The Evolution of Drug Discovery Strategies
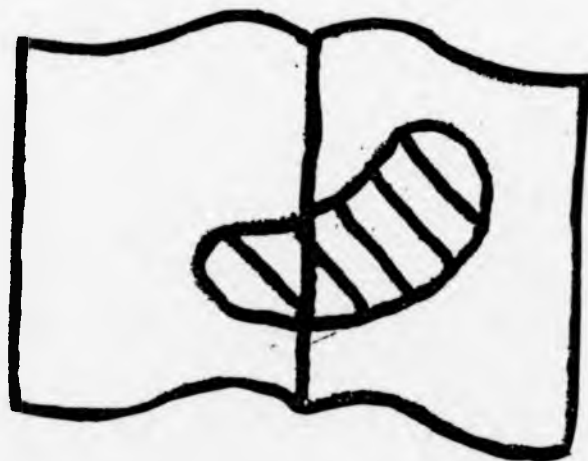
by

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A thesis submitted in partial fulfilment of the requirements for the degree of Doctor

of Philosophy in Engineering

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ACKNOWLEDGMENTS

DECLARATION

The thesis is the author's own work and has not been submitted for a degree at another university. Furthermore, the work in this thesis has been discussed in the following papers:

C. Tsinopoulos, I.P. McCarthy, 2002, An evolutionary classification of the strategies for drug discovery, *Manufacturing Complexity Network Conference*, Cambridge, pp. 373-385, ISBN: 1902546245

C. Tsinopoulos, I.P. McCarthy, 2001, The evolution of Strategies for Drug Discovery, *R&D Management Conference*, Dublin, Ireland, pp. 467-474

ABSTRACT

The modern pharmaceutical organisation is driven by the need to discover, develop and market innovative pharmaceutical products. Key to this mission is the process of drug discovery that involves allocating vast resources to (i) identify appropriate target diseases, (ii) discover and confirm appropriate solutions, (iii) clinically develop and legally approve the solution, for (iv) manufacture and supply of the product

Historically the drug discovery process was led by curiosity and pure research, but today it is akin to a factory system that conducts mass volume, applied and market focused research. This change in focus has also been companied by numerous advancements in science, technology and market expectations. As will be shown and verified in this thesis, there is relatively little in the way of existing literature and studies that focus on drug discovery strategies, and what does exist is fragmented across a number of disciplines including technology management, chemistry, automation, marketing, knowledge management and strategy.

With this background, the aim of this thesis is to make a contribution that includes understanding and defining the concept of drug discovery as a strategy, and exploring how such strategies change through time. Within management and organisational literature, there is a body of knowledge that seeks to understand how and why organisations develop different strategies and organisational forms. This thesis adopts this evolutionary and classification paradigm to examine, define and classify the different strategies that exist to discover drugs. In particular, four requirements of evolution (existence in populations, the process of variation, the process of heredity,

and the process of selection) are identified and translated into a strategic management
and drug discovery context to create four testable hypotheses. These are:

1. There are similar drug discovery strategies employed by different
   organisations to form populations whose (the population's) size follows a
   concave pattern of growth and decline.

2. Within a drug discovery population, there are strategies that differ to each
   other in terms of their characteristics and their fitness.

3. Those characteristics of drug discovery strategies credited with successful
   drug discovery performance are likely to appear in future strategic
   configurations, while those characteristics that are not, are likely to be absent.

4. With a change in the environmental conditions those drug discovery strategies
   that remain, are the ones whose strategic characteristics are favoured by the
   environment.

To address these hypotheses a business historical study is conducted using data that
investigates how the pharmaceutical industry has evolved in terms of technology,
knowledge, human capital and the surrounding environment. The result is an
evolutionary classification that has been constructed using the cladistic method. This
classification provides a system of information, evidence and assumptions that is the
basis for testing the four hypotheses. The classification also provides a framework
that integrates and presents the key contributions to knowledge made by this thesis.
These include:

- The creation of a definition for drug discovery strategy

- The identification of the factors that influence the change of drug discovery
  strategies

- The creation of an evolutionary classification that identifies and arranges different types of drug discovery strategy, and reveals the characteristics of the fittest

- The validation of evolution as a process for understanding change in drug discovery strategies

1. INTRODUCTION

During the next century we shall surely obtain a full understanding of the body (through the human genome project), and then discover how to cure the disease and save the patient (Mann, 1999, p. 197)

1.1. Background

With the virtual elimination of viral diseases such as smallpox; the ability to routinely produce images of fractures and tumours, and the commonplace transplantation of human organs, it seems that given enough time and money, almost any medical problem can be solved with science and technology. For pharmaceutical organisations such challenges motivate their business strategy and shape their competitive landscape in terms of profits, costs, and above all ethics. With significant technological advances in the drug discovery process (such as genomic based technologies that use genetic instructions that characterise organisms) and the development of the biotechnology industry, pharmaceutical organisations are facing increased pressure to produce more and better drugs, at a faster rate and with greater economic benefits to the business.

As with other industrial sectors, the pharmaceutical sector is a highly competitive and global industry. Yet, unlike most other sectors the pharmaceutical industry focuses on and allocates the majority of its resources to the process of innovation (drug discovery), whilst processes such as manufacturing, marketing, and logistics are very much secondary. In addition, the organisational characteristics that accompany the innovation process are relatively extreme in terms of time scales (new product development typically takes between eight and twelve years), search space (there are 10^{180} possible drugs, but only a possible 100 that may generate a profit), and

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investment (the average cost to research, develop, and bring to market a prescription drug in the US has reached $802 million)[1].

Today, the success of the drug discovery process relies heavily on the successful application of scientific knowledge and technology, yet back in the early 1900s there was a limited understanding of human biology and chemistry. During this period the majority of drug discoveries were unplanned and emerged from a process of scientific enquiry that was motivated by the curiosity and academic freedom of individual scientists. Since then, science, technology and market forces have created organizational systems that have shifted the process of drug discovery towards a more targeted, rational and planned business system.

Accompanying this development in the drug discovery process has been the increasing popularity of research into the formation and change of organisational strategy (Mintzberg, 1996, Mintzberg et al., 1998, Whittington 1993, Quinn, 1989) which has led to the identification and classification of various strategy types based on factors such as the degree of planning involved versus the emergent nature of change. At one end of this spectrum, fit strategies are those that are rational and planned, and involve a careful and detailed analysis of the strengths and weaknesses of the organisation, and the opportunities and threats of the surrounding environment. At the other end, fit strategies are those that are flexible and adaptive and can respond appropriately to unpredictable and uncertain environmental changes. It is important to note, that the terms "fit" and "fittest" refer to a condition where the configuration of an organisational strategy matches that of the environment and the frequency of its

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[1] This figure was calculated by the Tufts centre for the study of drug development (Tufts, 2002)

characteristics appearing in future strategies is high. These terms are discussed in detail in chapter 5.

This thesis examines these different strategic types and using an evolutionary and classification approach (cladistics) relates them to the area of drug discovery. At this point, it is important to note that evolutionary theory does not just apply to biological organisms. If an entity (technological, social, or economical) evolves, then systems and strategy research provides a framework to understand the evolutionary processes. Pharmaceutical organisations are complex adaptive systems that evolve. They do not exist in equilibrium or chaos, but rather as a periodic order of evolutionary progress based on four requirements: existence in populations, variation, heredity, and selection. As this thesis will explain, these requirements are developed into four hypotheses that are represented and evaluated using a cladistic classification of different drug discovery strategy configurations along with the defining characteristics and capabilities.

1.2. Research Questions

From this background, a number of research questions are developed and proposed (see Chapter 3). These are as follows:

1. How does the discipline of strategic management relate to the process of drug discovery and what is the definition of a drug discovery strategy?

2. What are the factors (internal and external) that influence and define different drug discovery strategies?

3. How can an evolutionary and classification approach be used to study drug discovery strategies?

4. What are the characteristics of the fittest drug discovery strategies?

1.3. Structure of this thesis

The current chapter (Chapter 1) provides an introduction to the thesis. It provides an overview of the challenges that pharmaceutical organisations face and introduces the research questions. This chapter also outlines the structure of the thesis as follows.

Chapter 2 introduces and justifies the research methodology and approach used to conduct this study. It provides an outline of the various research activities and each stage of the research. Furthermore, it introduces the rationale and forethought on using an evolutionary and classification approach.

Chapter 3 discusses and confirms the research questions that this thesis seeks to address. It considers and reviews existing drug discovery management and strategy literature and positions the thesis within this existing body of work.

The aim of chapter 4 is to address the first and second research questions. It reviews the literature on strategic management in terms of the origins of strategy, the strategic levels, the strategic types, and the strategic classifications. It shows and justifies that the factors that influence the changes in drug discovery strategy are technology, knowledge, organisation, and environment. The chapter concludes by providing a definition of *drug discovery strategy* within the scope of this thesis.

Chapter 5 reviews the concepts of evolution and fitness. There are two reasons for this review. The first is to provide the background for addressing the third research question i.e. identifying the requirements that evolving systems should meet for evolution to explain their change. These are existence in populations, variation, heredity, and selection. Chapter 5 develops the four requirements into four hypotheses for the evolution of drug discovery strategies as shown in Table 1-1. These hypotheses are examined and validated in chapters 7 and 8 by using the

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classification methodology *cladistics* as explained and justified in chapter 6. The second aim of this chapter is to provide the background for addressing the fourth research question by providing a definition of the term *fitness*.

Table 1-1 Hypotheses

Requirement	Hypothesis
Existence in populations	*There are similar drug discovery strategies employed by different pharmaceutical organisations to form populations whose (the population's) size follows a concave pattern of growth and decline.*
Variation	*Within a drug discovery population, there are strategies that differ to each other in terms of their characteristics and their fitness.*
Heredity	*Those characteristics of drug discovery strategies credited with successful drug discovery performance are likely to appear in future strategic configurations, while those characteristics that are not are likely to be absent.*
Selection	*With a change in the environmental conditions those drug discovery strategies that remain are the ones whose strategic characteristics are favoured by the environment.*

Chapter 6 explains and justifies the cladistic classification methodology used to test the four hypotheses. The chapter begins by substantiating the need for a classification and concludes by justifying the use of cladistics. The chapter then explains in detail the methodology of constructing cladistic classifications. Finally, it concludes by explaining specifically how cladistics is used for this research. It argues that two cladistic classifications will be constructed. The unit of analysis of both will be drug discovery strategies as defined in chapter 4. The first (a population cladogram) will use historical secondary data to identify and classify types or forms drug discovery strategies. The second (an organisation cladogram) will use data collected from the pharmaceutical industry to identify and classify drug discovery strategies found in individual organisations. Chapter 6 also justifies the benefits of this approach.

Chapter 7 presents the construction of the population cladogram. It explains how the classification data was collected (the sources that were used) and processed (the techniques, and the criteria employed), and then presents the classification. The chapter concludes by discussing how the population cladogram advances the research towards validating the hypotheses and hence addressing the third research question. It presents its limitations and verifies the need for the organisation cladogram.

Chapter 8 describes the construction of the organisation cladogram. Similar to chapter 7, it describes how the classification data was collected and processed and then presents the classification. The chapter concludes by discussing how the organisation cladogram validates the four hypotheses and explains and compares the insights and information provided by the two types of cladogram.

Chapter 9 is the conclusion chapter of this thesis. It summarises the progress and contribution made by the thesis and its constituent chapters towards the research questions listed in chapter 1 and confirmed in chapter 3. It also provides a discussion of the limitations of this work and suggestions for future work.

2. RESEARCH METHODOLOGY

2.1. Introduction

The scholarship and definition of a research project can benefit greatly from a carefully selected and well-defined research process. The aim of this chapter is to evaluate, justify and describe the research process of this work. It begins by addressing the question What is research?. Then it provides an account of the various types of research and concludes with a description and rationalisation of the methodology used. Finally, an explanation of how the research was organised and conducted is provided

2.2. What is research?

Despite the wider recognition of the importance of research, there is not a widely accepted definition of the term. From the many different definitions of research offered in the literature, there appears to be agreement on the following (Hussey and Hussey, 1997):

- It is a process of enquiry and investigation

- It is systematic and methodological

- It seeks to refine and advance knowledge

Phillips and Pugh (2000) distinguish between intelligence gathering and research. The former is concerned with answering the *what* questions. These questions are descriptive in nature, and require rigorous definition of the terms, unbiased collection of information, meticulous statistical treatment and careful summarising to obtain a balanced description of the situation. The latter is concerned with the *why and when*

questions that go beyond description and require analysis. They require explanations, comparisons, predictions, generalisations and theories. Although the *why and when* questions are similar to the *what* questions in that they require intelligence gathering, the information in the *why and when* questions is used for the purpose of developing understanding. All research questions require some form of generalisation and to be useful, explanations should be applicable in all situations (Phillips and Pugh, 2000).

2.3. Method and Methodology

To help enhance the quality of this research process and outputs a recognised methodology is used. Hussey and Hussey (1997) define *methodology* as the overall approach to the research process, including the theoretical underpinning to the collection and analysis of the data. They further distinguish *method* from methodology as the means by which data can be collected and/or analysed. Therefore, methodology is concerned with the following main issues:

- Why was the data collected? (e.g. to understand and define different drug discovery strategies)

- What data was collected? (e.g. data about how drug discovery strategies have evolved over time)

- Where was it collected from? (e.g historical databases, company annual reports etc.)

- When was it collected? (e.g during the last century)

- How was it collected? (e.g. by collecting annual reports, searching historical databases)

- How was it analysed? (e.g. using the evolutionary classification technique cladistics)

The methodology used when conducting research depends on the type of research that is being employed. Sekaran (2000) defines research as the *process of finding solutions to a problem after a thorough study and analysis of the situation factors*. From this statement, there are four possible aims of research:

- to gain familiarity with a phenomenon or to gain insight,

- to describe things,

- to determine associations between variables, and/or

- to test hypotheses.

