Neridronate (Nerixia)	Abiogen	A hypocalcaemic agent. Used in the treatment of osteogenesis imperfecta.	June	Italy
Nitisinone (Orfadin)	Rare Disease Therapeutics	A competitive inhibitor of 4-hydroxyphenyl-pyruvate dioxygenase. Indicated as an adjunct to restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosenemia Type I.	August	USA
Norelgestromi (Ortho Evra)	Ortho-McNeil Pharmaceutical (Johnson & Johnson)	A combination oestrogen agonist/ novel progesterone agonist used as a non-invasive form of reversible contraception.	April	USA
Olmesartan medoxomil (Benicar)	Sankyo & Forest Labs	An imidazole-5-carboxylic acid derivative. Used in the treatment of hypertension. Works as an angiotensin 2 receptor antagonist.	April	USA
Pazufloxaci (Pasil)	Mitsubishi / Toyama	A quinalone antibacterial. Used in the treatment of bacterial infections.	September	Japan
Pimecrolimus (Elidel)	Novartis	An ascomycin macrolactam derivative. Used in the treatment of atopic dermatitis.	March	USA
RhBMP-2 (Infuse Bone Graft) **(Bt)**	Medtronic Sofamor Danek	A recombinant bone morphogenic protein, used as an osteoinductive agent. It activates cells that form and remodel cartilage and bone.	July	USA
Sivelestat (Elaspol)	Ono	A neutrophil elastase inhibitor. Used in the treatment of systemic inflammatory response syndrome (SIRS) related lung injury.	June	Japan
Temoporfin (Foscan)	Biolitec AG	A photosensitising agent, used in the treatment of primary, secondary and advanced head and neck cancer.	January	UK
Teriparatide (Forteo)	Eli Lilly	Recombinant bone formation stimulant used in the treatment of osteoporosis	December	USA

Table v.5 (continued) **New medicine launches 2002**

Generic Name (First Brand Name)	Marketing Company	Action/Indication	Month of First Launch	Country of First Launch
Tiotropium bromide (Spiriva)	Boehringer Ingelheim / Pfizer	A M3 anti-muscarinic agent. Used in the treatment of chronic obstructive pulmonary disease.	June	Netherlands & Philippines
Valdecoxib (Bextra)	Pharmacia / Pfizer	A Cox-2 inhibitor. Indicated for the treatment of arthritis and pain.	April	USA
Voriconazole (Vfend)	Pfizer	An antifungal. Used in the primary treatment of acute invasive aspergillosis.	August	USA
Other products launched in 2002 (not classified as NMEs)				
Dexmethylphenidate HCl (Focalin)	Celgene	A single isomer of methylphenidate (Ritalin). Used in the treatment of attention deficit hyperactivity disorder.	January	USA
Escitalopram oxalate (Cipralex)	Lundbeck / Forest Labs	An S-enantiomer of citalopram. Used in the treatment of depression and panic disorders.	March	Switzerland
Mycophenolic acid (Myfortic)	Novartis	An immunorepresant designed to stop organ rejection in renal transplant patients.	October	Switzerland
Parecoxib (Dynastat)	Pharmacia	A Cox-2 inhibitor. Used as an anti-inflammatory and for the relief of acute pain. A prodrug of valdecoxib.	May	UK
Pegfilgrastim (Neulasta) **(Bt)**	Amgen	A covalent conjugate of recombinant methionyl human G-CSF (Filgrastim) and monometh-oxypolyethylene glycol. Used in the treatment of infection.	April	USA

***(B)** Biological; **(Bt)** Product of biotechnology*

APPENDIX VI

QUESTIONNAIRE:

GLOBAL ETHICAL DEVELOPMENT PIPELINE (2001)

Background

CMR International Ltd. collects confidential data annually from the leading pharmaceutical companies describing their pharmaceutical R&D expenditure, global sales, clinical development pipeline and new active substances launched on to the major pharmaceutical markets. The 50 leading companies by R&D expenditure, the 10 leading biotech companies, the 20 leading Japanese companies and all additional members of CMR International's Institute for Regulatory Sciences are being invited to provide information for 2001 with estimates for 2002. This information will be collected on three separate questionnaires: 1) R&D Expenditure and Sales, 2) Global Ethical Development Pipeline and 3) New Active Substance Activity. This Global Ethical Development Pipeline questionnaire is designed to collect up-to-date information on NASs in the pipeline annually.

