Technology Trends in Drug Discovery and Development: Implications for the Development of the Pharmaceutical Industry in Australia

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1. Introduction

The process of developing a new drug to treat an illness is long, costly and uncertain. A number of studies have tried to estimate the cost, the most quoted figures being those from the US Pharmaceutical Manufacturers Association (PhRMA)[1] which are based on work done by DiMasi and others[2] at the Tufts Center in Boston. PhRMA estimates the cost at US$500 million over a period of 11 years from the initial research stage to the successful marketing of a new drug. More recent estimates by DiMasi[3] put the average cost at US$802 million spread over 12 years, while the Boston Consulting Group estimates the cost as $880 million over 15 years.[4] These estimates are averages and there is significant variation in both time and cost, depending on the nature of the disease being targeted, the type of drug being developed and the nature and scope of the clinical trials required to gain regulatory approval.[5]

Because of the political sensitivity of drug prices, especially in the USA, these estimates of new drug costs have been disputed by a number of organisations. Public Citizen, a consumer interest group, for instance, estimates average cost at closer to $100 million[6], with these estimates in turn being disputed by PhRMA.[7]

The costly nature of drug development means that pharmaceutical manufacturers must make large investments in R&D over extended periods of time and draw heavily on fundamental research carried out in universities and other research organisations. The pharmaceutical industry has the highest ratio of R&D spending to sales (estimated at 18.5% in 2001) of any industry in the USA[8] and this investment in R&D has been growing by about 13% per year over recent years.

The cost of developing drugs is rising, and this, combined with a perceived decrease in the productivity of R&D[9], has been the one of the major reasons for the mergers and acquisitions among pharmaceutical companies over recent years, as they seek to find and exploit economies of both scale and scope in drug R&D.[10]

The evidence on the success of this strategy is somewhat mixed however. CenterWatch for instance found that research spending and productivity declined sharply during the three years after a merger[11], while DiMasi points to the success of companies such as Johnson & Johnson, Lilly and Merck in maintaining relatively high rates of new product introductions without participating in major mergers or acquisitions[12]. Gambardella has also pointed to the ability of companies such as Merck and Lilly to sustain competitive advantage over long periods of time.[13]

The Director of Strategic Planning at Astrazeneca, has highlighted for the industry as a whole, the "widening gap between research and development spending and the number of new products to actually reach the market".[14] This declining productivity is partly due to the fact that all the simple disease targets have been addressed and those that are left are much more difficult to address from a traditional chemistry perspective, or their role in disease is not well understood.[15]

At the same time as R&D productivity appears to be stalling, there is increasing pressure from governments and private pharmaceutical purchasing bodies to reduce the cost of drugs. This has lead companies to pay increasing attention to reducing the

cost of developing drugs at each stage of the pipeline from basic research to market. Their strategies for achieving this are to improve the portfolio of promising drug candidates, to ensure that ineffective drug candidates are eliminated earlier in the process, and to reduce the time that successful candidates spend in each stage.

Aside from undertaking mergers, pharmaceutical companies have responded to the crisis in productivity by developing new capabilities internally, principally through recruiting new staff and through the acquisition of new platform technologies. They have also recognised that they will never be able to develop new drugs by relying solely on their own resources[16] and have entered into a variety of agreements with biotechnology and other companies that are working on particular disease areas, are investigating promising drug candidates, or are developing new tools and services.

Paralleling the growth of pharmaceutical companies over the last twenty years has been the rapid development of the biotechnology industry. Several human biotechnology companies specialising in the development of new drugs are now large companies in their own right and they have also engaged in increasingly widespread alliances with the established pharmaceutical companies, other biotechnology companies and research groups.

This greater interaction of pharmaceutical and biotechnology companies with outside organisations has opened up the opportunities for small technology based companies in Australia to participate more easily in the global pharmaceutical industry, and provides an avenue for Australian research in the life sciences and allied fields to be commercialised more effectively.

This paper describes the drug discovery and development pipeline in Section 2 before a more detailed discussion of the impact of technology on the pipeline stages in Section 3.

Section 4 identifies the expertise and capabilities in Australia that can contribute at different stages and where there are deficiencies. Section 5 concludes with a discussion of where Australia might concentrate its effort to enable a better participation in the global industry.

2. The Drug Discovery and Development Process

2.1 The Drug Discovery Pipeline

The process by which a new drug is brought to market stage is referred to by a number of names – most commonly as the development chain or "pipeline",[17] and consists of a number of distinct stages. The description of the process by the PhRMA is one of the most commonly used, and a modified version of this is set out in the box on the next page.

There are various estimates of the cost of each stage of the pipeline.[18] Most show that clinical trials is the most expensive stage and accounts for at least 40% of costs.

Table 1, for instance reports on R&D spending by pharmaceutical companies in the USA and shows that Phase I to III clinical trials comprise 29% of cost, Phase IV trials (post-marketing) make up 12%, with pre-clinical trials being 7%. These estimates do not include the cost of manufacturing, marketing and distributing the final drug.

Table 1 Allocation of US Pharmaceutical R&D by Function 1999, as percentage of total R&D cost

R&D Function	%
Discovery/Basic Research	
Synthesis and Extraction	10.0
Biological Screening and Pharmacological Testing	14.2
Preclinical Testing	
Toxicology and Safety Testing	4.5
Pharmaceutical Dosage Formulation and Stability	7.3
Clinical Trials	
Clinical Evaluation Phases I, II and III	29.1
Clinical Evaluation Phase IV	11.7
Process Development for Manufacturing and Quality Control	8.3
Regulatory: IND and NDA	4.1
Bioavailability	1.8
Other	9.0
Total	100.0

Source: PhRMA Annual Survey 2001 as reported in PhRMA, Pharmaceutical Industry Profile 2001, p15.

As mentioned in Section 1, there have been a number of estimates of the cost of developing a new drug. Some of these, such as the study by the Boston Consulting Group reported in Table 2, have also put a value on the cost of each stage in the pipeline.