The aims of this research involve three of the above. Firstly, it seeks to gain familiarity with a phenomenon i.e. understand and define drug discovery strategies in terms of evolutionary change. Secondly, it aims to determine associations between variables as it identifies relationships between strategic management and drug discovery. Finally, it aims to test four hypotheses that emerge (see chapter 6) from research question 3 '*How can an evolutionary and classification approach be used to study drug discovery strategies?*' The testing of these hypotheses also advances the research towards meeting the other two aims.

Since research design is closely linked to a researcher's objectives, there are several types or approaches to research. The following section introduces some of the most common types, while positioning this types against this research.

2.3.1. Applied versus Basic Research

A common aspiration of research is to solve real problems that lead to benefits for industry, society, government or other stakeholders. In this research, an organisation may seek to improve the competitiveness of its drug discovery process by better understanding its current process and designing a new one. Such research is called *applied research*, as the output and research environment is pragmatic. The theory, methods and ideas that are used to examine the problem are usually the basis of the novelty.

If the research has no application in the short or medium term, but instead aims to generate a body of knowledge about how certain problems occur in organisations, then this type of research is called *basic research*. Basic research is considered more academic as its main aim is contribution to knowledge. This contribution is usually for the general good as opposed to the application to a specific problem of an organisation.

Table 2-1 summarises the differences between the two research types.

Table 2-1 Basic and Applied Research

Basic research	Applied research
Purpose: • Expand knowledge of processes of business and management • Results in universal principles relating to the process and its relationship to outcomes • Findings of significance and value to society in general	Purpose: • Improve understanding of particular business or management problem • Results in solution to problem • New knowledge limited to problem • Findings of practical relevance and value to manager(s) in organisation(s)
Context: • Undertaken by people based in universities • Choice of topic and objectives determined by the researcher • Flexible time-scales	Context: • Undertaken by people based in a variety of settings including organisations and universities • Objectives negotiated with originator • Tight time-scales

Source: Saunders et al. (2000), pg. 3

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The purpose of this research is to examine the change of drug discovery strategies in the pharmaceutical industry. This purpose is not directly linked to an industry need, but it does expand the knowledge of business and management in this sector. Furthermore, the results and findings of this research are not concentrated on one particular organisation. Rather, they focus on the strategic change of one business process (drug discovery) in one particular sector (pharmaceutical). Finally, this research is conducted by a university-based researcher as part of a four year programme research that has had relatively flexible time scales. Therefore, the current research falls under the category of *basic research*.

2.3.2. *Empirical versus Theoretical Research*

Empirical research is based on *the results of observation*, whilst theoretical research is concerned with *the theory of a subject*. Theoretical research begins by developing a theory using *a priori* knowledge; the theory is then tested using a variety of methods including data collection and case studies. Empirical research gathers the data (empirical evidence) and then processes this evidence using numerical tools. The observations identified and the resulting theories are formed primarily from this statistical process. Hence, the data employed is used to construct the empirical research, instead of supporting the research, as is the case with the theoretical approach.

Although it is obvious that these two approaches are different, they are both regarded as valuable ways of building knowledge. However, it is not always easy to distinguish them apart. Most research projects, including the one presented in this thesis, involve both theoretical and empirical approaches. Before any empirical investigation can be conducted, a researcher should have a degree of understanding

about the entity/subject under investigation and therefore holds some form of theoretical position. Without studying the subject, the empiricist is not able to properly understand the problems and hence is limited in the collection of empirical evidence. Likewise, the theorist, without the evidence presented by existing studies, is unlikely to have ideas or arguments to build on. Theoretical research, therefore, does not occur in a vacuum. It is the result of rationalising the findings of previous empirical studies and presenting different views from the interpretations previously made.

This thesis presents a combination of the theoretical and empirical approach. The theoretical part of the research uses the existing literature to understand the subject matter (drug discovery strategy), develop hypotheses, and design the research (Chapters 4, 5, and 6). This theoretical aspect of the research addresses research questions 1 and 2 (Chapter 4), while the empirical aspect, assesses the viability of the hypotheses (research question 3) by developing two cladistic classifications (Chapters 7 and 8). It also identifies the characteristics of the fittest strategies (Research question 4).

2.3.3. Positivistic versus Phenomenological Research

There are two main research paradigms or philosophies, these are the positivistic and the phenomenological (Hussey and Hussey, 1997) the main features and differences of which are shown in Table 2-2.

Table 2-2 Positivistic versus Phenomenological Research

Positivistic Research	Phenomenological Research
Tends to produce quantitative data	Tends to produce qualitative data
Data is highly specific and precise	Research concentrates on understanding and
Research concentrates on description	interpretation.
and explanation.	
Well-defined, narrow studies	Narrow as well as total studies (holistic
Uses large samples	view)
	Uses small samples
Concerned with hypothesis testing	Concerned with generating theories
Research concentrates on generalisation	Researchers concentrate on the specific and
and abstraction.	concrete ("local theory"), but also attempt
Generalises from sample to population	generalisations.
	Generalises from one setting to another
Reliability is high	Reliability is low
Validity is low	Validity is high
Statistical and mathematical techniques	Data is rich and subjective
for quantitative processing of data are	
central.	
Researchers are detached, i.e., they	Both distance and commitment; researchers
maintain a distance between themselves	are actors who also want to experience what
and the objective of research; take on	they are studying from the inside.
the role of external observer.	

Source: Gummesson (1991), pg. 153

Although there are several distinct differences between the two paradigms, they are seen as a continuum where at the one end there is the positivistic approach and at the other end the phenomenological. In reality, a combination of the two paradigms is also considered appropriate.

2.3.3.1. The Positivistic Paradigm

The positivistic paradigm is based on statistical approaches used in the natural sciences (e.g. physics chemistry and biology) for analysing data collected using descriptive and comparative studies and experiments. The use of these approaches in the natural sciences has been very successful and is the main reason why social scientists adopted this approach at the beginning of the nineteenth century. It was assumed that only knowledge obtained by means of measurement and objective

identification could be considered valid. The main principle of analysis is the cause and effect of the variables under study.

The positivistic paradigm seeks facts or causes of social phenomena without taking into account the subjective state of the researcher who conducts the study. It is based on the idea that studies of human behaviour should be conducted in the same way as the studies conducted in the natural sciences (Hussey and Hussey, 1997).

The process that is usually being followed when conducting positivistic research is to study the literature and establish an appropriate theory and construct hypotheses. The hypotheses are then tested using statistical analysis. Such an approach requires the data to be highly specific and precise. Therefore, the type of data required should be quantitative and considerably rigorous to ensure accuracy of the measurement.

Within the positivistic paradigm, there are three different types of methodologies:

- *Cross-sectional studies*: this is a methodology designed to obtain data on variables in different contexts, but at the same time. Different organisations or groups of people are selected and a study is conducted to identify how factors differ. Statistical analysis is then performed to identify how the variables of the study differ. This methodology is useful when a snapshot of reality is required e.g. in the investigations of economic characteristics of large numbers of people.

- *Experimental studies*: this is a methodology conducted in a systematic way in a laboratory or in a natural setting. Its aim is to change the *independent* variable and to identify what is the effect of this change on the *dependent* variable. This allows the causal relationships between the independent and the dependent variables to be defined.

- *Longitudinal studies*: the study of a variable or a group of subjects over time. Its aim is to explore the dynamics of the problem under investigation by examining the same situation or group of people several times over the period that the problem occurs. This period can be many years and permits the examination of the change processes within a social, economic and political context.

2.3.3.2. The Phenomenological Paradigm

Criticism of the positivistic paradigm resulted in the development of the phenomenological paradigm. Table 2-3 includes a list of the most common criticisms of the positivistic approach.

Table 2-3 Criticisms of the positivistic paradigm (From Hussey and Hussey, 1997, p. 53)

• It is impossible to treat people as being separate from their social contexts and they cannot be understood without examining the perceptions they have of their own activities.
• A highly structured research design imposes certain constraints on the results and may ignore more relevant and interesting findings.
• Researchers are not objective, but part of what they observe. They bring their own interests and values to the research.
• Capturing complex phenomena in a single measure is, at best, misleading. For example, is it possible to assign a numerical value to a person's intelligence?

The *phenomenological* approach uses a more personal and interpretative process to "understand reality". The concept of reality is interpreted by the researcher who observes and experiences the situation. Without this interacting role between the researcher and the situation, rich insights into the complex research areas are often lost. Therefore by interpreting and understanding a problem from different viewpoints, an enhanced understanding is achieved. In other words, by translating the realities and having empathy with reality allows knowledge to be accumulated.

Phenomenology is the science of phenomena. A phenomenon is a fact or occurrence that appears or is perceived, especially one whose cause is in question. Therefore, the

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phenomenological paradigm is concerned with understanding human behaviour from the participant's own frame of reference, which in the case of this research is evolutionary and classification based. Social reality is within us and consequently the study of the reality has an effect on the reality (Hussey and Hussey, 1997). Phenomenologists believe that social reality is dependent on the mind and therefore, what is being researched cannot be unaffected by the process of research.

As opposed to the positivistic paradigm the process of conducting a phenomenological study seeks to construct a theory that explains the phenomena or the pattern that emerges in the data. The type of data that is being collected is usually qualitative as the emphasis is on the quality and the depth.

There are various methodologies used to conduct phenomenological research. The ones, most relevant to this thesis, are:

- *Case studies*: this is an empirical inquiry that investigates a contemporary phenomenon within its real life context, especially when the boundaries between phenomenon and context are not clearly evident (Yin, 1994 p.13). Case studies are often used in areas where there are few theories or a deficient body of knowledge.

- *Grounded theory*: this is when a theory is derived from data that has been systematically gathered and analysed through the research process. With this method, data collection, analysis and eventual theory stand in close relationship to each other. Research begins with an area of study and allows the theory to emerge (Strauss and Corbin, 1998).

2.3.3.3.   Mixing the methodologies

The research presented in this thesis (and like most management research projects) is a combination of both phenomenological and positivistic approaches. This research seeks to define and map the evolution of different drug discovery strategies, while understanding the factors that influence and shape different strategies. The research extends from the beginning of the nineteenth century to current time. A pure positivistic approach would require accurate and comprehensive collection and analysis of empirical data for this period, while a pure phenomenological approach would require the careful examination of one or more cases. Although not impossible, neither of the two options is difficult to realise with the appropriate level of resource (time and money). However, a careful combination of the two approaches can provide the research with better reliability and credibility. Such a research process is described by Hendry (1992) and has been labelled *business strategy and business history.* This methodology determines the role that history can play in social science theory building and is in accord with and complementary to the aims and objectives of this thesis.

This business history methodology combines the features of case study research and longitudinal analysis (Hendry, 1992) and like most case study research (Yin, 1984), to which it is most closely related, it is situationally and temporally context sensitive, embraces multiple data sources and cross checks the validity of different sources through a process of triangulation i.e. the use of different research approaches, methods and techniques in the same study (Hussey and Hussey, 1997). It differs from longitudinal case study research in adding to its own primary methodological concern with the relative status of different types of source material (primary documentary, but also physical and recollective) and with the limitations of justifiable inference

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from such materials. As part of this concern it seeks to satisfy the scientific principle of replicability, placing its raw data in the public domain, referencing its statements in detail to this data and so opening up its analysis to critical cross examination.

In relation to the social sciences in general, the methodological strength of the business history approach lies in its ability to apply the longitudinal approach to research with the contextual sensitivity and richness of the case study approach, and in its ability to bring to case study research both a longitudinal dimension and critically, a highly developed (if largely implicit) set of standards and principles of evidence (Hendry, 1992).

The limitations of the business history approach are essentially those associated with the impossibility of real time observation, interrogation or experiment, together with those of the case study approach in general. Though historians can and do employ quantitative techniques drawn from social sciences, their discipline is essentially an interpretative one, in which general conclusions are established by the subjective interpretation and comparison of specific instances rather than by the analytic reduction of data from multiple events.

Historical comparison may be used for hypothesis testing, and in particular for testing the robustness of a hypothesis generated from one branch of the social sciences or one type of data with respect to considerations drawn from other disciplines and other data sources. Of all the areas of management research, business strategy is one, that is most reliant on cross disciplinary perspectives, and this suggests that both the critical and synthetic aspects of business history should be of particular relevance to theory building in this area (Hendry, 1992).

2.3.4. Research Process

As presented above research can take many forms, but there is a common characteristic - *systematic inquiry*. For systematic inquiry to take place, a researcher should develop plans and project management, because research, like any other project is a series of highly interconnected activities subject to time and cost restraints. The stages in the research process overlap continually and it is an oversimplification to state that every research project follows a neat and ordered sequence of activities. Nevertheless, research can often follow a generalised pattern. The six stages observed by Zikmund (2000) are (1) defining the problem, (2) planning a research design, (3) planning a sample, (4) collecting data, (5) analysing data, (6) formulating the conclusion and preparing the report. These six stages are shown in Figure 2-1 as a cyclical process or as a circular-flow concept, because conclusions from research studies usually generate new ideas and problems that lead to further investigations.
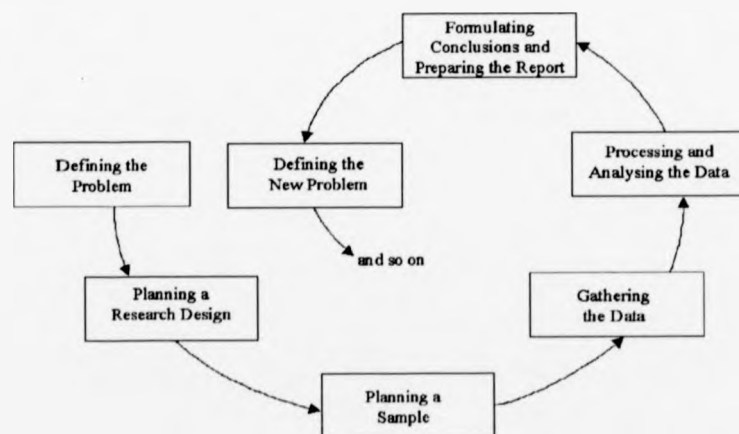
Figure 2-1 Cyclical research process

Source: Zikmund (2000), pg. 54

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2.3.5. Research Process of the Present Research

The research process that was followed to conduct this research is shown in Figure 2-2.