Confidentiality

All information collected from individual companies will be kept strictly confidential. No information which will identify an individual company will be reported, and no details will be made available to a third party. The report will include only aggregated figures and any appropriate analytical interpretation. CMR International has over 20 years' experience in handling highly confidential information and the continuing and growing support for the Centre's surveys demonstrates the confidence which respondents have in its integrity.

Inclusion criteria

Provide details of all NASs that were in your development pipeline in 2001. Include all NASs which have completed the first animal toxicity study required for the first ever administration to humans, but have not been approved for marketing before 31st December 2001. Any NASs that were identified in last year's survey as being in development on 31st December 2000 have been automatically included. The phase of development of these NASs on **31st December 2001** should be indicated. If you are unable to provide all of the information requested, please leave the relevant boxes blank.

Definitions

Section 1. Definitions for NASs in development	
New active substance (NAS)	*A new active substance (NAS) is a chemical, biological or radiopharmaceutical substance that has not been previously available for therapeutic use in humans and is destined to be made available as a **'prescription only medicine'**, to be used for the cure, alleviation, treatment, prevention or in vivo diagnosis of diseases in humans.* ***The term NAS also includes:*** • *an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously available as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously available* • *a biological substance previously available as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process and which will require clinical investigation.* • *a radiopharmaceutical substance that is a radionuclide or a ligand not previously available as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide has not been previously available.*
Generic name	*The accepted name or company code of the NAS.*
Origin of NAS	
Self-originated	*The NAS was discovered as a result of research conducted either entirely by your company, by a wholly owned subsidiary of your company, or by an entity that is wholly a part of your merged organisation.*
Licensed-in or acquired	*Licensed, purchased or otherwise acquired from outside your company (e.g. from another company, a university, government agency, or an individual).*
Collaboration/spon. research	*The NAS was discovered as a result of research carried out in collaboration with, or sponsored by, another: company, a university, government agency or an individual.*
Priority Scale 01	*Select the term which best matches the priority this NAS had within your company as of 31st December 2001. If this NAS is not prioritised then select No priority.*

Definitions (continued)