Stages in drug discovery and development[19]

Discovery/Basic Research

- Synthesis and Extraction – the process of identifying new molecules with the potential to produce a desired change in a biological system
- Biological Screening and Pharmacological Testing – studies to explore the pharmacological activity and therapeutic potential of compounds

Preclinical Testing

- Toxicology and Safety Testing – tests to determine the potential risk a compound poses to humans and the environment, involve use of animals, tissue cultures or other test systems
- Pharmaceutical Dosage Formulation and Stability – the process of turning an active compound into a form and strength suitable for human use

Regulatory Review : IND

- Application to regulatory authority to use compound in human testing. In the US the compound is then called an Investigational New Drug (IND)

Phase I Clinical Trials

- Testing of a new compound in 20-80 healthy human volunteers to determine tolerance, pharmacological effects, and absorption, distribution, metabolism and excretion (ADME) patterns

Phase II Clinical Trials

- Trials in 100-300 patients with the targeted condition to determine effectiveness in treating disease or medical condition and short term risks

Phase III Clinical Trials

- Trials on 1000-5000 patients to determine clinical benefit and incidence of adverse reactions

Process Development for Manufacturing and Quality Control

- Engineering and manufacturing design activities to establish capacity to produce in large volumes and to ensure stability, uniformity and overall quality

Bioavailability Studies

- Use of healthy volunteers to show that formulation used in trials is equivalent to product to be marketed

Regulatory Review: NDA

- Application for approval to market a new drug. In the US this is called a New Drug Application (NDA)

Phase IV

- Post marketing trials to identify undetected adverse effects and long term morbidity and mortality profile

Table 2 Drug Discovery and Development Process
Boston Consulting Group, 2001

	Cost US$m	Cost %	Time years
Biology			
Target Identification	165	18.8	1.0
Target Validation	205	23.3	2.0
Chemistry			
Screening	40	4.5	.4
Optimisation	120	13.6	2.7
Development			
Preclinical	90	10.2	1.6
Clinical	260	29.5	7.0
Total	880	100.0	14.7

Source: Boston Consulting Group, A Revolution in R&D, November 2001 p12.

An alternative estimate by PAREXEL, based on a composite of sources, assigns more of the cost to the trials stages but is similar in the amount of time a drug spends at each stage (Table 3).

Table 3 Drug Discovery and Development Process
PAREXEL, 2001

	Years	% of cost
Basic research	2.5	4
Discovery	3.0	15
Preclinical development	1.0	10
Phase I	1.5	15
Phase II	2.0	22
Phase III	2.5	31
FDA review and approval	1.5	3
Total	14.0	100.0

Source: PAREXEL, PAREXEL's Pharmaceutical R&D Statistical Sourcebook, 2001, p 96.

These estimate, as well as the one by the Tufts Center, include an opportunity cost for the capital involved, as well as the cost of developing drug candidates that are ultimately unsuccessful. This recognises the very high rates of failure that occur as compounds move through the pipeline. A commonly cited ratio[20] is that for every drug that is finally approved by the regulatory authority for sale, 5 enter Phase I testing, and 250 enter preclinical testing after 5,000 -10,000 have been tested in the discovery stage.

CMR International has made more precise estimates of attrition rates at each stage based on reports from pharmaceutical companies, as shown in Table 4.[21]

Table 4 Attrition Rates for Compounds, 1998

Start of stage	Probability of reaching market %
Preclinical development	10.3
Phase I	18.4
Phase II	28.1
Phase III	65.8
FDA review and approval	90.6

Source: CMR International survey of 29 pharmaceutical companies in 1998 as reported in PAREXEL, op cit, p 195.

2.2 Types of Drugs

The traditional pharmaceutical industry has its roots in the dye and chemical industry over 100 years ago. The first pharmaceuticals were based on the somewhat accidental discoveries that chemicals derived from tars could have beneficial effects on some human diseases. Experiments were undertaken to create variants of these drugs to see if they could also be used to treat other diseases, and this approach proved to be very successful in the discovery and development of new drugs.[22]

This success created the dominant approach within the pharmaceutical industry to the creation of new drugs, namely the synthesis of variants of small molecular weight compounds as drug candidates. The compounds from which these variants are made were initially discovered by a combination of accident and luck, but became increasingly based on systematic attempts to exploit the increasing knowledge base of chemistry, biology and medicine. Over time, companies and research groups developed large libraries of compounds, which could be tested for effect against the disease of interest.

A second approach to drug development was to use the body's own biological molecules as disease treatments. This approach had already been pioneered in the 1920s by companies such as Lilly, which developed injectable insulin for the treatment of diabetes, but is most closely associated with the rise of biotechnology companies over the past 30 years. These companies sought to identify which naturally occurring biological molecules are associated with disease and to use newly discovered biotechnology methods to manufacture these compounds.

The main types of biotechnology drugs to reach the market have been monoclonal antibodies. These are proteins in the body that are part of the immune system that fights disease. They are made by a process of generating the antibodies in mice, then fusing these antibodies with immortal cancer cells, which produce further quantities of antibody through multiplication. The antibody is then separated from the culture.[23]

Other biotechnology based drugs include recombinant proteins such as cytokines, which are manufactured using recombinant DNA techniques. Here the gene which is responsible for making the protein is spliced into the genome of a bacteria or other vector which then produces the entity as it multiplies. The culture is then treated to remove and purify the entity.

Naturally occurring proteins are also made by non-recombinant techniques and collectively these types of drugs are usually referred to as biopharmaceuticals or biologicals.

Biologicals have a number of advantages and disadvantages when compared to synthetic drugs. Because they are naturally occurring compounds, there is less difficulty in convincing regulators of their safety and efficacy, which means that the cost of clinical trials is less and they can arrive at market earlier. On the other hand, their manufacture is more difficult and expensive, which means their price is often higher than traditional drugs. In addition, it is generally harder to ensure purity in manufacturing than it is for traditional drugs. The ability to manufacture biologicals in quantity is currently a serious issue with capacity severely limited around the world.[24] This has lead to efforts to find cheaper and more effective ways of manufacturing biologicals, such as through the use of genetically engineered crops.[25] Biologicals are often not suitable or effective for certain diseases. Finally, biologicals are often destroyed in the digestive system, so can only be administered by injection.

While it is often useful to differentiate established pharmaceutical companies from biotechnology companies in the pharmaceutical industry, in practice the distinction is becoming somewhat blurred. The established companies are increasingly turning to biotechnology techniques and approaches to discover and test new drugs,[26] either directly or through alliances, while the biotechnology companies are also making small molecule drugs.