2.3.5.1. Formulating the research problem

This stage involves the identification of the area of interest and includes establishing a boundary and purpose for the general area of study (drug discovery strategy) and the development of research questions to be addressed. This stage is reported in chapters 1 and 3.

2.3.5.2. Formulating the research approach

This stage involves the identification and justification of the approach that will be used to meet the aims of this research (i.e this chapter – Chapter 2). More specifically, it explores the various research approaches found in the literature and then rationalises and selects those which are viable to this research.

2.3.5.3. Conducting the literature review

Once the topic of interest and the research approach are defined, the next step is to conduct the literature review. The aim of this stage is to *interpret and synthesise the published research* (Merriam, 1988 in Hussey and Hussey 1997 p.109) and thus identify and confirm a potential area of novelty. To achieve this a literature review was conducted in the following areas, drug discovery (chapter 3), strategic management (chapter 4), and biological evolution (chapter 5).

2.3.5.4. Reformulate research questions

The completion of the above stages provides a thorough and scholarly understanding of the topic of interest. This understanding permits the research questions to be reformulated i.e. they are evaluated and rewritten to become more specific on the subject. The final form of the research questions is the one reported in section 3.3 of this thesis.

2.3.5.5. Development of hypotheses

This stage involves the development of *guesses about what lies behind the 'how' in the research question* (Robson, 1993, p. 29). The third research question of this thesis (How can an evolutionary and classification approach be used to study drug discovery strategies?) requires the investigation of how the requirements of evolution (chapter 5) relate to drug discovery strategy. To achieve this, four hypotheses are developed, one for each requirement (chapter 5).
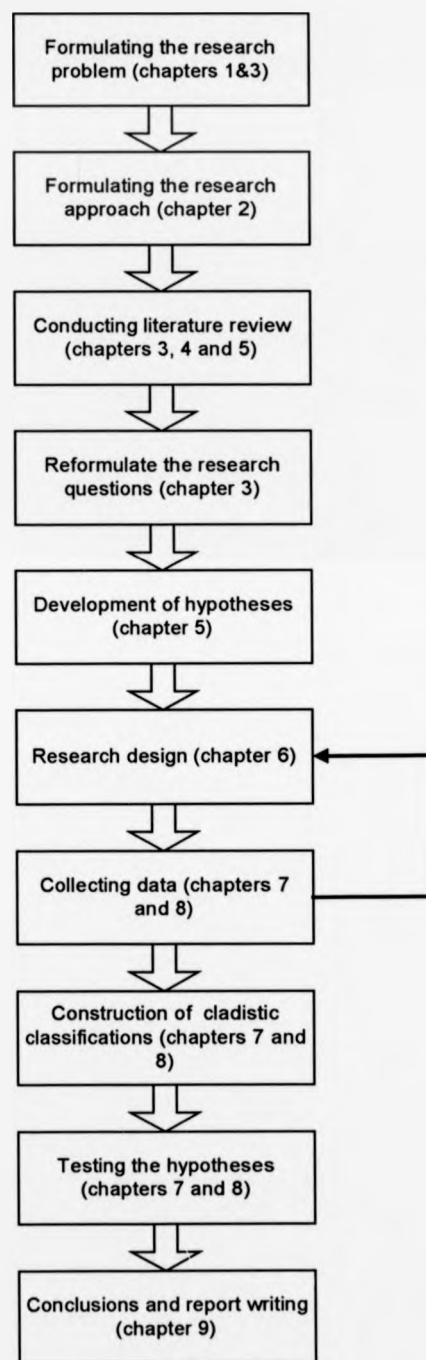
Figure 2-2 Research process of this thesis

2.3.5.6.   Research design

This stage involves the design of the activities that are carried out to test the four hypotheses developed in the previous stage. These activities include the collection of data and the framework used to analyse the collected data i.e. the evolutionary classification technique *cladistics*. In chapter 6 the rationale for using cladistics and the detailed methodology to be used is reported.

2.3.5.7.   Collection of data

This stage involves the collection of data about the pharmaceutical industry. It was collected from three sources: books, journal papers, online papers, industrial articles, historical databases, and company annual reports. The data was gathered and stored in a chronological order. Chapters 7 and 8 report how the data was collected, the sources used, and the criteria imposed. Once this stage was complete, the research design stage was revisited to ensure that the limitations of the data collection method were taken under consideration.

2.3.5.8.   Construction of cladistic classifications

This stage involves the construction of the cladograms i.e. the cladistic classifications. Two cladograms were constructed. The first (population cladogram) used data from available historical secondary data to identify and classify types or forms drug discovery strategies. The second (organisation cladogram) used data from the pharmaceutical industry to identify and classify drug discovery strategies found in individual organisations. This stage is reported in chapters 7 and 8.

2.3.5.9. Testing hypotheses

This stage involves the validation of the four hypotheses using the two cladograms. This stage is reported in chapters 7 and 8.

2.3.5.10. Conclusions and report writing

This is the final stage of this research process and includes the conclusions of the study and the writing of the current report. It also evaluates to what degree this thesis has addressed the research aims, questions and hypotheses. It reviews the limitations of the research and outlines future areas of work. This stage is reported in chapter 9.

2.4. Conclusions

This chapter selects, justifies and introduces the reader to the research methodology and process used throughout the thesis i.e. the business history approach. This provides a method to conduct a systematic investigation into the research problem – understanding the *evolution of drug discovery strategies*. Developed from a general research model, this research can be divided into ten stages. For each stage, the research activities and its outcomes are discussed.

3. INTRODUCING AND DEFINING THE RESEARCH PROBLEM

3.1. Introduction

This chapter introduces the subject area of this thesis – drug discovery strategies, and presents and justifies the overall research aim and research questions. This is achieved by reviewing the modern process of drug discovery, along with its defining stages and key characteristics. This review illustrates (i) that modern drug discovery is a highly automated and sophisticated process, and (ii) provides the theoretical basis by which to study the diversity of drug discovery strategies and how they have evolved. To confirm the research questions and contribution made by this thesis, the final section of this chapter provides a review of the existing literature, which straddles the areas of strategic management and drug discovery. This is followed by a discussion of each of the research questions in detail.

3.2. Introduction to Drug Discovery Process

The average cost to research, develop, and bring to market a prescription drug in the US has reached $802 million (this figure was calculated by the Tufts centre for the study of drug development (Tufts, 2002)). This figure has tripled in nine years (allowing for inflation) and includes the cost of failures and research on compounds abandoned during development as shown in Figure 3-1.
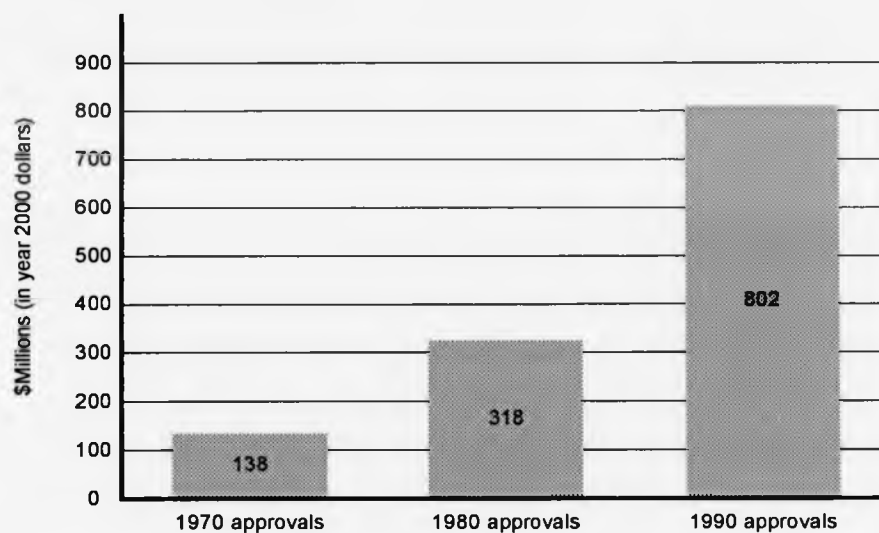
Source: Tufts center for the study of drug development (Tufts, 2002)

Figure 3-1 Average cost to develop a new drug, from discovery to Approval

For every 5,000 compounds tested only five make it to clinical trials according to the Pharmaceuticals Research and Manufacturers of America (PhRMA, www.phrma.org). Of these five, only one is eventually approved for patient use. On average it takes 12 years from the time a new compound is synthesised in the lab until it receives approval from the Federal Drug Administration (FDA) to be marketed.

Much time and effort is spent yearly by large pharmaceutical organisations attempting to reduce the required time and the resulting high costs. Any shortening of the time required to produce a drug could produce large benefits for an organisation. In fact one pharmaceutical organisation estimated that getting a new drug to market a year earlier increased revenues by $580 million, and this excludes the benefits associated with the strengthening of the company's competitive position (Schneider, 2000).

Pharmaceutical organisations seek to achieve higher performance of their drug discovery process to maintain their current revenue and growth trajectories. Just to keep pace with an annual industry growth rate of 10 percent, the top 10 global pharmaceutical players will need to launch at least five significant NCEs (new chemical entities) per year. Thus, even modest growth objectives present an unprecedented challenge for drug discovery. Allocating more people and money for research does not achieve the necessary performance gains (Reuters, 2000). The research and development function needs to fundamentally rethink their approach to drug discovery, their organisational models, processes, utilisation of technology and information/knowledge management capabilities to achieve higher growth objectives

A popular view of the discovery of new therapeutic drugs is that of a random and unplanned process (Cox et al, 1975), but the reality is that most pharmaceutical companies cannot afford to share this view. To survive in the long term modern pharmaceutical companies need to create a continuous flow of drugs into the market. This means that pharmaceutical organisations must provide and manage adequate resources and commitment to their drug discovery process. This was demonstrated using empirical evidence very early on in pharmaceutical history (Comanor, 1995), where the relationship between research and development, and the rate of new product technical change was investigated.

Over the last quarter of the 20th century the process of drug discovery has gone through a revolution, which has been triggered by advances in biological science (Henderson at al., 1999). Progress in the ability to understand the mechanism of action of some of the existing drugs and the biochemical and molecular roots of many diseases made it possible to design significantly more sophisticated drugs or, to use Henderson's (1994) analogy, *if the action of a drug on a 'receptor' in the body is*

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similar to that of a key fitting into a lock, advances in scientific knowledge have greatly increased knowledge of what the locks' may look like (p. 614). In addition new technologies such as combinatorial chemistry and high throughput screening have increased an organisation's experimentation capacity as shown in Figure 3-2.
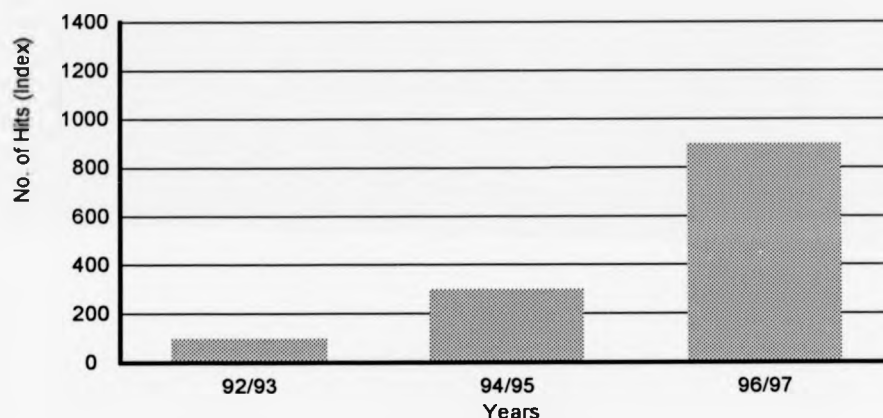
A hit is any molecule with minimal threshold binding affinity and/or threshold functional activity on a given target
Source: Thomke and Kuemmerle (2002) p. 628

Figure 3-2 Growth in output as measured by the number of hits

A typical modern drug discovery process consists of four stages as illustrated in Figure 3-3. The first two stages are devoted to the discovery and optimisation of one or a few 'lead' chemical compounds that appear to hold sufficient application promise and thus merit investment in the next stage - *clinical development*. The process of clinical development typically consists of three phases aimed at determining and documenting the safety and the efficacy of the proposed drugs. During these phases the proposed drug undergoes controlled trials on humans. When the three phases are

complete the information collected is submitted to the relevant authority for regulatory approval (Thomke et. al, 1998).

The flowchart presented by Figure 3-3 serves to define the boundary and scope of the subject under investigation by this thesis and is used as a reference hereafter. In accord with Figure 3-3, the following sections describe each of the stages of the drug discovery process.

3.2.1. Target Research

The aim of this stage is to identify the molecular targets associated with a specific disease process (Williams and Malick, 1987). The selection of targets depends on a number of organisational and technological issues. Organisational issues include commercial validity and strategic issues such as alliances, franchises, and patents. While, technological issues would include the specialisation/expertise of a given company to a certain therapeutic area, the link to a disease, and technical feasibility (Williams and Nadzan, 1987, Williams and Malick, 1987).