Type	*Use the categories below to describe the compound type if none of the categories are suitable, describe it in your own words. NCE: a new entity (excluding new salts or esters) produced by chemical synthesis. Biotech product: a naturally occurring or modified polypeptide, protein, DNA or RNA product (produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals or transgenic plants) for therapeutic, prophylactic or in vivo diagnostic use in humans. The only vaccines included are recombinant vaccines. Biological: a substance isolated from animal tissues eg vaccines, hormones, antigens. Gene Therapy Product: gene or oligonucleotide produced by recombinant DNA technology delivered using a non-endogenous vector.*
Projected peak annual sales of NAS	*This is the maximal level of annual sales that you are expecting from this NAS.*
Pharmacological mode of action	*The pharmacology of the NAS, e.g. selective 5HT2 antagonist.*
Established mode of action	***Yes, established:*** *a compound with the same mode of action as this NAS has been marketed by either your company or by any other company.* ***No, established:*** *the mode of action for this NAS is novel (i.e an NAS with the same mode of action has not already been marketed).* ***NA, information not available:*** *your company is unable to supply the mode of action for this NAS.*
Therapeutic area	*Describe the general therapeutic class of the NAS, e.g. CVS, Nervous system*
Definitions for latest stage of clinical development on 31-Dec-2001	
Preclinical	*Preclinical development to support administration to man. Starts from the first animal toxicity study required for the first ever administration of this NAS to humans.*
Phase I	*The administration of the NAS to healthy volunteers (or when appropriate, to patients, e.g oncology compounds) to assess dose range, tolerability and/or pharmacokinetics or pharmacodynamics.*
Phase II	*The administration of the NAS to patients,(between 100-300) in controlled trials to assess the safety profile, dosage and efficacy of the NAS for the target indication.*
Phase III	*The administration of an NAS in large-scale patient studies (between 1000-3000), in controlled multi-centre trials to demonstrate safety, efficacy and clinical benefit.*
Pre-submission	*The last patient visit for the last pivotal study to be included in the regulatory dossier is complete and the dossier is being prepared, but has not yet been submitted to a regulatory authority.*
Submitted	*A dossier relating to an NAS has been submitted to a regulatory authority, but your company has not yet received a marketing authorisation.*
Approved	*The NAS has been approved in one or more markets.*
Marketed	*The NAS has been launched in one or more markets.*
Terminated	*The NAS is no longer in active clinical development; its development has been terminated. Provide the termination date and reason(s) in Section 4.*
Section 2. Definitions for Drug Discovery Technologies	
Bioinformatics	*The use of search programmes (public domain, proprietary or in-house programmes) to analyse DNA and protein sequences to predict the function of a gene sequence.*
Chemo-informatics	*A generic term that encompasses the design, creation, organisation, storage, management, retrieval, analysis, dissemination, visualisation and use of chemical information, not only in its own right, but as a surrogate or index for other data, information and knowledge.*
Combinatorial chemistry (molecular diversity)	*Generation of large numbers of diverse chemical compounds (proteins, nucleic acids, carbohydrates) for use in screening assays against disease target molecules.*
Comparative genomics	*The use of model organism databases to identify genes that are conserved across species in order to gain insight into the possible function of human genes.*

Definitions (continued)

Functional genomics	*The assignment of a function to a gene (and hence to a protein) that previously had no known function, through knock-in (gene insertion) or knock-out (gene deletion) technology in animals, or other models/studies designed to elicit cellular or physical responses.*
High through-put screening	*The use of fully-automated, flow-through systems that rapidly evaluate and characterise the activity, potencies, target specificity's and cell-type selectivity's of compounds to identify the most promising potential therapeutic compounds based on their functional biological properties.*
Proteomics	*The separation, identification and characterisation of proteins present in a biological sample and comparison of disease and control samples to identify "disease specific proteins". These proteins may have potential as targets for drugs or as molecular markers of disease.*
Rational drug design *(structure-based drug design)*	*Use of high resolution molecular imaging techniques (NMR, x-ray crystallography) to identify the active site of the target molecule and use of this information to construct an NAS which binds to this active site.*
Section 3. Definition of Prioritisation Policy	
Priority policy	*Indicate if your company has a policy to prioritise compounds in development.*
Section 4. Definitions for All Terminated NASs	
Toxicology	*Identification of potential hazards (e.g. biochemistry, clinical chemistry, pathology) in non-clinical studies (in vitro and in vivo), conducted at any time during the development of the NAS which, when extrapolated to the potential risk to humans, precluded further development.*
Preclinical pharmaco-kinetics/bio-availability	*The absorption, distribution, metabolism and elimination (ADME) characteristics in non-clinical studies, from which extrapolation of potential pharmacokinetic/bioavailability profile in humans precludes further development.*
Clinical pharmaco-kinetics/ bio-availability	*The absorption, distribution, metabolism and elimination (ADME) characteristics in human subjects (patients and healthy volunteers), suggests that the pharmacokinetic/bioavailability profile in humans precluded further development.*
Preclinical efficacy	*Evidence that the ability of the NAS to have a beneficial disease modifying effect or diagnostic value in non-clinical studies, was weak/less than expected as measured by objective or subjective parameters and was directly due to the pharmacology of the NAS*
Clinical efficacy	*Evidence that the clinical effect of the NAS is either therapeutically not meaningful, therapeutically not sufficient (compared to competitors) or not statistically significant*
Clinical safety	*The safety of the NAS, for example based on the benefit-to-risk ratio established during clinical development, was considered to be unacceptable.*
Formulation	*The properties of the NAS (e.g. solubility, stability, absorption, palatability, odour, irritancy, bulk density, flow and compressive properties), or the chemical manufacture of the NAS, preclude pharmaceutical formulation.*
Cost of goods	*The cost of manufacturing and production of the NAS precluded further development.*
Portfolio considerations	*Development of the NAS is no longer justifiable as multiple scientific issues preclude its development (e.g. the characteristics of competitor NASs will not be matched or bettered) or the development is terminated for business purposes such as the rationalisation of the company portfolio or budget or resource constraints.*
Patent or commercial legal	*Patent issues, commercial legal reasons e.g. merger divestments preclude the further development of the NAS.*
Regulatory	*Issues which stem directly from regulatory authority decisions (e.g. restricted labelling) or a change in the regulatory requirement(s) for this NAS i.e. "a shift in the regulatory hurdle" mean further development would not be feasible.*
Other (specify)	*If this NAS was terminated for a relative reason that is not listed in the relative list then describe this reason.*