In 2001, for instance, the US Food and Drug Administration (FDA) approved 32 new medicines of which 24 were small molecule drugs while 8 were biologicals. Biotechnology companies were responsible for 6 drugs and 6 biologicals, while pharmaceutical companies contributed 18 drugs and 2 biologicals – including Lilly's sepsis treatment Xigris, a recombinant version of human activated protein C.[27]

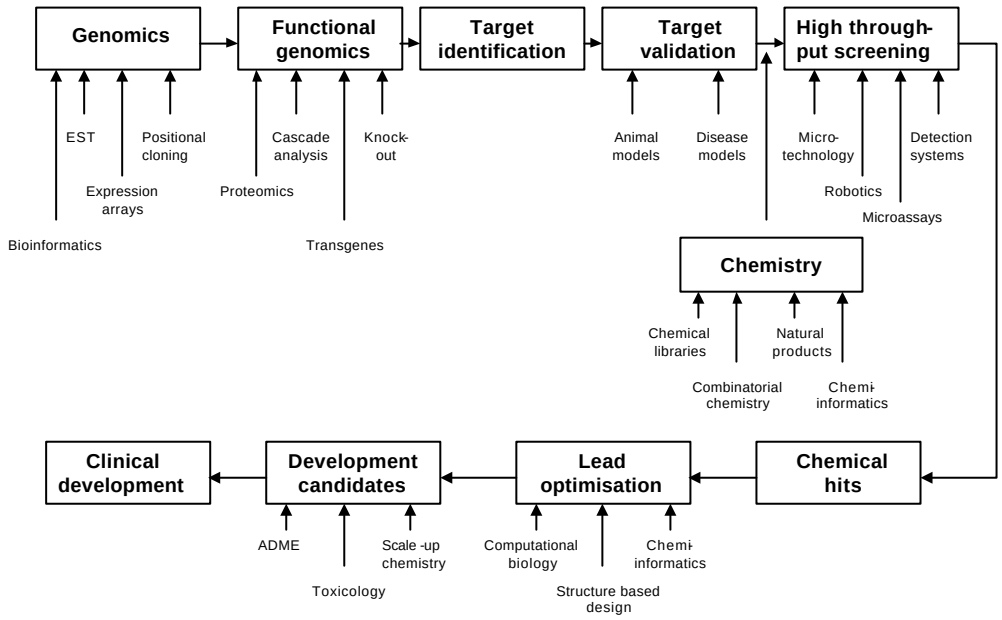
Some of the longer established biotechnology companies are now starting to reach a size comparable to the traditional pharmaceutical companies – Amgen for instance has a market capitalisation of about US$80 billion. They are therefore facing exactly the same pressures as the traditional pharmaceutical companies and this has lead to a similar wave of mergers and acquisitions as these companies seek to overcome R&D productivity problems and fill their drug pipelines.[28]

3. The Impact of Technologies on the Drug Development Process

This section looks at some of the technologies and techniques used by researchers at different stages of the drug development pipeline as they seek to improve the process of identifying promising new drug candidates and taking them to market.

As mentioned in Section 2, there are a number of ways of describing the stages of the pipeline. In January 2001, analysts at the US finance and consulting company, Lehman Brothers undertook a study of the impact of genomics on the drug development process. They illustrated the potential contribution of genomics and other technologies using a diagram, a modified version of which is reproduced as Figure 1. It shows how these various technologies are employed from initial research through to the clinical trials stage.[29]

Figure 1 Genomics to Clinical Development



The diagram illustrates the influence on the identification of therapeutic targets of recent technologies in the general field of genomics, such as bioinformatics and proteomics. Target validation is undertaken with the use of animal and disease models. Techniques in chemistry such as combinatorial chemistry and chemi-informatics are used to generate multiple lead compounds which are tested against the targets using high through-put screening. Microtechnology, nanotechnology, robotics and new array techniques are having a major influence on this screening process. Promising drug candidates arising from this are optimised using techniques from computational biology and structure based design, before being subject to toxicology and other preclinical testing. Having passed all these hurdles, a drug candidate is tested further in trials involving both healthy and sick patients.

Many of these technologies are quite recent and subject to rapid change and development, often in unpredictable ways. Their full potential therefore is uncertain as is their ultimate importance. Nonetheless the development of each is being actively pursued by research groups, start-up biotechnology companies and established drug companies and they are all attracting substantial funding.

The following sections discuss some of these technologies, concentrating on those that are more established.

3.1 Discovery

The drug discovery process can be described as the identification and validation of a disease target and the discovery and development of a chemical compound to interact with that target. This interaction can be to block, promote or otherwise modify the activity of the target.

The history of drug development over the past century has been the accumulation of knowledge and techniques that provide a progressively more detailed understanding of both the target and the compound that could become a drug.

Targets are usually proteins, either those occurring within the human body of in outside agents such as viruses and other pathogens. The major difficulty faced by drug researchers is understanding the complex chemical pathways involved in the disease process in order to find the most appropriate intervention point, and then to discover or design a compound that modifies the chemical process at that point.

a. Leads/Compounds

Experience gained in the development of drugs combined with insights from rational drug design and medicinal chemistry over an extended period of time have lead drug researchers in pharmaceutical companies to concentrate on small molecules with a molecular weight of less than 500 as the preferred compounds to make new drugs.[30] Larger compounds are more difficult for the body to absorb and are less stable.

However, it has been estimated that the number of possible molecules with a molecular weight less than 500 is 10^{200} of which perhaps 10^{50} might possess drug-like properties.[31]

The pharmaceutical industry has navigated this universe of possibilities by using insights gained over years of experience. In the process most companies have amassed large libraries of compounds that could be possible candidates for new drugs. These libraries combine naturally occurring compounds with those that have been synthesised. In addition specialist companies have been formed to develop libraries and to provide services to drug discovery groups either within existing large pharmaceutical companies or other research groups.

The owners of these libraries are continually seeking to add new compounds and some have engaged on systematic searches among animals and plants for new molecules. This is often done in conjunction with government agencies within

countries supporting a large range of unique flora and fauna. Examples of such efforts in Australia are described in Section 4.