Once the target has been selected, the process moves onto the synthesis of chemical entities using techniques like combinatorial chemistry. This technique involves the generation of a large number of organic compounds from chemical building blocks (Reuters, 2000) that are screened to identify desired biological activity that could trigger further development.
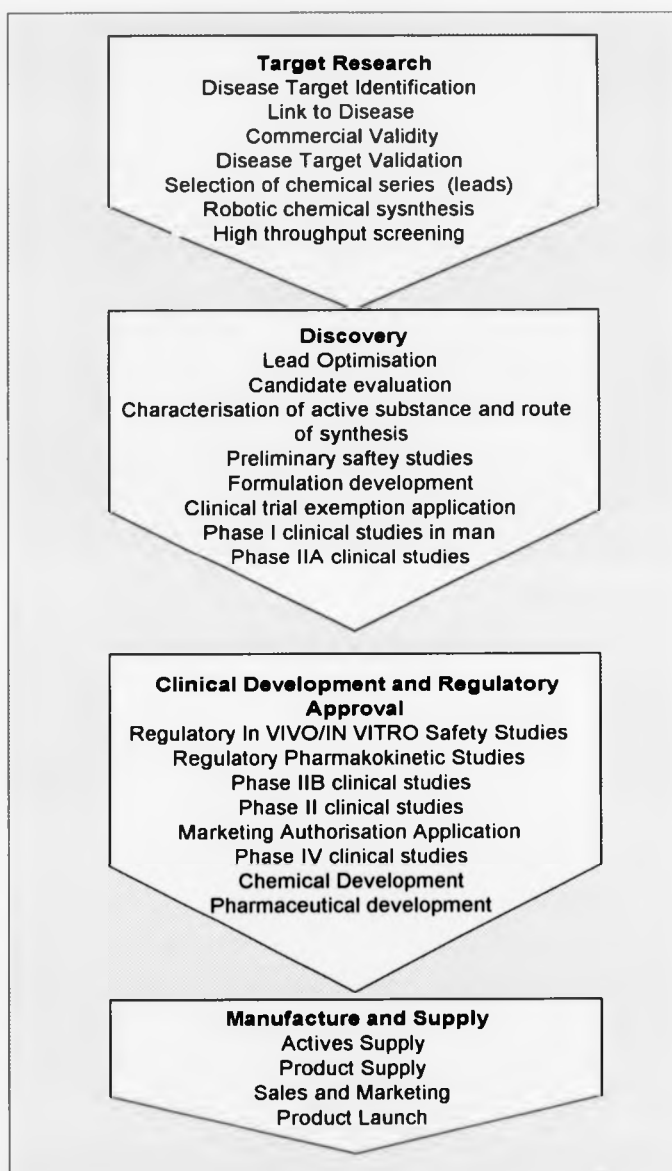
Figure 3-3 Flowchart of drug discovery process

3.2.2. Discovery

Once the active compounds have been identified the next stage involves their optimisation, evaluation, and the first stages of clinical testing. Prior to this stage a research team has knowledge about the basic chemical and biological properties of a new compound and a basic understanding (based on theoretical assumptions and some animal testing) of its therapeutic properties (Drews, 1988 p. 126). The optimisation of the compound involves screening out negative characteristics i.e. making sure that the compound is free of toxicity and does not cause any significant side effects. The aim of the clinical studies is to establish safety and effectiveness in human beings in relation to the substance under investigation.

Before moving onto the first stages of clinical development the new compound is evaluated both technically and commercially. Technical evaluation involves exploring how the new substance acts on living tissue and organisms, how the organism alters the substance, how the new substance is distributed into the organism, and by what pathways and mechanisms they again leave the body (Drews, 1988 p.127).

The commercial validation of the drug consists of activities that examine the business-related dimensions and market potential of the drug to the company i.e. it addresses the question: *how will the company benefit from the development of the drug under question?* The answer to this question is vital and primarily decides the future of the project.

The discovery stage also includes the first phases of clinical studies. In total there are three phases. Phase I primarily examines the safety of a new compound and tests are carried out on several healthy patients (Drews, 1988). Such tests are usually

clinical-pharmacological studies i.e. the medicine under test is administrated as a very small single dose and the patients are monitored carefully, since at this point there is no information about the safety of the new drug to humans. If the subjects show no ill effects the dosage is increased in small increments and the test repeated until side effects appear.

3.2.3. Clinical Development and Regulatory approval

This stage of the drug discovery process is the last before it is produced in large numbers and becomes available to the public. It involves the later phases of clinical studies, regulatory approval and chemical and pharmaceutical development.

Phase II seeks to determine the effectiveness of the drug using tests with target patients i.e. those patients who are carrying the disease that the drug aims to cure (Krogsgaard-Laarsen, and Bundgaard, 1996). These studies are normally carried out with two or three different dosage levels as well as a placebo control group (a group of patients who are prescribed a medicine with no therapeutic effects in order to compare the results in their treatment with another group that has been prescribed the medicine under trial and to eliminate any effects due to the mind-body connection (Hart, 1999)). In many cases, where the disease is serious such as AIDS, and severe hypertension, the placebo part of the study is replaced with various dosages of already established drugs. One issue that is tackled whenever a new drug reaches this stage, is the definition of its effectiveness. In the case of AIDS for example the aim of the drug would be the prolongation of life. Such an experiment would require years of data and this would make the experiment itself impossible. Therefore, alternative criteria are identified and used to indicate the effectiveness of a drug.

The final stage of clinical studies, Phase III, involves testing a new drug to larger and more diverse populations. These trials are normally controlled, multi-clinic studies, enrolling several hundred to more than a thousand patients, and designed to establish the efficacy of the drug and define its diverse effect profile as precisely as possible. During this phase, some evidence of uncommon side effects and adverse laboratory changes may be obtained (Reines and Fong, 1987). Therefore once this phase is completed, a more accurate picture of the drug behaviour is available. Similar to Phase II, Phase III involves testing of two or three different dosages against a placebo and/or against comparison treatments. To achieve the numbers required for such a study, usually a number of institutions participate, all of which must follow the same data collection rules and procedures. These trials are called *multi-centre trials*.

Once the clinical and pre-clinical data have been collected, the next stage is to apply for approval from the relevant authority of each country. This stage is a very expensive, laborious and time-consuming process which can take up to two years and often results in disapproval. The document that is submitted for approval includes information on drug chemistry (how it will be manufactured and all related control processes), validation (packaging and labelling), pre-clinical pharmacology and toxicology, pharmakokinetics and bioavailability, clinical data, and clinical safety.

3.2.4. Manufacture and Supply

This final stage of the drug discovery process involves those activities involved in the preparation of the pharmaceutical organisation to manufacture, supply and market of the new drug. These activities are seen as part of the drug discovery process because they can include the construction of a new chemical plant (to develop and provide the active compounds), market research, long-term safety and efficacy

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3.3. Review of Drug Discovery Strategy Literature

The scope of this thesis is to relate and transfer the discipline of strategic management to the process of drug discovery, to understand the change and diversity of drug discovery strategies. As will be shown and verified by this section, there is relatively little in the way of existing literature and studies that focus on drug discovery strategies, and what does exist is fragmented across a number of disciplines including technology management, chemistry, automation, marketing, knowledge management and strategy.

Existing studies of drug discovery focus on the optimisation of the drug discovery process mainly through the use of new knowledge and technology (e.g. FitzGerald, 2000, Harvey, 1995, Jensen, 1998, Kniaz, 2000, Koretz and Lee, 1998, Krantz, 1998, Merritt, 1998, Bernhardt and McCulley, 2000, Danheiser, 1997, Erickson et al., 1990, Schneider, 1999, 2000, Spence, 1999). Although knowledge and technology are fundamental to the formation of strategy, there is limited application of the principles of strategic management to drug discovery.

Some work has been carried out on the effect of organisational networks on the process of drug discovery. For instance, Gambardella (1992) studied the effect of in-house scientific programs and the exploitation of outside scientific information. In particular, he examined the proposition that in-house scientific research raises the ability of organisations to take advantage of public science i.e. science that is developed by the academia and other non-profit scientific institutions. The findings of this research suggest that organisations with better in-house scientific capabilities have been able to make better use of both internal and external science. He concludes by suggesting that to be part of a network and to be able to effectively exploit the

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information that circulates in the network, has become even more valuable than being able to generate new knowledge autonomously (Gamardella, 1992)

In a study carried out by Arora and Gambardella (1990) on biotechnology firms it is suggested that the locus of innovation in biotechnology should be thought of as *a network of interorganisation relations (p. 374)*. In their paper they explored the relations among the strategies of external linkage of the large chemical and pharmaceutical producers in the new biotechnology business. Their findings suggest that agreements with other organisations, research agreements with universities, minority participations in new biotechnology firms, are positively correlated. They concluded that these strategies are complementary to each other as they target distinct and complementary sets of resources (Arora and Gambardella, 1990).

Oliver (2001) analysed the relationship between organisational lifecycle and the formation of strategic alliances of biotechnology organisations. In particular she tested the propositions that the inability of dedicated biotechnology organisations to form strategic alliances is associated with organisational death and that organisational growth makes it possible to reduce network learning through alliances allowing an organisation to enter a period of exploitation. Her findings suggest that firstly, there is no increasing linear pattern in the odds for forming new alliances as biotechnology organisations grow. Secondly, the lack of alliances was indeed associated with organisation death.

In a similar study Deeds and Hill (1996) also found evidence to support that an entrepreneurial biotechnology organisation can increase its rate of new product development by entering into strategic alliances with organisations that possess complementary assets. They argued that the rate of an organisation's new product development increases the number of strategic alliances an organisation has entered,

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but in a non-linear fashion. In fact they suggest that the relationship between the number of alliances and the rate of new product development may be an inverted U-shape (Deeds and Hill, 1996).

Other empirical work in this area includes studies about the *absorptive capacity* of pharmaceutical organisations i.e. an organisation's ability *to recognize the value of new, external knowledge, assimilate, and apply it to commercial ends* (Cohen and Levinthal, 1990, p. 128). For instance, Lane and Lubatkin (1998) examined the factors that influence an organisation's absorptive capacity by testing the ability of one organisation to learn from another. They found that the absorptive capacity in this respect (from one organisation to another) is positively correlated to the similarity of the two organisations' i) knowledge bases (a general understanding of the traditions and techniques upon which a discipline is based), ii) organisational structures (the degree of formalisation and centralisation used by an organisation when allocating tasks, responsibilities, authority, and decisions) and compensation policies, and iii) dominant logics (the *common thread* running through an organisation's commercial objectives).

Cockburn and Henderson (1998) further studied the absorptive capacity of pharmaceutical organisations by focusing on the interface between for-profit and publicly funded pharmaceutical research. They argue that the relationship between the public and private sectors cannot be described *by a waterfall model in which the public sector produces knowledge that spills over costlessly to downstream researchers* (Cockburn and Henderson, 1998, pp. 179-180). In the contrary, they found that the ability to take advantage of knowledge generated in the public sector requires investment in a complex set of activities that, taken together, may change the nature of private sector research (Cockburn and Henderson, 1998).

Lee and Harrison (2001) examined the US pharmaceutical industry bifurcation into groups of innovative and imitative strategies. They labelled *innovative* those strategies pursued by organisations who survive by seeking innovative drugs and selling them at premium prices. On the other hand they labelled *imitative* the strategies of the organisations that survive by producing me-too drugs and selling them at me-too prices. They developed a model of industry evolution and found that strategic group emergence is dependent on low exit rates and thus, they concluded, innovative strategies are most viable when organisations are somewhat shielded from short-term survival pressures.

A series of empirical studies have focused on the effects of mergers, acquisitions and firm size in research productivity. Graves and Langowitz (1993) suggest that mergers in the pharmaceutical industry may yield less innovative productivity than managers expect. They studied the innovative output of 16 US pharmaceutical organisations. Their results indicate that there is a positive relationship between the research and development expenditure and the innovative output (measured in new chemical entities produced). However, the proportion of that output decreases as research and development expenditures generally related to organisation size increase i.e. innovative effectiveness decreases with increasing organisational research and development budget and with organisation size. They suggest two reasons for this phenomenon. The first is that possibly large organisations may undertake more risky research. However, Mansfield (1981) has found that there is no statistically significant relationship between large corporations and risky research and development. The second reason is that large organisations are inherently inefficient so that their size stands as an impediment to innovative results. This may be due to

bureaucracy and the conservative nature of large organisations (Graves and Langowitz, 1993).

In a contrasting study Henderson and Cockburn (1996) examined the relationship between firm size and research productivity. They investigated the internal records of ten pharmaceutical organisations. The level of their investigation was the individual research program that covers the range of major research and development performing pharmaceutical manufacturers. Their results indicate that large organisations appear to have an advantage in the conduct of research. Also, they suggested that superior performance flows from economies of scope (by say combining the multiple groups of researchers under the same roof) as well as from economies of scale. The main reason for this is that large pharmaceutical organisations are able to sustain an adequately diverse portfolio of research projects, and to capture and use internal and external spillovers of knowledge. However, Henderson (2000) in a later article argues that drug industry mergers will not necessarily benefit their research and development. She argues that there is a threshold in the size of organisations beyond which there are diseconomies of scope. This threshold size is six to seven major research programs. As this size has now been reached even by medium sized organisations, she argues that it is unlikely that large mergers will benefit research and development.

Henderson et al (1999) attempt to gain insight into the national systems of innovation. They examine the regional differences in the impact of biotechnology on pharmaceutical industry structure and the nature of competition. Biotechnology may be used as a production technique and as a research tool (McKelvey, 1996). They found that when used as a production technique, biotechnology made several of the core competencies of existing organisations, particularly those related to process

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development and manufacturing, obsolete. Biotechnology as a research tool was adopted by pharmaceutical organisations as a way to use molecular biology to enhance the value and productivity of their existing assets and competencies. However, Henderson at al. (1999) found that the new techniques enhanced the competencies only of those organisations that were already oriented towards *high science* research and were already firmly embedded in the scientific community.