1. NASs in development

Please ensure that all NASs in your pipeline in 2001 (defined as an NAS which has completed the first animal toxicity study required for the first ever administration to humans, but has not been approved for marketing before 31st December 2001) are entered into this form and where possible identify by the generic name. NASs that have been provided in a previous round of data collection have been pre-entered to facilitate updating of active NASs. Terminated NASs have also been returned, complete with their termination date. If development of a terminated NAS has been resumed, indicate this by writing "reactivated" next to the generic name. For each NAS listed, please give information as requested in the table (definitions are provided on pages 2, 3, 7 and 8 of the questionnaire). Where a series of options are provided please circle the appropriate response. For the question relating to the latest stage of development achieved by 31st December 2001 please tick the relevant phase. For those NASs that entered phase I or were terminated during 2001 more information is required. Please turn to page 6 and complete the relevant table.

Representation of data table in questionnaire:

Generic Name	Type [1]	Origin [2]	Priority	Priority Scale [3]	Projected Peak Sales [4]	Pharmacological Mode of Action	Established Mode of Action	Therapeutic Area
		SO / LI / JR	Yes / No	H / M / L / NP	A / B / C / D / E / F		Yes / No / NA	
		SO / LI / JR	Yes / No	H / M / L / NP	A / B / C / D / E / F		Yes / No / NA	

[1] *NCE/ biological/ biotech/ gene-therapy/ other*
[2] *SO = self originated / LI = licensed-in / JR = joint research*
[3] *H = high / M = medium / L = low / NP = no priority*
[4] *A = $100-249m / B = $250-499m / C = $500-749m / D = $750m-1bn / E = >$1bn / F = <$100m*

Latest stage of clinical development as of 31st December 2001								
Preclinical	Phase I	Phase II	Phase III	Presubmission	Submitted	Approved	Marketed	Term Date

2. Drug Discovery Technologies

For NASs which entered Phase I in 2001 select from the list provided below the technologies which you believe were pivotal in the discovery of each NAS.

Bioinformatics	Chemoinformatics	Combinatorial chemistry
Comparative genomics	Functional genomics	High through-put screening
Proteomics	Rational drug design	Other (specify).

Generic name	*Drug Discovery Technologies*

3. Prioritisation of NASs

Does your company have a policy to prioritise NASs? Yes/No

4. All Terminated NASs

For all NASs that were terminated prior to 31st December 2001 provide the date and reason(s) for termination. If the decision to terminate a compound was for an absolute consideration (i.e. scientific or technical) then select a **single** reason from the **absolute** list. If the decision to terminate was **relative** e.g. multiple scientific/technical reasons or, was business-led then select the most appropriate reason(s) from the **relative** list.