Once a potential disease target has been identified, the action of these compounds can be tested against it to see which demonstrate some activity with respect to the target. Even though promising candidates are identified by this screening process, they are invariably not in a form suitable to be made into a drug. Medicinal chemists take these candidates and synthesise new analogue compounds by modifying them in ways that are expected to increase their suitability. This process traditionally was laborious - a chemist might synthesise one compound a week using traditional techniques, submit the compound for testing in biological assays, wait for the results, then modify the design of the compounds and go through the same cycle again.

This was a major rate-limiting step in developing new drugs and has seen remarkable increases in productivity over the past ten years or so through the use of combinatorial chemistry linked to high throughput screening.

Combinatorial chemistry is an approach to chemical synthesis that enables the creation of large numbers of organic compounds by linking chemical building blocks in all possible combinations. Compounds are synthesised on plastic beads that are segregated into different containers. In each container, a different chemical building block is added to the beads. The beads from each container are then divided among a new set of containers. When the next building blocks are added to each container, they attach to all the first building blocks at the same time, providing all possible combinations.[32]

The process is highly automated using robots and is multiplicative so a small number of steps can rapidly produce large libraries of compounds, for instance 390,625 unique compounds (25^4) can be generated after 4 iterations by starting with 25 compounds in 25 containers.

Combinatorial chemistry is used in this fashion for lead identification.

Once these compounds have been tested against potential drug targets, the leading candidates can be refined further through a similar technique called parallel synthesis, which produces large number of multiple variants of these candidates. This process can be characterised as lead optimisation.

In order to test these large libraries of compounds against one or more targets, it has been necessary to improve the productivity of the screening or assay process in a similar fashion to that which has occurred with synthesis.

High-throughput screening is a highly automated robotic system that tests small amounts of large numbers of compounds against potential targets. Protein targets are prepared in 96-well microplates which are standardised plastic trays with 96 "wells," or depressions, for holding small quantities of material. The 96 wells are uniformly located in 8 rows of 12 wells each. Recent advances have increased the number of wells to 1536, enabling what is being called ultra high throughput screening. Compounds are tested using multiple plates in parallel.

As an example of the impact of combinatorial chemistry and HTS, Lilly screens about 40,000 compounds a day and expects to increase this to 100,000 when it acquires ultra HTS technology. Lilly acquired a specialist company called Sphinx Pharmaceuticals (now Sphinx Laboratories) in 1994 to access these technologies.[33]

Specialist companies such as Pharmacopeia in the USA and Tripos in the UK provide equipment and resources for companies wishing to carry out combinatorial chemistry and HTS but also offer services in this area as well.

Protein targets often occur in very low amounts so it has been necessary to use techniques used in semiconductor manufacturing as well as microtechnology to design and manufacture these microplates and to improve the sensitivity of detection techniques. This enables picolitre volumes of the target to be used in each test rather than microlitres.

Most pharmaceutical and biotechnology companies now carry out some form of combinatorial chemistry and HTS in their laboratories, and the technologies are relatively mature.[34]

The massive increase in the number of compounds and tests however can be very expensive and there has been some scepticism about the efficacy of these techniques.[35] Dean et al argue that HTS has not been as "attractive as hoped for two reasons (1) the numbers of compounds that can be economically screened is small compared to the chemical space available, and (2) the theoretical coverage of molecular diversity within the screening set is limited".[36]

To date there appear to have been few drug candidates to emerge from these processes, although the techniques themselves have not been widely used for very long. Bristol-Myers Squibb has a compound BMS-201038, a MTP inhibitor in clinical trials and Merck has a series of molecules that interact with somatostatin receptors.[37] On the other hand, 50% of the drug leads identified by GlaxoSmithKline in 2000 originated from HTS.[38]

The combination of combinatorial chemistry with high throughput screening can be described as a "brute force" or "big, dumb science" approach to testing drug candidates. Its worth seems to be highly dependent on the quality of the initial library of compounds, and the intelligence used to select the initial lead candidates and to guide the screening process.[39]

In addition, as Schmid et al. note "While screening large libraries allows one to obtain leads, it is likely that further chemistry will be required to improve potency, solubility, pharmacokinetics, and so forth. To do this requires structure activity relationships to be followed in a learning, systematic, sequential manner. This is the traditional domain of the medicinal chemist and single compound synthesis".[40]

Because these technologies and their associated computing hardware and software have enabled massive increases in productivity and the numbers of drugs that can be tested, their use is increasingly being referred to as the "industrialisation" of drug discovery. Analogies are often drawn to similar automated processes in the semiconductor manufacturing industry.

A further refinement that has emerged recently is the ability to do at least some of this work *in silico*, i.e. using computers to simulate the screening of lead compounds. This technique depends crucially on knowing the 3D atomic structure of the target protein. The compounds that can be screened are either existing compounds where a known structure has been stored on the computer, or virtual collections of compounds whose structure is generated by the computer.[41]

3D structure is usually obtained using X-ray crystallography or nuclear magnetic resonance (NMR) techniques.

Boston Consulting Group have estimated that *in silico* technologies can save US$130 million from the US$880 million required to develop a new drug and save 8 months in development time.

b. Targets

While significant gains have been made in the technologies to generate and test potential new drugs, the most difficult problem associated with new drug discovery is the identification and characterisation of the most appropriate target within a disease pathway. There are likely to be few positive outcomes from screening programs aimed at non-validated or poorly validated targets.

Drews has estimated that all drugs developed to date address about 500 molecular targets within the human body, with cell membrane receptors (principally G protein-coupled receptors) and enzymes accounting for 73%.[42]

Genomics seeks to exploit the findings from the sequencing of the human and other genomes to find new drug targets.

Since the completion of the human genome sequencing programs, it has been estimated that the human genome consists of a sequence of around 3 billion nucleotides (the A C G T bases) which in turn probably encode 35,000 – 50,000 genes, although the actual number of genes is still unknown.

Drews estimates that the number of genes implicated in disease, both those due to defects in single genes and those arising from combinations of genes, is about 1,000. He only considers the 100-150 diseases that "pose a major medical problem in the industrial world". Based on 5 or 10 linked proteins per gene, he proposes that the number of potential drug targets may lie between 5,000 and 10,000.

While some genes have been identified as contributing to disease, these have mainly been for conditions caused by defects in single genes, and these conditions are relatively uncommon, accounting for fewer than 2% of diseases. Where there is a genetic component to disease however, it is more likely to be due to the interaction of several genes and much less is known about the relationship of these genes to specific diseases.