Henderson (1994) studied the evolution of integrative competence, i.e. the ability to integrate knowledge across both organisation and disciplinary boundaries, as a factor in productive research. She found that these competencies are readily identifiable and include the use of cross-disciplinary teams in the management of research, the promotion of individuals on the basis of their standing in the scientific community, and the organisation of research by discipline rather than by therapeutic area. However, her conclusions suggest that these findings are complex entities that evolve slowly over time and thus it may be difficult to develop normative prescriptions from cross sectional analyses of competencies. Therefore, she concludes, those organisations that were fortunate to have focused early on more rational modes of drug discovery have been much more successful in developing the integrative capabilities than those that initially achieved it by the more traditional random method of drug discovery. These capabilities are fundamental to modern drug discovery (Henderson, 1994).

In a continuation of this study Henderson and Cockburn (1994), distinguish between component (unique disciplinary expertise and expertise in particular disease areas) and architectural (the ability to integrate the component competencies) competence and examined the variance in research productivity across organisations. Their findings suggest that competence is important as a source of advantage in research

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productivity. In particular, they conclude that research productivity increases with historical success. Moreover, they suggest that the differences in local capabilities, i.e. resources, knowledge and skills, or technical systems, may play an important role in shaping enduring differences between organisations. Finally, their findings suggest that in organisations in which publications records are important criteria for promotion and in organisations which use committees to allocate resources the research productivity is higher.

In a later study Cockburn et al (2000) investigate the origins of competitive advantage and they explore two possible hypotheses. The first suggests that competitive advantage is largely determined by factors put in place at an organisation's founding. This hypothesis is inline with the population ecology theory, which suggests that most performance differentials can be explained by differences in initial conditions and that these initial conditions are largely the result of difficult to explain differences in each organisation's initial allocation of resources and capabilities (Hannan and Freeman, 1977) (population ecology theory is explained in greater detail in chapter 4). The second hypothesis suggests that competitive advantage results from an organisation's strategic response to changes in the environment or to new information about profit opportunities. This hypothesis is inline with the planned view of strategy making that suggests that organisations respond to and exploit environmental signals (Porter, 1980) (planned strategies are also explained in greater detail in chapter 4). To test these hypotheses they evaluate the adoption of science driven drug discovery strategy in the worldwide pharmaceutical industry. Their findings are consistent with a perspective in which both population ecology and planned strategy have an important role to play in explaining patterns of organisational heterogeneity. They argue that initial conditions

on the one hand play an important role because the differences observed at the beginning of the period of their study persisted for many years. On the other hand their findings suggest that organisations that were furthest from best practice at the beginning of the period moved aggressively to adopt it.

In a similar study Thomke and Kuemmerle (2002) investigated the micro-level mechanisms by which assets are built and the reasons why some organisation assets are more difficult to imitate and trade than others. In particular they examined the dynamic process of accumulating chemical libraries and related technology assets used for drug discovery in nine pharmaceutical organisations. Their findings indicated three primary causes i) difficulty of imitating a particular asset, because of interdependence with other assets, ii) difficulty of trading assets, because of some structural inertia in adoption with an organisation's core, and iii) difficulty of fully specifying all factors affecting imitation or adoption, because of rapid technological change (Thomke and Kuemmerle, 2002).

Although these studies (a summary table of which is provided in Table 3-1) provide valuable theoretical and empirical research about the drug discovery business, and its effectiveness (profitability and innovation) in terms of networks, mergers and structural organisation, there is almost no information about the defining strategies and the strategic management process that accompanies and influences such practice. There is no existing introductory account to and definition of drug discovery strategy,

Table 3-1 Summary of drug discovery strategy literature

Topic	Key finding	Authors
Optimisation of drug discovery process	Related to technological and knowledge advances	FitzGerald, 2000, Harvey, 1995, Jensen, 1998, Kniaz, 2000, Koretx and Lee, 1998, Krantz, 1998, Merritt, 1998, Bernhardt and McCulley, 2000, Danheiser, 1997, Erickson et al., 1990, Schneider, 1999, 2000, Schneider, 2000, Spence, 1999
Effect of organisational networks	Exploitation of outside information	Gambardella (1992)
	Complementary strategies	Arora and Gambardella (1990)
	Organisational life cycle and organisational networks	Oliver (2001)
	New product development and strategic alliances: U-shape relationship	Deeds and Hill (2001)
Absorptive capacity	Ability of two organisations to learn for each other	Lane and Lubatkin (1998)
	For-profit and publicly funded research	Cockburn and Henderson (1998)
Innovative and imitative strategies	Strategic group emergence is dependent on low exit rates	Lee and Harrison (2001)
Mergers, Acquisitions, organisational size	Reduction of innovative productivity	Graves and Langowitz (1993)
	Larger size means better research	Henderson and Cockburn (1996)
	Existence of threshold size	Henderson (2000)
Integrative competence	Complex entities that evolve slowly over time	Henderson (1994)
	Research productivity is a function of historical success, local capabilities, and promotion criteria	Henderson and Cockburn (1994)
Effect of adoption of science driven drug discovery	Biotechnology enhances competencies only of *high science* oriented organisations	Henderson et al. (1999)
	Both initial conditions and strategy planning important in drug discovery success	Cockburn at al. (2000)
Asset accumulation	Three cause for causes difficulty of imitating	Thomke and Kuemmerke (2002)

let alone a working classification that would help identify and understand different drug discovery strategies, and the possible relationships and connectivity between them. This gap is the motivation and aim of this thesis. It seeks to define and map the evolution of different drug discovery strategies, while understanding the factors that influence and shape different strategies. Addressing these issues requires a comprehensive and robust link between the discipline of strategic management and the process of drug discovery. Such a link could provide the platform for further empirical research and the development and validation of theories related to drug discovery strategies.

The research carried out and presented in this thesis aims to provide such a link by examining and classifying the change of drug discovery strategies.

Thus, the research questions addressed in this thesis are:

1. *How does the discipline of strategic management relate to the process of drug discovery and what is the definition of a drug discovery strategy?*

This research question requires the investigation of the links between strategic management and drug discovery strategies. As it was argued in the previous paragraphs there is little information that rigorously links the two disciplines. Critical to the investigation of any such link is the definition of the concept of *drug discovery strategy*. This definition should encompass the thinking on strategic management, the purpose of drug discovery in pharmaceutical organisations, and the thesis of the present enquiry.

Chapter 4 deals with this question by reviewing the literature on organisational strategy and relating it to the process of drug discovery. It concludes by creating a working definition of the term *drug discovery strategy* within the scope of this thesis.

2. What are the factors (internal and external) that influence and define different drug discovery strategies?

As it will be shown in chapter 4 existing literature in strategic management explores the factors that influence and define different organisation strategies. These factors originate both from within and outside an organisation. Also, as this thesis seeks to define and map the evolution of different drug discovery strategies, the identification of such internal and external factors specific to drug discovery strategies is essential for addressing the aim of this enquiry and this is the scope of this research question.

The review of literature in chapter 4 identifies four generic factors that influence the formation of organisational strategies regardless of industry. These factors are *knowledge, technology, organisation*, and *environment*. These are defined and related to the drug discovery process to help identify and classify different drug discovery strategies as required by the following research question.

3. How can an evolutionary and classification approach be used to study drug discovery strategies?

Evolutionary and classification approaches have provided useful insights in studies in several disciplines such as biology (e.g. Dawkins, 1989, Ridley, 1996), organisations (e.g. Aldrich, 1999, McKelvey, 1982, Allen, 2000), and economics (e.g. Metcalfe, 1997, Nelson and Winter, 1990). Having defined the concept of drug discovery strategies (1st research question) along with the factors that influence their change (2nd research question), this third research question seeks to investigate how such an approach may be used to study these strategies.

Chapter 5 identifies four requirements of evolution: existence in populations, variation, heredity, and selection. Following a review of the literature on strategic

evolution the four requirements are converted into four hypotheses. Chapters 7 and 8 address this research question by providing two cladistic classifications of drug discovery strategies.

4. What are the characteristics of the fittest drug discovery strategies?

This research question is not directly linked to the aim of this thesis. However, the process followed to address the previous research questions has revealed that some characteristics of drug discovery strategies are more sustainable than others i.e. they lead to more successful drug discovery and this leads to a higher frequency of appearance of these characteristics in future strategies. It is therefore, almost unavoidable, due to both academic curiosity and potential industrial implications, to investigate these characteristics. As explained in chapter 2 the research questions were reformulated following the completion of the literature review. This research question was added at this stage.

To address this research question chapter 5 defines the term fitness as *the condition where the configuration of an organisational strategy matches that of the environment and the frequency of its characteristics appearing in future strategies is high.* The classification created in chapter 8 provides a list of characteristics, which are in line with that definition, and thus addresses this research question.

4. STRATEGY FORMATION IN DRUG DISCOVERY

4.1. Introduction

This thesis seeks to define and map the evolution of different drug discovery strategies, while understanding the factors that influence and shape different strategies. To understand such issues it is vital to comprehend and adopt an appropriate school of strategic study (in this case evolutionary), along with the underlying mechanisms and drivers that govern the formation and implementation of strategy. Such knowledge relates strategic management to the drug discovery process, and is the subject of the first research question (How does the discipline of strategic management relate to the process of drug discovery and what is the definition of a drug discovery strategy?) and the aim of this chapter. In addition, this chapter identifies and justifies the factors that influence and define the change of a strategy. These factors are then related to drug discovery to address the second research question (What are the factors (internal and external) that influence and define different drug discovery strategies?).

In summary, this chapter reviews the literature on strategic management in terms of the origins of strategy, the strategic levels, the strategic types, and the strategic classifications. It shows that the factors that influence how strategy changes are the environment, resources, and organisation. These are related and translated into a drug discovery context.

Thus the objectives of the chapter are:

- To examine the relevance and value of existing strategic management literature to the area of drug discovery.

- To identify and justify the factors that influence the change of drug discovery strategy.

- To propose a definition of drug discovery strategy.

4.2.   What is Strategy?

Strategy is a concept that has been in existence for thousands of years and the word strategy comes from the Greek, *strategos*, strictly meaning a general in command of an army (Evered, 1983). Strategos is composed of two other words: *stratos* (the army) and *agein* (to lead). By extension the concept of strategy implies *the art of the general to conduct war* (Costin, 1998 p. x). Yet despite its ancient origins, strategy did not become a field of academic interest until the 1960s when key texts by Chandler (1962) and Ansoff (1965) examined and developed theories on how strategies are created and what makes them successful.

Strategy is a process and way of thinking for achieving goals in war, politics, and nowadays business. Henderson, (1989) argues that elements of strategy can be recognised ever since humans combined intelligence, imagination, accumulated resource, and co-ordinated behaviour to wage war. Political and military leaders have always had to make choices about direction and policy, and how best to distribute the resources at their disposal in pursuit of certain objectives (Segal-Horn, 2000). Classic texts such as Sun Tzu's the Art of War written in China 2,500 years ago, the political strategy of Machiavelli who wrote The Prince in 1513, or German military strategists such as Clausewitz in the nineteenth century, are still well known and highly influential (see Clausewitz, (1908), Clavell, (1981), and Machiavelli, (1992)). Also,

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numerous books have been published that explicitly focus on the analogies that can be drawn between these military and political works, and modern management.

Not surprisingly, the first business definitions of strategy can be found in military books. To illustrate this, a definition of the term strategy in connection with the activities of the German army in WWII, is given below:

'Strategy is defined as conceptual planning tied to options and directed towards success, normally embracing the fields of politics, military activities, economics and technology. Strategic planning in essence, offers various possibilities of action based on the concrete evaluation of a given situation, combines calculation with prognosis, and finally covers the execution of the plan with a view to achieving the objective.'
(Magenheimer, 1999, p.10)

Although this definition has been abstracted from a military book that studied Hitler's strategic decisions, its context and relevance to business is obvious. To illustrate this, two popular definitions of business strategy are listed below:

'Strategic management is concerned with determining the future direction of an organisation and implementing decisions aimed at achieving the organisation's long term and short term objectives' (Boseman and Phatak, 1989 p. 4)

Corporate strategy is the pattern of major objectives, purposes or goals and essential policies and plans for achieving those goals, stated in such a way as to define what business the company is in or is to be in and the kind of company it is to be (Andrews, 1971 p. 28)

These two business strategy definitions, together with many others, illustrate the view that the study of organisational strategy may be seen as a continuation of the study of war. In addition, although the two definitions are very representative and

have been produced by influential writers in the field, they do not cover the whole spectrum of strategy, as it currently exists. Also, they suggest that strategy is a linear process that involves identifying-planning and executing. This rational view of strategy has been critically debated (e g. Mintzberg et. al 1998, Whittington, 1993).

Mintzberg and Quinn (1996) presented five definitions of the term strategy in a framework called the *Five Ps for Strategy*. The five Ps stand for *plan, ploy, pattern, position,* and *perspective*. Strategy as a plan is a consciously intended course of action set to deal with a situation. Strategy as a ploy is a specific manoeuvre intended to outwit an opponent or a competitor. Strategy as a pattern implies consistency in behaviour regardless of whether this strategy is intended or not. The fourth term, position, views strategy as a way of matching the environment with the organisational intentions. Lastly, the content of strategy as a perspective consists not just of a chosen position, but also of an ingrained way of perceiving the world.