ABSOLUTE

Toxicology
Preclinical pharmacokinetics/bioavailability
Clinical pharmacokinetics/bioavailability
Preclinical efficacy
Clinical efficacy
Clinical safety
Formulation
Cost of goods

RELATIVE

Portfolio considerations
Patent or commercial legal
Regulatory
Other (specify)

Generic name	*Last phase of development*	*Termination date (dd-mm-yy)*	*Termination reason(s)*

APPENDIX VII

THERAPEUTIC AREA CLASSIFICATION

All studies were allocated to therapeutic areas based on the indication under investigation within the study as provided by companies, using the WHO ATC system (WHO, 2002). *Additional categories to allow for more detailed allocation.

Table VII.1 Therapeutic area classification

Code	Description
	OTHER ALIMENTARY AND METABOLISM
A02	Antacids, drugs for peptic ulcer and flatulence
A03	Antispasmodic, anticholinergics and propulsives
A04	Antiemetics and antinauseants
A05	Bile and liver therapy
A07	Antidiarrheals, intestinal anti-Inflammatory/anti-infectives
A08	Antiobesity preparations, excl. diet products
A09	Digestives, incl. Enzymes
A10	Drugs used in diabetes
A15	Appetite stimulants
A16	Other alimentary and metabolism products
	BLOOD
B01	Antithrombotic agents
B02	Antihemmoragics
B03	Antianaemic preparations
B05	Blood substitutes and perfusion systems
B06	Other haematological agents
	CARDIOVASCULAR
C01	Cardiac therapy
C02	Antihypertensives
C03	Diuretics
C05	Vasoprotectives
C10	Serum lipid reducing agents
C11*	Renal failure
C12*	Septic shock
	DERMATOLOGICALS
D01	Antifungals for dermatological use
D02	Emollients and protectives
D03	Preparations for the treatment of wounds and ulcers
D04	Antipruritics incl. antihistamines and anaesthetics
D05	Antipsoriatics
D06	Antibiotics & chemotherapeutics for dermatological use
D07	Corticosteroids, dermatological preparations
D10	Anti-acne preparations
D11	Other dermatological preparations
	GU/SEX HORMONES
G02	Other gynaecologicals
G03	Sex hormones, modulators of the genital system
G04*	Urologicals
	HORMONES
H01	Pituitary, hypothalamic hormones and analogues
H03	Thyroid therapy
H05	Calcium homeostasis

Code	Description
	ANTI-INFECTIVES
J01	Antibacterials for systemic use
J02	Antimycotics for systemic use
J05	Antivirals for systemic use
J07	Vaccines
J08*	HIV
	ANTICANCER & IMMUNOMODULATORS
L01	Antineoplastic agents
L02	Endocrine therapy
L03	Immunostimulants
L04	Immunosuppressive agents
L05*	Adjunct therapy to cancer
	MUSCULOSKELETAL
M01	Anti-inflammatory and antirheumatic products
M03	Muscle relaxants
M04	Antigout preparations
M05	Drugs for treatment of bone diseases
M06*	Osteoporosis
M09	Other drugs for disorder of the musculoskeletal
	NERVOUS SYSTEM
N01	Anaesthetics
N02	Analgesics
N03	Antiepileptics
N04	Drugs for the treatment of Parkinson's disease
N05	Psycholeptics
N06	Psychoanaleptics
N07	Other nervous system drugs
N08*	Neurodegenerative Disease
N09*	Stroke
N10*	Multiple Sclerosis
	ANTIPARASITIC
P01	Antiprotozoals
P02	Antihelmintics
	RESPIRATORY
R01	Allergic rhinitus
R03*	Asthma
R06	Antihistamines for systemic use
R07*	Other respiratory system products
R08*	COPD
	SENSORY
S01	Ophthalmologicals
S02	Otological preparations
	VARIOUS
V08	Contrast media
V09	Diagnostic radiopharmaceuticals
V10	Therapeutic radiopharmaceuticals