One technique that is now being used is to compare the genomes from both healthy and sick people and to identify where their genomes vary. This is being done through

the use of Single Nucleotide Polymorphism (SNP) libraries. SNPs are single nucleotide variations in the genome sequence (eg an A rather than a T) and are expected to provide good markers for disease genes.

Most major pharmaceuticals and biotechnology companies now have access to genomic and SNP databases which they are using to identify suitable gene targets.

Boston Consulting Group argues that the impact of genomics technologies could save up to US$140 million and 11 months of time on average per new drug, although the savings are more likely to occur some time after the introduction of these technologies when researchers have become adept in their use.

Lehman Brothers in association with McKinsey & Co are more cautious.[43] Their analysis leads them to conclude that "despite the current need for better target validation through functional genomics, these technologies are unlikely to add value in the near term. These technologies are simply not yet robust enough to yield truly validated targets".

The human genome-sequencing project was only attainable through the parallel application of automated sequencing equipment, in a manner similar to that being used in lead identification and optimisation. The result of this was to significantly reduced the time and cost involved in determining the nucleotide sequences of genomes. This has lead in turn to a rapid increase in the sequencing of other genomes, eg for favourite research model systems such as the mouse and fruit fly. The technology for sequencing is now becoming available for many research groups around the world and they are applying it to a multitude of plant and animal systems.

As the technology is relatively mature and understood and has become highly automated, attention has turned to analysing the huge amounts of genetic information produced from these sequencing projects, particularly the comparison of sequences among systems, and the use of SNP databases.

More importantly, there has been an increasing realisation that the focus should now be on the proteins that the genes encode. Proteins are closer to disease processes and drug action than genes, as most drug targets are proteins. In addition, proteins now form a significant proportion of drugs, as recombinant proteins such as monoclonal antibodies.

Proteomics[44] is the study of the proteome i.e. the ensemble of proteins found within a system (sometimes referred to as structural genomics or functional genomics). While there are may be some 35,000–50,000 genes in the human genome, they are responsible for the production of 5000,000–1,000,000 proteins. The link from the genome to the proteome therefore is not straightforward, there being over 100 known biochemical post-translational modifications such as phosphorylation and glycosylation. The structure and function of proteins are modified significantly according to the nature and state of the cells in which they are found and by external environmental factors. "Whereas the genome is static (aside from occasional mutations…) and is determined at conception of the organism, the proteome varies constantly with the nature and state of the cell, making proteomics a much more complicated endeavour".[45]

Proteomics has been the subject of intense investment and research interest since the sequencing of the human genome. There are moves to form an international effort similar to the genome-sequencing project, to understand the structure and function of all relevant human proteins.[46] In addition several companies have announced alliances to sequence all human proteins, although these programs seem to be unrealistically ambitious. The action of proteins depends crucially on their shape, so there are now proposals to understand the 3D structure of all proteins using highly automated X-ray crystallography.[47]

The established techniques for the study of proteomics analysis are 2-D gel electrophoresis for separating proteins and mass spectrometry for analysing them. These techniques have also been modified and improved through the application of microtechnology techniques, in a similar fashion to high throughput screening. This has also lead to the production of protein chip arrays similar to DNA chip arrays.

The importance and potential of proteomics has been underlined by the Lehman/McKinsey report – "The evolving area of proteomics promises ultimately to make knowledge of all pathways in the human body available in much the same manner as the knowledge of genes is becoming available today. This effort, however, is still in its infancy and current technologies have not been automated in the robust manner of the DNA sequencers. We expect this automation to happen in the next few years. Experts we have consulted with have confirmed that the value of proteomics will far exceed the value of sequencing the human genome".[48]

3.2 Development

The outcome of the discovery phase is a handful of lead candidate compounds that have shown promising activity against a drug target.

It is often at this stage that promising candidates are patented, with most patents having a 20-year lifespan. These candidates are subject to further testing for safety and efficacy firstly in a preclinical development stage and then in clinical trials using human patients.

Most of the profitability arising from selling a drug occurs while it is being sold as the sole treatment protected by patent. This window of opportunity will be maximised if the period between grant of the patent and the drug's commercial release – i.e. the development stage of the drug - can be made as short as possible.

As shown in Section 2, the development stage is the most costly in terms of bringing a drug to market, so technologies or approaches that reduce the time a drug spends in trials, that reduce the number of patients in trials, or that make the data gathering and data analysis more efficient, can make a two-fold contribution to a drug's ultimate profitability – by reducing development costs and increasing the period over which it is marketed.

The clinical trials stage is often outsourced to Clinical Research Organisations (CRO), which undertake the recruitment of patients and clinical research staff, the collection of data, and the preparation of reports on the trials. While CROs are often subject to

criticism, their use is virtually inevitable for smaller drug companies that cannot carry the cost of in-house expertise.

Preclinical Testing

The preclinical stage is really concerned with whether the compound can be made into a drug that will treat the disease, is not toxic and has minimum unwanted side effects.

Toxicity tests are undertaken to show safety while pharmacokinetics testing is done to provide data on how a drug is absorbed, distributed, metabolised and excreted (ADME) from the body. These tests have traditionally be done on animals such as mice, dogs and non-human primates, but fortunately these are increasingly being replaced by tests using cell cultures, i.e. mammalian cells grown outside the body. In addition computer systems that simulate these tests have been developed and are beginning to be deployed.

There is a limit however in the amount of information that can be obtained from preclinical testing. In some disease, such as depression, bipolar disorder, and schizophrenia it is not possible to understand the efficacy of a treatment by testing in animals or cell culture.

Over two thirds of preclinical candidates fail because they cannot be developed into drugs either because of their toxicity or because of poor ADME properties.[49] Because of this, methods such as combinatorial lead optimisation that automate and miniaturise toxicity and ADME testing have been developed. These will enable lead compounds to be tested earlier in the discovery process, before they enter the more expensive development stage.

The other principal concern in the preclinical development stage is the manufacturability of the drug, i.e. how to formulate the compound so that it is stable, has the correct dosage and is suitable for economic large-scale manufacturing.

Clinical Trials

Clinical trials are used to test the efficacy and safety of new drugs in humans. In Phase I trials, the drug is administered to a small number (20-80) of healthy volunteers to test for toxicity and side effects and for correct dosage levels. In Phase II this is replicated in a larger number (100-300) patients with the disease to be treated, while in Phase II trials yet larger numbers (1,000-3,000) of patients are used to verify the efficacy of the drug and to monitor adverse effects during longer-term use.