Hax, (1990), in an attempt to define the concept of strategy assumes that it embraces all the critical values of an organisation, while it provides a sense of unity, direction, purpose and facilitates the necessary changes induced by an organisation's environment. Based on these assumptions he describes *six critical dimensions* that must be included in the definition of the concept of strategy. The first dimension views strategy as a coherent, unifying, and integrative pattern of decisions. Strategy in that respect provides a blueprint for an organisation as a whole and it is conscious, explicit and proactive. In reality however, this is usually not the case, because to identify and understand a strategy, requires an examination of the history of an organisation and how the decisions were taken. Historical changes or discontinuities discern an organisation's strategic pattern and may be used to identify the future direction of an organisation. The second dimension that Hax (1990) identifies,

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examines strategy as a means of establishing an organisation's purpose in terms of its long-term objectives. The third dimension views strategy as a definition of an organisation's competitive domain i.e. the businesses that an organisation intends to be in. The fourth dimension views strategy as a response to external opportunities and threats, and to internal strengths and weaknesses. According to this perspective, the aim of a strategy is to establish a long-term competitive advantage over its rivals. The fifth dimension examines strategy as a logical system for differentiating managerial tasks at corporate, business and functional levels. The sixth and last dimension described by Hax, (1990), views strategy as a definition of the economic and non-economic contribution an organisation intends to make to its *stakeholders* i.e. those who directly or indirectly receive benefits or sustain the costs from an organisation's actions.

The preceding paragraphs provide a brief discussion on the origins and current thinking of strategic management with the aim of understanding and defining drug discovery as a strategic process. To help achieve this aim, the next section reviews the different levels of strategy that exist within an organisation. It also argues that drug discovery strategy as viewed from within an organisation is a business strategy.

4.3. Levels of Strategy within an organisation

Hay and Williamson (1997) define six levels of strategy. These are *vision*, *mission*, *plan*, *key initiatives*, *individual objectives* and *budgets*. *Vision* has two dimensions external and internal. The external *vision* involves sharing an understanding throughout an organisation of what makes the market tick, what drives the customers, who are the most important competitors, and how the dynamics of competition are changing. The internal dimension involves a vision of how an organisation sees itself

developing, what capabilities it must acquire to succeed competitively, and what in essence it sees itself becoming. *Mission*, involves the *expression of purpose* of an organisation (Hay and Williamson, 1997) and is usually summarised in a document called *the mission statement*. The mission statement defines the guiding purpose of an organisation, the destination at which the purpose leads, and the rationale behind the purpose. It delineates the directions an organisation wants to pursue or avoid (Drew, 1999). However, one of the common problems with mission statements is that they are often too generic (Simpson, 1998) and fail to focus on specific goals. The second level, *plan*, focuses on how the mission will be achieved by defining the specific steps that are to be taken and the sequence of these steps. The next level of strategy requires each step of the plan to be broken down into specific *initiatives*; tasks that individuals can both relate to and believe to be actionable. The *individual objectives* are derived from the set of initiatives being pursued; the individuals relate directly to the initiatives and are wholly consistent with them. The final level of the strategy, *budget*, relates these initiatives to everyday expenditure and management accounting.

The process of discovering new drugs as described in chapter 3 consists of 4 clearly defined steps (i) target research, (ii) discovery, (iii) clinical development and regulatory approval, and (iv) manufacture and supply. Also, the aim of the drug discovery process is to be the innovation engine that creates new products consistent with the mission of the pharmaceutical organisation. Since the second level of the above categorisation, *plan*, is associated with the definition of the specific steps that will be followed to achieve the aims of the mission it may be argued that drug discovery can viewed as a plan with initiatives, individual objectives and a budget.

The categorisation provided by (Hay and Williamson, 1997) permits strategy to be analysed *bottom-up*. The more traditional top-down view examines strategy from

three distinct levels *corporate* strategy, *business* strategy, and *functional* strategy (Figure 4-1) (Boseman and Phatak, 1998, Grant, 1998, Clarke-Hill and Galister, 1995, Thakur, 1998). Corporate strategy defines the scope of an organisation in terms of the industries and markets in which it competes. It identifies the portfolio for an organisation to be engaged in (Clarke-Hill and Glaister, 1995) and is concerned with the identification of objectives for an organisation and the best way that these may be achieved in terms of the strategic orientation of an organisation. For instance, the decision made by the pharmaceutical organisation Glaxo in the 1980s to concentrate on ethical pharmaceuticals (Jones, 2001) is part of the corporate strategy.

Corporate strategy seeks to address the following questions (Boseman and Phatak, 1998, p. 86):

1. What business or businesses are we in?

2. Will our current business or businesses enable us to achieve our long and short-term strategic objectives, particularly growth, profitability, and financial performance?

3. Should we get into a new business area that will enable us to achieve our strategic objectives?

4. Which and how many resources do we have at our disposal now; which and how many resources that could be allocated to our businesses are we capable of gathering in the near future?

5. Which and how many of our resources should we allocate to each of our businesses? Are there any businesses that do not deserve to receive resources in the future at the same level as in the past?

Analysis and planning of corporate strategy requires an organisation to fully understand its current strategy and then develop a balanced portfolio of options that enable it to achieve certain corporate objectives, e.g. profitability, growth, and market share. To achieve this, the corporate strategists employ analysis techniques such as *what if* analysis, analysis of *key* or *critical* success factors, financial analysis of competitors and *Strengths Weaknesses Opportunities Threats* (SWOT) analysis (Glaister and Falshaw, 1999, Boseman and Phatak, 1998).

The second level of strategy, *business strategy*, is concerned with how an organisation competes within a particular industrial market (Grant, 1998, p 19). For an organisation to prosper within a certain industry it must develop a competitive advantage over its rivals (Porter, 1980). A successful business strategy is one that provides an organisation with the competitive approach that enables it to achieve its business objectives as defined by an organisation's corporate strategy (Boseman and Phatak, 1998). Hence this area of strategy is also referred to as competitive strategy (Grant, 1998). Porter (1980) has identified three generic approaches for obtaining a competitive advantage. These are overall cost leadership, differentiation, and focus. The first, overall cost leadership, involves the construction of efficient operations, cost minimisation, cost and overhead control, etc. The second, differentiation, focuses on creating a unique product or service. This is the objective of the drug discovery process, which seeks to develop and maintain an appropriate and relatively constant stream of new pharmaceutical products. The third, focus, aims at serving a particular target market exceptionally well by focusing an organisation's attention on a particular buyer group, segment of the product line, or geographic area.

An example of a business strategy in the pharmaceutical industry is the sale of Glaxo's subsidiaries like Vestric in 1984 (Glaxo's wholesaling organisation), and

Matburn in 1985 (a group of surgical engineering companies). The sale of these subsidiaries helped realise the corporate strategy of the organisation, which was to concentrate on the discovery and manufacture of ethical drugs (Jones, 2001). Another example is the focus of Glaxo on the discovery of new drugs as opposed to the manufacture and distribution of generics (Jones, 2001)

The third level of strategy *functional strategy*, is concerned with the elaboration and implementation of business strategies through functional areas as production, research and development, marketing, human resources, and finance as shown in Figure 4-1 (Grant, 1998, p. 20, Clarke-Hill and Glaister, 1995). The main aim of functional strategies is to obtain the maximum productivity from the available resources. The functional level of strategy requires an organisation to conceptualise itself as a series of business processes (Armistead et al., 1999). This requires the development of a matrix of functions and processes to clarify the roles and responsibilities of the people responsible for completing these functions.

Critical to the overall success of an organisation is the synchronising of the three levels of strategy.
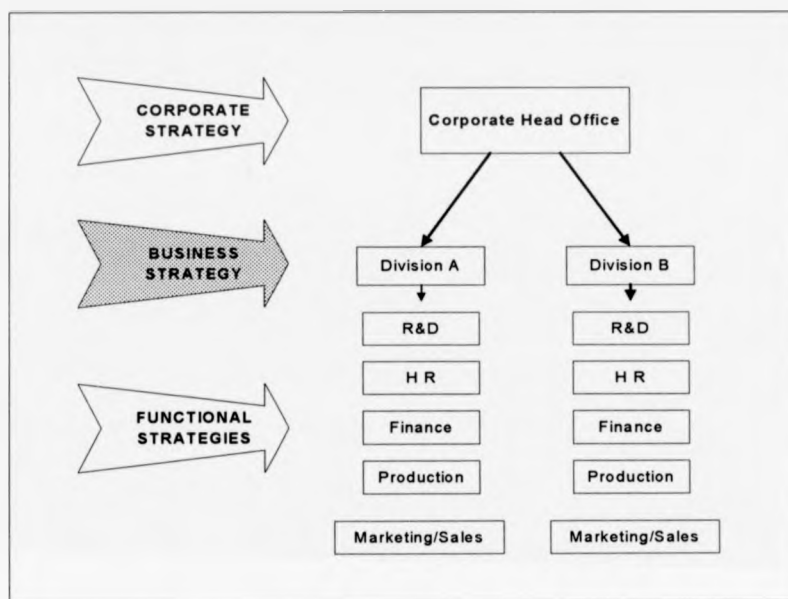
Figure 4-1 Classification of levels of organisational strategy

In the case of pharmaceutical organisations, the same levels of strategy also apply (Figure 4-2). Corporate pharmaceutical strategies examine and assess the markets an organisation might concentrate on Business strategies focus on the development and acquisition of new technologies, the type of diseases research groups would focus on, the termination or continuation of R&D projects, etc. Finally, at the functional level, the strategies focus on day-to-day operational problems that deal with tasks such as scientific research, manufacture and the supply of drugs
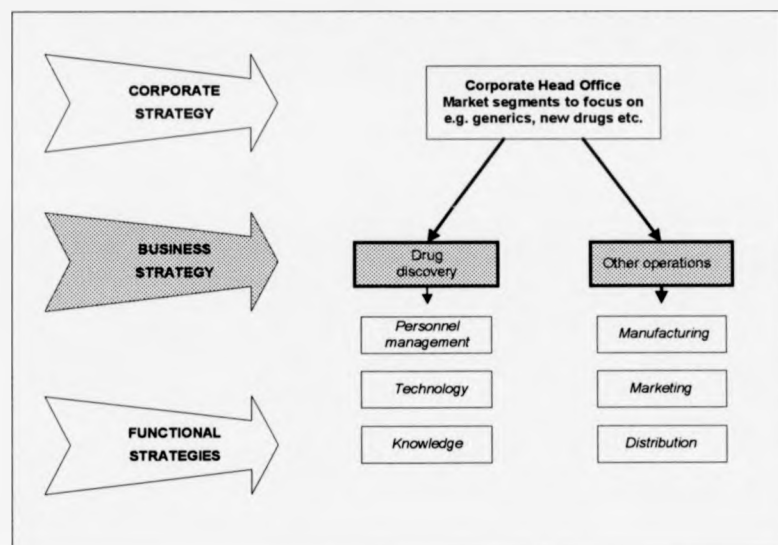
Figure 4-2 Pharmaceutical strategy categorisation

Thus, drug discovery strategy could be classified at either the functional or the business level. Classifying the strategy at the functional level implies that drug discovery is seen solely as a process within an organisation whose aim is to materialise the business strategy. Although this would clearly be the case in manufacturing dominated industrial sectors e.g. electronics and automotive, the pharmaceutical industry focuses on and allocates the majority of its resources to the process of drug discovery, whilst processes such as manufacturing, marketing, and distribution are very much secondary. Therefore, the ability of an organisation to discover new drugs within certain therapeutic areas may provide a pharmaceutical organisation with the competitive advantage required to sustain its presence within the industry. Thus within the scope of this thesis the drug discovery strategy is seen as a business strategy responsible for effectively materialising the corporation's goals and policies to achieve a competitive advantage. The functional strategies would therefore, focus on the policies towards daily research activities e.g. the management

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of personnel, the allocation and management of resources such as knowledge and technology.

4.4.   Schools of thought on strategy

One of the objectives of this thesis is to classify drug discovery strategies. To achieve this it is important to review and learn from existing classifications of organisational strategies, because any classification is heavily dependent on both the objectives and underlying assumptions of the classifier. Prior to that however, the philosophies, i.e. schools of thought, which have led to the development of these strategic types must also be reviewed. This will aid understanding of the dimensions of existing strategy classifications and thus determine and justify the key components of the drug discovery classifications created in chapters 7 and 8.

Bowman (1995) divides the work on strategy into three major categories, the *institutionalists*, the *economists*, and the *behavioural scientists*. The institutionalists describe the issues facing organisations from the inside out. The economists draw on the background of industrial organisational economics to analyse the problems of an organisation. This category has recently developed to include game theory. Finally, the behaviouralists focus on the function and survival of an organisation and the behaviour of its people. Bowman (1995) further argues that the relative impact of these three groups has followed an historical progression.

McKiernan (1997) divides the modern contributions to strategy into four schools of thought, *planning and practice, learning, positioning* and *resource based*. The planning and practice school is analogous to military strategy i.e. it is essentially about large and long term decisions which require very careful planning and assessment of the organisational and environmental conditions. The learning school

assumes that the environment is so unpredictable that synoptic models do not provide protection from the constant buffeting organisations have to face. Therefore, organisations are forced to adapt and survive. The positioning school sees the root of competitive strategy as linking an organisation to its environment. Industry structure should be analysed and an organisation should position itself within the industrial sector where it can best defend its capabilities. Finally, the resource-based school emphasises the accumulation of scarce resources through skill acquisition and learning, thus placing an organisation at the centre stage.

Finally, Mintzberg et. al's book Strategy Safari (1998) describes ten schools of thought as shown in Table 4-1.