A number of technologies such as pharmacogenomics, bioinformatics, and Internet-based technologies can and will significantly influence the clinical phases of drug development, both in terms of better selection of patients and drugs for clinical trials but also in the more efficient collection and analysis of data from trials.

Pharmacogenomics is based on the recognition that drugs developed for mass markets will not work for many people who have the disease targeted. Beta blockers do not work for between 15% and 35% of patients, tricyclic antidepressants have no

effect on 20% to 50% of patients, while interferons are of no use to 30% to 70%[50]. Part of the reason for this variation in response among patients is due to differing genetic makeups. As the genome is better understood, the genetic variation in response will be correlated with other factors such as drug metabolism and toxicokinetics to help predict how an individual patient will respond to a given drug in terms of efficacy and safety.[51]

Pharmacogenomics is expected to have a number of positive effects on drug discovery, development and marketing. It will enable doctors to prescribe the medicines best suited to a patient's genetic profile as well as the optimal dose. It will also enable drug companies to improve the selection of participants in clinical trials as it will weed out those that will not respond to the drug. It will also rescue drugs that might have failed in clinical trials because of adverse reactions from very small groups in the population.

While these effects are largely positive, the possibility of multiple variants of drugs for multiple sub groups of the population could increase the cost of drug development and manufacture for pharmaceutical companies if individualised therapies are demanded by patients or managed care intermediaries.

3.3 Information Technology

Clinical trials involve the collection of a large amount of data from patients by investigators and other clinical staff. By and large this data is collected on paper forms that need to be manually processed into a form suitable for submission to regulatory authorities and for use by clinical researchers.

To maintain historical growth rates and meet market expectations, pharmaceutical and biotechnology companies are increasing the number of drugs being tested. This has in turn increased the demand for patients for trials and the number of trials undertaken.

The result is that the amount of data that needs to be collected and analysed is increasing rapidly. Information technology enables data to be collected and analysed more efficiently and is being increasingly deployed to improve efficiency and speed. Call centres and data warehouses, which are used in other industries such as banking and telecommunications, are being used to assist in patient recruitment and data analysis.[52]

Professor John Houghton covers the impact of information technology on pharmaceuticals and heath care extensively in a report in this series.[53]

Bioinformatics

The advent of combinatorial chemistry in conjunction with high throughput screening has meant that researchers can quickly generate large volumes of data points. The application of techniques such as mass spectrometry and X-ray crystallography for determining the structure of proteins and the generation of nucleotide and SNP data from genomics research have also contributed to an explosion in the amount of data generated by researchers in pharmaceuticals and the life sciences. This has created challenges for the computer industry in storing and managing such data.

As a lot of genomics and proteomics research involves comparison of experimental data with established genomic and proteomics databases, there are also significant challenges for the computer software industry in enabling quick and accurate searches within these databases.

These challenges have lead to the creation of a separate discipline within the life sciences called bioinformatics and most large pharmaceutical and biotechnology companies now have bioinformatics teams. In addition a rash of start up companies have been formed to develop technologies and sell information from databases. Examples include Double Twist, Lion Biosciences, Rosetta Inpharmatics and Structural GenomiX. The company that sequenced the human genome – Celera Genomics (now part of PE Corp) is essentially a bioinformatics company.

As computers become more powerful, it is increasingly feasible to simulate various aspects of the drug discovery and development pipeline *in silico* rather than undertake experiments or trials in the real world. This could lead to significant savings in both time and cost. As knowledge expands, it is becoming more possible to simulate complex interactions among targets and leads, and among all the proteins involved in complex pathways within the body.

The complexity of these bioinformatics applications has attracted information technology providers to the life sciences. IBM for instance is in the process of building an advanced petaflop supercomputer to tackle Grand Challenge problems in areas such as protein folding. It is also undertaking other research programs in pattern discovery, protein structure and structural genomics.[54]

Computer companies have entered into alliances such as Hitachi and Oracle with Myriad Genetics to sequence the human proteome, and IBM with Proteome Systems to identify and analyse proteins.

Part of the reason for this is that pure bioinformatics companies are having a difficult time with a business model that relies on selling bioinformatics software and access to databases. The market is necessarily restricted and reaching saturation as established companies acquire these capabilities. Bioinformatics companies have therefore responded by entering the drug discovery arena using their own tools and information.[55]

4. Australian Capabilities in Drug Discovery and Development

4.1 Introduction

While Australia has some capabilities in all aspects of the drug discovery and development process, its strengths have historically been concentrated in only a few of the stages. Australia is acknowledged for the strength of its basic research in medicine, biology and biotechnology and has developed a strong presence in clinical trials (principally in Phase III) as a result of this strength. A recent analysis of publication citations undertaken for the National Health and Medical Research Council, for instance, highlights Australia's expertise in genetics, oncology and carcinogenesis, haematology, immunology, gastrointestinal and neurological diseases, and the more general fields of microbiology, parasitology, virology, biochemistry and clinical chemistry.[56]

On the other hand, Australia is relatively weak in areas such as drug related chemistry.

The sections below review Australia's capabilities in key aspects of the drug development process.

4.2 The Australian Pharmaceuticals and Biotechnology Industry

The Australian pharmaceuticals and biotechnology industry consists of the Australian operations of a range of large multinational pharmaceutical companies, a few Australian-based pharmaceutical wholesalers and manufacturers and a number of smaller Australian biotechnology companies.

Many of the Australian subsidiaries of the multinational pharmaceutical companies have been here for a long time and have well established distribution and marketing operations. Some such as Merck, Sharpe & Dohme and GlaxoSmithKline have significant formulation and manufacturing plants while others such as Eli Lilly have made significant investments in clinical trials. Their research programs in Australia are largely conducted through Australian university and medical research institutes. As described below, AstraZeneca has played an important part in developing the natural library, combinatorial chemistry and high throughout screening capabilities in Queensland.

The larger Australian operations – Fauldings (now part of Mayne Health), Sigma Pharmaceuticals and Australian Pharmaceutical Industries, are principally wholesalers though Fauldings and Sigma manufacture generic drugs both on their own account and on contract. Their involvement in technology development is generally small.

The Australian biotechnology sector consists of both listed and unlisted companies. While there has been no exhaustive study of the complete biotechnology sector in Australia, a number of comprehensive directories have been compiled, usually with the support of government. Bio-Accent, a biotechnology consulting company, has prepared directories for Victoria, Queensland and New South Wales,[57] while the Australian Biotechnology Association has complied an on-line BioDirectory of organisations involved in Australian biotechnology. [58]

The listed Australian biotechnology companies are tracked by both Deloitte Touche Tohmatsu and Deutsche Bank.[59]

Appendix One lists the companies in the Deloitte's index with market capitalisation at October 2001, as well as their classification from the Deutsche Bank index. Some companies not appearing in the Deutsche Bank list have allocated to categories according to their activities. Market capitalisation can vary considerably for a variety of reasons and may be poor indicator of ultimate worth, especially for early stage research based companies. This list does not contain Antisense Therapeutics which was listed in November 2001.

The list is dominated by CSL with a market capitalisation of $7.1 billion. It is primarily a blood products company with some presence in the vaccine distribution market and with a portfolio of research projects targeting peptic ulcers, genital warts, cervical cancer, melanoma, periodontal disease, and glandular fever.

The "Medical Devices" group of 16 companies has a collective capitalisation of about $6.6 billion, of which Resmed and Cochlear are together worth $5.7 billion. They make devices for sleep apnoea and profound hearing loss respectively.

The "Research Biotechnology" group includes 42 companies with a total worth of about $1.7 billion, or an average worth of $41 million. There are 11 biotechnology companies with a capitalisation greater than $50 million, and 30 with a capitalisation exceeding $10 million.

Those listed companies whose operations are most closely related to the drug discovery and development business, therefore are small by international standards, even allowing for the fact that the cost of doing biotechnology R&D in Australia is half that in the USA.[60]

4.3 Leads

While most focus in Australian biomedical research is on understanding disease pathways and identifying suitable targets for drugs, a number of organisations are active in developing libraries of lead compounds and using high throughput screening to identify promising drug candidates.

Australia has a unique and diverse biota, the country accounting for instance for about 10% of global plant biodiversity.[61]

This resource has been recognised by researchers and industry as a potentially valuable source of drug lead compounds and a number of organisations have compiled libraries of natural compounds for this purpose.

Astrazeneca has entered into an agreement with the State of Queensland that gives the company first rights of refusal to develop compounds based on the State's biota, i.e. plants and other organisms unique to the State. In return the company is helping the State to complete its survey of the biota and providing screening facilities at Griffith University to screen for potential new drug candidates.[62]

BioProspect Limited[63] is a listed company based in Western Australia that has a licence granted by the Western Australian Government giving it access to plant species collected by the WA Herbarium. It provides profiled plant extracts to drug discovery companies from this library as well as screening services, in conjunction with partners such as Southern Cross University and Royal Perth Hospital. The library has produced compounds with promise as a human sedative and an organic pesticide.

Cerylid Biosciences Ltd was founded in January 2000 when as an offshoot of Amrad Corporation. It has a number of microbial and plant and marine macro-organism libraries sourced from a number of Australian States and territories as well as Papua New Guinea and Sarawak in Malaysia. It offers screening services and bioassay development using extracts from these libraries. In addition it operates an internal drug discovery and development program concentrating on drugs for multiple sclerosis, endometriosis and type I diabetes.

Other companies are working on developing new forms of lead compounds, Starpharma, for instance, is commercialising new polyvalent compounds called dendrimers for action against a broad range of viruses and other human diseases, including HIV/AIDS and cancer.

Discussions with senior managers from Griffith University, Starpharma, the Institute for Molecular Bioscience and other groups working in the general area of developing lead compounds, have identified a serious shortage in medicinal chemists in Australia. Although courses are offered at some tertiary institutions in Australia, they are having difficulty attracting students, partly because of the poor image of chemistry. This is a significant bottleneck in the process of identifying lead compounds and converting them into commercial drugs.

4.4 Targets

Of the "Research Biotechnology" companies listed in Appendix One, IDT manufactures active ingredients while Clover Corporation manufactures lipid-based nutrients.

Biotech Capital, Circadian Technologies, Genetic Technologies and Medica Holdings are essentially investment companies that have supported a range of instrument companies such as Axon Instruments, Proteome Systems, Optiscan Imaging and X-Ray technologies, as well as small unlisted drug discovery companies, such as Alchemia, Antisense Therapeutics, Cytopia and Xenome.

To identify the listed companies working primarily in drug discovery with a capitalisation greater than $10 million, these other companies were removed from the list in Appendix One. Table 5 shows these companies, as well as their technology base and diseases targeted.

This table still includes some companies whose main activities are in biologicals manufacture, diagnostics, and drug delivery which would reduce the list of pure drug discovery and development companies still further.

These drug discovery companies are primarily targeting disease where there is an unmet need such as skin cancer, solid tumours, obesity, osteoporosis, HIV/AIDS, Alzheimer's disease and other inflammatory diseases.

4.5 Technologies Supporting Drug Discovery

In addition to companies working on drug leads and targets, there is a range of companies in Australia that produce supporting technologies for drug discovery and development.

The principal companies in this area are Axon Instruments, Gradipore, and Proteome Systems.