Table 4-1 The schools of thought from Minzberg et al. (1998) p. 5

Group 1	Design school	Strategy formation as a process of conception
	Planning school	Strategy formation as a formal process
	Power school	Strategy formation as a process of negotiation
Group 2	Positioning school	Strategy formation as an analytical process
	Entrepreneurial school	Strategy formation as a visionary process
	Cognitive school	Strategy formation as a mental process
	Learning school	Strategy formation as a process of negotiation
	Cultural school	Strategy formation as a collective process
	Environmental school	Strategy formation as a reactive process
Group 3	Configuration school	Strategy formation as a process of transformation

The ten schools fall into three groupings. The first group is prescriptive in nature i.e. concerned more with how strategies should be formulated than how they necessarily do form. The design school introduced in the 1960s presented the framework on which the planning and positioning schools were built. Its main premise is that it

focuses on strategy formation as a process of informal design, essentially one of conception. The planning school formalised this perspective, seeing strategy making as a more detached and systematic process of formal planning. The positioning school focuses on the selection of strategic positions in the marketplace, while it is less concerned with the process of strategy formation and more with the content of the strategy.

The second group is less concerned with prescribing ideal strategic behaviour and focused on how strategies get made. The entrepreneurial school describes the process of strategy making in terms of the creation of a vision by a great leader. The cognitive school uses the messages of cognitive psychology to 'enter the strategist's mind.

The learning school describes strategy making as an emerging process where an organisation adapts or learns in a complex world. The power school treats strategy making as a process of negotiations either between the members of an organisation or between organisations of a certain environment. The cultural school views strategy as collective and co-operative. The environmental school describes strategy as a reactive process where the initiative lies outside an organisation in its environment.

The final group, configuration, includes only one school of thought and is considered a combination of the other nine. It views the process of strategy formation as a series of episodes that an organisation goes through i.e. the organisational life cycle (Kimberly and Miles, 1980). For example the leadership of a start-up organisation is likely to belong to the entrepreneurial school, but when the organisation matures the entrepreneurial spirit may give way to a more prescriptive strategy as professional managers become involved in an organisation.

4.5. Classifications of Strategies

Following the above review of the schools of thought, this section evaluates the most influential classifications of organisational strategies. There are two aims of this review. The first is to provide the theoretical background that justifies the value and need for a classification. The second aim is to identify and propose a rigorous structure for reviewing and classifying different drug discovery strategies, which is one of the aims of this thesis.

McKelvey (1982) classifies organisational theories, and the way organisational strategies are created, according to the source of organisational variation i.e. the change or alteration in form, appearance, function or substance (McKelvey, 1982 pp. 75). He defines two broad theoretical categories into which these theories fall. These are *autogenic* and *allogenic* theories. Autogenic theories suggest that variation is self-generated or caused by forces within an organisation, while allogenic suggest that organisational variation is caused by forces found in the environment of an organisation. According to McKelvey (1982) the strategies developed vary according to the emphasis on the allogenic or autogenic sources. Most of the theories that have been developed to date are autogenic i.e. they are based on the decisions and actions taken from within an organisation.

From these two broad categories, McKelvey (1982) identified various models that explain the formation of organisations. The autogenic category led to the *rational model*, the *natural system model* and the *market process model*. The rational model views organisations as bureaucratic institutions that consist of a set of people who continuously work towards the achievement of pre-defined goals. The natural system model views an organisation as a 'natural whole'. The emphasis is on inherent forces

towards survival, which give rise to several organisational needs, while organisational change is the result of unplanned responses of the system. Finally, the market process model views organisations as places where people exchange a variety of things, thereby satisfying their own desires and in the process creating cognitive maps, perceptions of externalities, social relations, norms, values, social and organisational structure, and ultimately collective organisational behaviour (McKelvey, 1982 p 83).

Mckelvey's allogenic category includes three statements made by Warriner (1978), Hannan and Freeman (1977), and Aldrich (1979) on the use of population ecology theory as derived from natural selection. According to this theory the environment consists of certain levels of resources and constraints. Within this environment a population of organisations, which have relatively similar characteristics emerges, survives, and grows until it is no longer able to compete effectively for additional resources. At this point the population will stabilise both in size and in characteristic form (McKelvey, 1982). The population ecology theory is further discussed in section 4.5 later in this chapter.

Whittington (1993) in his influential book *'What is Strategy and does it matter?'* discusses four approaches to strategy, which vary along two dimensions, its outcomes and the processes by which it is made. The four approaches are *classical*, *evolutionary*, *processualist*, and *systemic* as shown in Figure 4-3.

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                    OUTCOMES
                    Profit-Maximising


            CLASSICAL            EVOLUTIONARY


PROCESSES
Deliberate  _____ Emergent


            SYSTEMIC            PROCESSUAL


                    Pluralistic
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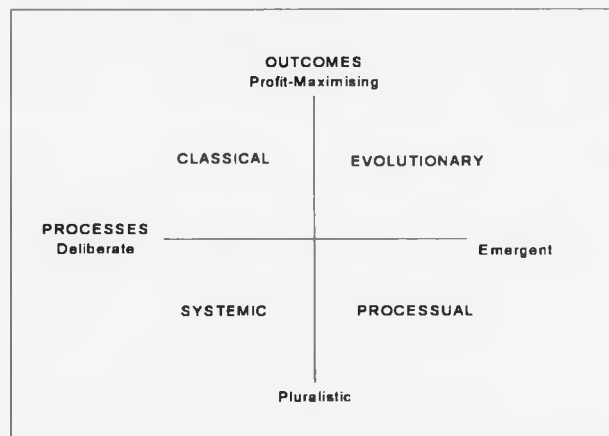
Figure 4-3 Generic perspectives on strategy (Whittington, 1993 pp.3)

The classical approach relies on rational planning and execution of the plan using methods outlined in dominant strategy textbooks. The aim of these plans is to maximise profitability and consequently a large influence in the development of these plans, is the discipline of economics as well as that of military strategy.

The evolutionary approach suggests that businesses are like biological species and that the fittest will be selected in, and while the rest will be selected out. Profit maximisation is a result of the influence of the markets rather than the managers. Similar to the allogenic models of McKelvey (1982), the most influential work of the evolutionary approach is population ecology theory (Hannan and Freeman, 1977). In practice, change management programs will always manifest emergent and unpredictable properties, but managers are paid to make decisions that ensure current and future survival of their organizations, and therefore change management will involve some form of rational planning and identification of alternative configurations, and potential impediments.

The processualist approach suggests that long range planning is, as in the case of the evolutionist, futile, but is more optimistic about the fate of the business than the evolutionist approach The original plan designed at the beginning of the strategy process often changes as business and market circumstances change. The final strategy (or realised strategy (Mintzberg and Waters, 1998)) is a result of bodging, learning, and compromising and not of a rational series of grand leaps The processualists radically downgrade the importance of rational analysis; as it limits the search for strategic flexibility; and it reduces expectations of success (Whittington, 1993). Strategy is not just about choosing markets and then policing performance, but about carefully cultivating internal competencies.

Finally, the systemic approach suggests that strategy is the reflection of the particular social system in which strategists participate i.e. defining for them the interests in which they act and the rules by which they survive. Similar to the classical view the systemic view places faith in an organisation's capacity to plan forward and act effectively. However, this view refuses to accept the forms and ends of classical rationality as anything more than historically and culturally specific phenomena Systemic theorists insist that the rationales underlying strategy are peculiar to particular sociological contexts (Whittington, 1993 pp.28).

Along the same lines as the above classification, Mintzberg and Waters (1998) discuss a classification of strategies based on eight categories They vary according to the degree of planning encountered, along with how closely they match the original intentions of the strategy maker. An organisational strategy is born whenever an organisation seeks to move from one state to a different state in the future. Depending on the nature of the origins of a strategy, it can be an *intended* or a *realised* strategy (Mintzberg et. al, 1998). An intended strategy is one where organisations develop

plans for future (e.g. the introduction of research for a new therapeutic area), whereas a realised strategy is one where patterns are evolved from an organisations' past (e.g. the entrance to a new market segment due to the serendipitous discovery of a new drug) (Mintzberg et. al, 1998, p. 10). Ideally, intended strategies should match the realised strategies. However, environmental uncertainties and complexity often inhibit the realisation of intended strategies (Figure 4-4). Depending on how closely the intended strategy matches the realised, the strategy could be entirely deliberate (perfect match) or entirely emergent (total absence of the intended strategy).
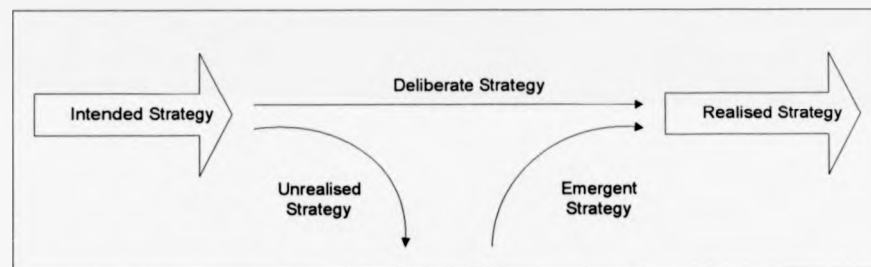
Figure 4-4 Types of Strategies from Mintzberg and Waters (1998) pp. 21

Within the deliberate and emergent strategy spectrum, Mintzberg and Waters (1998) identify eight different types of strategy; *planned, entrepreneurial, ideological, umbrella, process, unconnected, consensus,* and *imposed.* The eight-category strategy classification suggested by Mintzberg and Waters (1998) will be used in the remainder of this section to further discuss various strategy types. The reason for this is that this classification provides a well-structured rigorous framework that encompasses the plethora of organisational strategies implemented by organisations and analysed by the scholars. It also provides a categorisation of the different strategies along the continuum deliberate-emergent, which helps justify the evolutionary paradigm that is later presented and adopted by this thesis.

A planned strategy holds that strategy makers are able to carefully plan and implement their intentions. The aim of strategy making is to match the internal state with the external expectations (as defined by the environment) (Learned et. al 1965). A milestone in the development of the planned strategy type is Michael Porter's book *Competitive Strategy* (Porter, 1980). Porter's (1980) model holds that there are only a few key strategies that are desirable for an industry. An organisation has to position itself competitively within a profitable industrial sector to be successful. To do this it should develop a competitive advantage. that flows from the creation, ownership, protection and use of difficult to imitate knowledge assets. Superior performance depends on the ability of organisations to innovate, to protect intangible knowledge assets and to use knowledge assets (Teece, 2000).

A branch of the planned strategy is the *resource based theory*. This approach suggests that defining the capabilities of an organisation provides a more durable basis for strategy than defining what the business seeks to satisfy. Focusing on the unpredictable environment does not provide a foundation for establishing long term strategy planning. In the contrary, an organisation's resources and capabilities provide a much more stable foundation for effective strategy planning (Grant, 2000, Barney, 1986, 1991, Prahalad and Hamel, 1990, Dierickx and Cool, 1989, Rumelt, 1987). Therefore for managers, the challenge is to identify, develop, protect and deploy resources and capabilities (an organisation's capacity to deploy resources) in a way that provides an organisation with a sustainable competitive advantage and thereby a superior return to capital (Amit and Schoemaker, 1998).

A more recent development of the resource-based view of an organisation is the *dynamic capabilities framework* (Teece et al. 1997, Eisenhardt and Martin, 2000, Spanos and Lioukas, 2001, Foss, 1996), which focuses on capability building rather

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than resource picking (Makadok, 2001). Dynamic capabilities are specific to each organisation and may include identifiable processes such as drug discovery, strategic decision-making, creating alliances and interpretative flexibility (the degree to which users of a technology are engaged in its constitution during development and use (Dougherty et al. 1998)). The essence of an organisation's dynamic capabilities and competitive advantage depends on the organisational processes, shaped by the organisation's asset positions (Helfat, 1997) and moulded by its evolutionary and co-evolutionary paths. Common features are also included in the organisation's specific dynamic capabilities that are associated with effective processes across organisations (popularly known as best practice) (Eisenhardt and Martin, 2000).

Despite the criticism of the planning strategy type (Mintzberg, 1998, Quinn, 1989, Simpson, 1998) strategic planning is still considered to be of benefit (Glaister and Falshaw, 1999, Brews and Hunt, 1999, Bowman and Helfat 2001, McGahan and Porter, 1997).

The second strategy type, *entrepreneurial*, holds that one person is in control of an organisation and attempts to realise his or her vision of the organisation. This type of strategy is usually found in new entrepreneurial organisations where one individual in personal control of an organisation is able to impose his or her vision of direction on it (Mintzberg and Waters, 1998). It may also describe situations of personalised leadership. For instance, several organisations consist of several business units that are managed as independent companies. Within such units entrepreneurial strategies may also appear (Oijen and Douma, 2000). Their objective is to create something new and different (Drucker, 1985) by aiming to be highly flexible and responsive (Teece, 2000), alert to opportunities, and proactive in trying to control events (Day et al., 1998). Due to the flexibility of entrepreneurial strategies established organisations

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find it difficult to emulate them, this in turn causes variance in the performance (Walker et al., 2002). The gap an entrepreneur identifies provides an initial strong position. However, early entrants are often overtaken by competitors with more and better resources or capabilities (Liebermann and Montgomery, 1998). The ability, however, of an organisation to be positioned as an early entrant, depends on its relative degree of strategic agility[2] (Webb and Pettigrew, 1999).

An entrepreneurial strategy is less deliberate than the planned type. The person in control has some strategic intentions, and although these may not be clear to all the persons involved, they may be deliberate as long everyone follows the lead of the person in charge. There is evidence, however, to support that those small organisations that use strategic planning perform better than those organisations that leave things to chance and deal with problems as they occur (Smith, 1998).