Table 5 Australian Drug Discovery Companies

Company	Value* $m	Technology base	Diseases targeted
Peptech	342.1	Tumour Necrosis Factor antibodies Polyunsaturated fatty acids	Inflammatory diseases
Novogen	102.7	Development of isoflavinoids	Osteoporosis, inflammatory diseases
Gropep	83.3	Biologics manufacture In-licensing candidates for development	Diabetic neuropathy, venous ulcers, oral mucositis, osteoporosis
Amrad	70.2	Virology and cytokines	Nerve damage, hepatitis B, severe pain, cardiovascular disease, stroke
Metabolic	65.6	Human growth hormone	Obesity, type II diabetes
Genesis R&D	59.5	DNA sequencing, transcription regulators, cytokines	Tuberculosis, asthma, psoriasis
Norwood Abbey	53.2	Mainly laser-based drug delivery, GnRH analogues	Immune based diseases
Bresagen	49.0	Interleukin GF, human GF, cell therapy	Leukaemia, rheumatoid arthritis, asthma, solid tumours
Provalis	38.1	Vaccines	Pneumonia, ear infection, streptococcus
Agenix	37.8	Agen immunoassays, vaccines	Medical diagnostics, vaccines
Panbio	34.1	Development of diagnostics for infectious diseases	Dengue fever, Ross River fever, glandular fever
Autogen	30.3	Genomics for novel therapeutic targets	Obesity, type II diabetes
Peplin	29.0	Pharmaceuticals from plants	Skin cancer, solid tumour cancer
Biota	27.8	Rational drug design	Influenza, rhinovirus
Starpharma	27.5	Development of dendrimers	STDs, angiogenesis inhibitors
Progen Industries	22.0	Biologics manufacture, inhibitors of carbohydrate-protein interactions	Cancer angiogenesis inhibitor, anti-thrombotic inhibitor
Meditech Research	21.8	Hyaluronic acid as anti-cancer drug delivery	Skin cancer, bowel cancer, breast cancer
Anadis	21.5	Bovine colostrum	Diarrhoea, osteoporosis, H pylori
Prana Biotechnology	20.3	Oxidation proteins	Alzheimer's disease
Bionomics Ltd	16.8	Genomics	Breast cancer, epilepsy
Solbec Pharmaceuticals	15.9	Steroidal glycosides	Cancer, mesothelioma
Virax Holdings	14.5	Immunotherapy vaccines	HIV/AIDS

* Value of shares at October 2001.

5. Policy Directions

New and existing technologies are likely to reshape the drug discovery and development process in the future. Their impact will change the way in which drugs are discovered, developed and manufactured and this will present opportunities for Australian companies and researchers to participate in all aspect of the drug discovery and development pipeline, from basic research through to clinical trials and marketing.

Unlike the situation in North America and Europe, the Australian biotechnology community is relatively immature and its companies are small by world standards. In particular it suffers from a shortage of personnel with management and financial experience in the pharmaceutical industry. A program to encourage expatriate personnel with this experience to take up positions in Australian pharmaceutical and biotechnology companies could alleviate this shortage.

These companies will require considerable nursing by governments, research institutions and financial organisations for some time.

There is a serious lack of experienced medicinal chemists with the expertise to convert promising lead compounds into drugs that can be marketed. This is an area where government can be proactive in encouraging the pharmaceuticals industry in Australia.

In addition, there is a major deficiency in the preclinical stage of drug development, forcing companies with promising drug candidates to have the toxicology and ADME testing done overseas. A group of commercial and research bodies are encouraging the Commonwealth Government to fund the establishment of preclinical testing units within existing medical research institutions and this should be supported.

Proteomics is an area in pharmaceuticals which will have major consequences for drug discovery over the next few years. Australia has a recognised capability in this field, through companies such as Proteome Systems and Axon Instruments that are growing strongly and have significant strategic alliances with major companies. There is intense interest in proteomics and it is a prime candidate for programs of support from both government and the pharmaceuticals industry.

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APPENDIX ONE

Listed Australian biotechnology companies

	Market Capitalisation*	Segment
CSL	7,124,815,977	CSL
Resmed Inc	3,312,331,811	Medical Devices
Cochlear	2,425,178,217	Medical Devices
Peptech	342,056,934	Research Biotechnology
Axon Instruments	306,164,421	Medical Devices
IDT	178,927,736	Research Biotechnology
Vita Life Sciences	103,902,978	Medical Devices
Novogen	102,675,357	Research Biotechnology
Polartechnics	100,988,726	Medical Devices
Gropep	83,301,838	Research Biotechnology
MicroMedical Industries	79,874,626	Medical Devices
Gradipore	78,751,018	Medical Devices
Compumedics	78,400,000	Medical Devices
Amrad	70,168,340	Research Biotechnology
Circadian	65,938,589	Research Biotechnology
Metabolic	65,556,766	Research Biotechnology
Genesis Research & Development	59,546,082	Research Biotechnology
Cellestis	53,723,994	Research Biotechnology
Norwood Abbey	53,183,115	Research Biotechnology
Genetic Technologies	51,870,783	Research Biotechnology
Bresagen	48,958,704	Research Biotechnology
Chemeq	41,186,692	Research Biotechnology
Provalis	38,079,467	Research Biotechnology
Agenix	37,774,698	Research Biotechnology
Panbio	34,064,714	Research Biotechnology
Ellex Medical Lasers	33,808,228	Medical Devices
Autogen	30,253,737	Research Biotechnology
SSH Medical	29,581,094	Medical Devices
Peplin	29,000,526	Research Biotechnology
Biota	27,758,889	Research Biotechnology
Starpharma	27,532,529	Research Biotechnology
Biotech Capital	26,400,033	Research Biotechnology
Medica Holdings	26,097,636	Research Biotechnology
Optiscan Imaging	24,971,731	Medical Devices
Progen Industries	21,952,682	Research Biotechnology
Meditech Research	21,829,366	Research Biotechnology
Anadis	21,537,355	Research Biotechnology
Ambri	20,754,949	Medical Devices
Clover Corporation	20,282,780	Research Biotechnology
Prana Biotechnology	20,256,637	Research Biotechnology
Bionomics Ltd	16,789,863	Research Biotechnology
Solbec Pharmaceuticals	15,926,978	Research Biotechnology
Sirtex Medical	14,509,184	Medical Devices
Virax Holdings	14,477,092	Research Biotechnology
Bioprospect	8,930,995	Research Biotechnology
Psivida	8,062,860	Research Biotechnology
Biotron	7,353,000	Research Biotechnology

Pharmaction Holdings	7,323,039	Manufacturing
VRI Biomedical	6,810,847	Research Biotechnology
Genesis Biomedical	6,614,590	Medical Devices
Brain Resource Company	5,957,688	Medical Devices
Australian Cancer Technologies	5,425,829	Research Biotechnology
Xcell Diagnostics	4,238,522	Research Biotechnology
Australian Vaccine Technologies	4,187,272	Research Biotechnology
Prima BioMed	4,105,976	Research Biotechnology
Aquacarotene	4,021,512	Research Biotechnology
NSL Health	3,858,206	Medical Devices
Inovax	3,758,601	Distributor
Epitan	3,391,992	Research Biotechnology
Psiron	2,249,318	Research Biotechnology
Pi2	1,235,160	Research Biotechnology

* value of shares at October 2001