The next strategy type, ideological, takes place both at the individual and collective levels. The members of an organisation share and embrace a vision, which consists of the unwritten rules they pursue as an ideology or culture (Womack et al., 1990, Crosby, 1980). A strategic vision is *a coherent and powerful statement of what the business can be ten years hence* (Wilson, 1992). The mechanism, by which the individuals acquire the beliefs of the organisational ideology and culture, is a tacit and non-verbal process of acculturation or socialisation (Mintzberg et al, 1998 p. 267). This results in the origins and the explanations of the ideology being obscure. Sources of the origins of this strategy could be the original philosophy and strategy of an organisation's founder (Thorelli (1995) refers to this as the *entrepreneurial*

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[2] This agility depends on managers finding apprpriate solutions while at the same time maintaining an ability to detect change in their environment and mobilise an appropriate response

philosophy), or the institutional environment that surrounds an organisation (Oliver, 1991, 1997, Meyer and Rowan, 1977). Adaptation to this type of strategy requires a change in culture i.e. the collective mind. Thus adaptation is not impossible and therefore an ideology strategy is not considered to be entirely deliberate.

An umbrella strategy type relaxes the condition of tight control imposed by the previous types. Here, leaders have only partial control of the actions of the members of an organisation. Their role is to set the guidelines and define the boundaries of behaviour and let other members manoeuvre within them. Whenever this is not the case, the leadership takes corrective action. In a complex, uncertain, environment it is presumed that various members of an organisation should be able to respond to it. These members are allowed to apply their own strategy and therefore strategies emerge within the boundaries set by the leadership. In all types of strategy there is some degree of umbrella behaviour in the sense that there is a centre leadership with intentions, which tries to direct others with their own ideas. The organisational structure that is most capable of applying these strategies is the network organisation (Quinn et al., 1998) where lateral ties are substituted for vertical ones. Strategy emerges incrementally firstly to handle urgent matters, and then to start longer term sequences whose specific future branches and consequences are perhaps unclear.

Although the boundaries of action are often set by one central leader, the actions of an organisation are not set deliberately. Therefore, this type of strategy may still be characterised as deliberate although its main driving force is emergent. This type of strategy emerged in the 1960s, due to the extensive diversification of the information required to make strategic decisions, thus making it unavoidable to delegate some strategic functions to lower levels (Thakur, 1998). This in turn triggered a more

decentralised planning approach leading many organisations towards a divisional structure (Mintzberg et al, 1976).

The next type of strategy type, *process*, (Mintzberg and Waters, 1988), goes a step further in removing control from the making of strategy. In this case the leadership does not set any boundaries or targets as in the case of umbrella strategies. Instead, it controls the process of strategy making, while leaving its content to the members of an organisation who are involved with it. Since the leadership selects both the people that will work in the organisation and the process of strategy making the process type of strategy is characterised as *deliberate*. This is because the leadership may indirectly impose its intentions. However, this type is also one of the most emergent, since members of an organisation regardless of how they find themselves in that position can implement their own strategies and respond to the environmental as quickly and as effectively as they are able to.

The *unconnected* strategy is one where a sub-unit of an organisation (maybe a single department or person), which is loosely coupled to an organisation, applies its own behaviour pattern through a stream of actions. This type is usually found in organisations like universities, hospitals or national and private research laboratories where individuals have the ability to follow their own way of thinking while still under their organisation's protection.

Simpson and Powell (1999) have produced a classification of organisation archetypes focusing on research-based organisations such as pharmaceutical organisations. Their classification may be seen as a sub-classification of the unconnected strategies. They identify four archetypes the *solitary genius, the technology push, the market pull, and the multiple project*. The solitary genius views an organisation as a set of isolated scientists working long hours. Inspiration and

insight come in sudden and unexpected ways and the new knowledge generated in this process cannot be foretold. The role of management is to provide the needs of the individual, but otherwise to stand back and allow the creative process to unfold at its own pace. The technology push archetype is characterised by objectives and motivations similar to those of the solitary genius with the main differences being the *reliance on collegial interactions to cultivate experience*. Therefore, the new recruits of a technology push organisation can reasonably expect that the ongoing development of their expertise will be fostered through their associations with more experienced colleagues. The market pull archetype stands as an antithesis to the technology push. It explicitly recognises the market, rather than the scientific expertise as the sole arbiter of innovation requirements as the sole arbiter of organisation requirements. Therefore an organisation is designed to maximise the efficiency with which it can respond to market requirements. Finally, the multiple project archetype is a combination of the technology push and market pull archetypes. The most apparent characteristic of this organisational form is its constantly changing structure. The members of these organisations combine specialist expertise with a breadth of experience arising from frequent interactions with customers and market specialists (Simpson and Powell, 1999).

Although unconnected strategies are emergent, to a degree they are also deliberate. To meet an organisation's goals a certain pattern of activities should be followed. This pattern may exist in the members' minds i.e. as an ideological strategy that influences the institutional environment or the socialisation between the members of the organisations. Nevertheless, the freedom of the individuals to act based on their own pattern, which in extreme cases may be opposite to the pattern of the overall organisation, clearly offers an emergent character.

The consensus strategy holds that different stakeholders converge on the same theme or pattern so that it becomes pervasive in an organisation, without the need for any central direction or control (Mintzberg and Waters, 1998, p. 28). Therefore, this strategy emerges without any prior intention. This strategy type resembles the ideological strategy in that a number of organisation members converge to seek the goals of an organisation following a tacit pattern. However, unlike the ideological strategy, in which the tacit pattern comes from a system of beliefs, the consensus strategy comes from mutual adjustment among the various members of an organisation. This adjustment results in the development of a common and unexpected pattern that suits them. The resulting pattern could of course be affected from the influence that one individual exerts to the members of an organisation. Even in this case, however, the resulting strategy is not the product of collective intention, rather it is the product of collective action.

The section of the literature that views the formation of strategy as the result of order emerging from chaos (Allen, 2000, Stacey, 1995) also falls within this category. According to Stacey (1993), chaos has been described as the *unpredictable variety within recognisable categories defined by irregular features* (Stacey, 1993, p 14) and the irregular, unpredictable behaviour of deterministic nonlinear dynamical systems (Stewart, 1984). Strategy emerges as the members of an organisation respond to the feedback they receive about the effect of their actions. This condition is referred to as *self-organisation* and is defined as *the spontaneous clustering and reorganisation of spatial configuration that occurs as a system runs* (Allen, 2000, p 85).

Using chaos theory in organisational science denotes the perception of an organisation as a *complex evolving system* i.e. a system that is neither rigidly ordered nor highly disordered. According to this perception organisations are not only

systems created and controlled by those who manage them, but also self-organising entities that evolve through learning (Price, 1995). Complexity theorists are interested in non-linear systems whose behaviour falls in the region between fixed order and deterministic chaos and whose behaviour is influenced by, and takes advantage of random noise (Arrow et al., 2000).

Competence theory is also another type of strategic thinking that falls in this category (Sanchez, 1997). According to competence theory strategic management becomes an effort to reduce the complexity and uncertainty on organisations by devising simple rules for ordering organisational processes in ways capable of maintaining *quasi-stability* while an organisation adapts to a complex dynamic environment (Sanchez, 1997). An important distinction in competence theory is between *competence building* and *competence leveraging*. Competence building is any process by which an organisation achieves qualitative changes in its existing stocks of assets and capabilities. Competence leveraging is the application of these competencies. Therefore, strategy as leverage means that an organisation has to compete now by leveraging its current competencies to the greatest possible effect (Post, 1997).

The final type of strategy identified by Mintzberg and Waters (1998) is the *imposed strategy*, in which the environment imposes actions. With all the strategy types discussed so far, there was some form of direction from within an organisation, while the environment has been considered acquiescent. With this type of strategy the environment is the dominant force that imposes a strategy on an organisation while the organisation is unable to resist. The imposed strategy in effect becomes deliberate, since the organisation knows the pattern to follow from the start.

A classic work associated with this type of strategy is the *population ecology theory* of organisations, which was created in the mid-seventies by Hannan and Freeman (1977). Hannan and Freeman (1977) argued that there are limitations in the ability of an organisational structure to adapt to these environmental changes. They called these limitations *structural inertia*. Structural inertia is a function of both the internal (organisational) structure and the external (environmental) pressures. Examples of the internal structure include organisational assets, and political and history constraints. Examples of the external structure include legal and fiscal barriers, incomplete information, legitimacy constraints, collective rationality problem, and interorganisational networks. Also, structural inertia increases with *population density* (Ruef, 1997) i.e. the size of the population relative to the carrying capacity of the pertinent niche (Delacroix and Swaminathan, 1989). The higher the structural inertia, the lower the ability of an organisation to adapt. Therefore, according to the population ecologists, the adaptation of individual organisations cannot be the main force for change in an organisational population. In fact this is the difference between population ecology theory and other theories. It focuses on the effect of the environment on organisations rather than the intra-organisational factors. It has been argued that population ecology models provide potentially powerful explanations for the phenomena of organisational birth, mortality, and evolution (Betton and Dess, 1985).

The third research question of this thesis (How can an evolutionary and classification approach be used to study drug discovery strategies?) requires the examination of how an evolutionary and classification approach can be used to study drug discovery strategies. This question is addressed in more detail in the following chapters. However, it is important to note that population ecology theory is related to this

research question, as it deals with the issues of populations, variation, selection and heredity. As will be explained in chapters 5 and 6 these issues are key to the evolutionary approach. Consequently, it is important to examine the population ecology theory in greater detail

Population ecology explains organisational change by examining the nature and distribution of resources in an organisation's environment. The competitive intensity increases both innovation and refinement (Mezias and Eisner, 1997). Therefore, competition for resources becomes the main force for organisational change. A general model that explains how organisations are created, survive or fail, and are diffused in a population is the *'variation selection and retention'* model illustrated in Figure 4-5 (Aldrich 1979 p. 28).
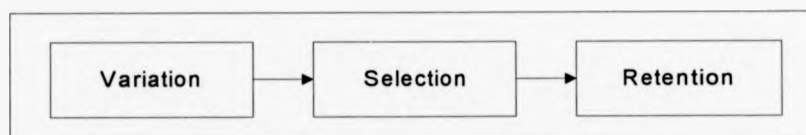
Figure 4-5 Variation Selection Retention Model from Aldrich (1979)

Variation both between organisations and environments is the first requirement for organisational change. The likely sources of variation could be error, chance, luck and conflict. Stinchcombe (1965), in his attempt to summarise the reasons why people form organisations, lists five conditions that lead to the formation of new organisations and thus generate variation within an organisational population. These conditions are

a) The finding of alternative and improved ways of doing things that are not easily done within existing social arrangements,

b) The belief that the future will be such that an organisation will continue to be effective enough to pay for the trouble of building it and for the resources invested,

c) The better way of doing things will be received by either the founders or some other social group,

d) The allocation of the resources required to build an organisation is possible, and

e) The existing opponents of an organisation are less competent and therefore they may be defeated (Stinchcombe, 1965, p146).

In any case, variation provides the raw material for the selection (internal and external) process that is the next stage of the population ecology model. The external selection process can be affected by three types of variation:

a) Selective survival or elimination of whole organisations,

b) Selective diffusion or imitation of successful innovations of partial organisation structure or activities, and

c) Selective retention of successful activities resulting from variations in behaviour over time.

According to population ecology theory, selection of organisations depends on environmental constraints. Those organisations that are well suited (i.e. a good fit) to their environment will survive, while those that are not, will fail. Environments are described in terms of the resources and the information they provide to organisations. A successful organisation will be one that has both better information and a better position in the environment in terms of the acquisition of the resources.

The third stage of the organisational change model is retention. Retention of organisational species[3] depends on the environmental and organisational characteristics (organisational structure). This stage can be interpreted as the stability in organisational forms or in specific structures and activities of individual organisations.

Selection pressures may support or eliminate entire organisations or forms of organisations. The organisations that are more likely to survive are the ones that are more successful in a particular environment. Similarly, those organisational forms, which are more successful, are the ones that are more effective for a particular environment. In this situation a variety of forms may survive in a particular *niche*. The niche of a population is defined as that area in constraint space (the space whose dimensions are levels of resources etc.) in which population out-competes all other local populations (Hannan and Freeman 1977). Therefore, the environment could be viewed as numerous distinct niches.

Hannan and Freeman (1989) make a distinction between *specialist* and *generalist* organisations. Generalist organisations to some degree customise their output for individual customers using flexible techniques. In contrast, specialists create a competitive advantage by efficiently serving a narrower market with a more standardised and more stable product line (Miller, 1991). Specialists are considered to be fitter in continuously changing environments (coarse grained) while generalists are fitter in stable environments (fine grained). Specialism and generalism are relatively comparative notions that vary by degree among competitors (Miller, 1991).

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[3] An organisational specie is defined as a form of organisation which exists through generations which are members of the specie (McKelvey 1978).

This distinction is clear when considering the pharmaceutical industry. A pharmaceutical organisation that focuses on the research and development of new drugs will not necessarily gain a competitive advantage by investing in technology and knowledge for producing generics (those drugs that can only be launched after an innovative drug has lost its patent protection). For instance, Syntex Corporation, an organisation which is on *the boundary between being a 'pure' research company and a 'true' drug manufacturer* (Gambardella, 1995, p. 100), intensified its research into the process of manufacturing one of its key drugs *Naprosyn* to eliminate competition from generic manufacturers (Gambardella, 1995). Syntex patented various processes to produce Naprosyn, and thus it became more difficult for generics producers to manufacture the product after its patent expires. Being a *generalist* organisation, Syntex chose to focus on its current research to strengthen its competitive advantage, rather than entering the generics market

4.5.1. Strategy as a dialectical process

Strategic thinking and strategic planning may also be seen as two interrelated modes in a dialectical process, where both are necessary for effective strategic management and each mode on its node is necessary, but not sufficient (Heracleous, 1998). According to this view, the above strategies may be seen as different phases of the organisational change rather than different organisational modes. Wilson (1998) suggests that these different strategic modes or *strategic opposites* must coexist within an organisation. Harnessing with the strategic opposites provides an organisation with a long-term objective and short-term attention required to succeed (Wilson, 1998).

4.5.2. Classifications of strategy: concluding remarks

The above discussion reviewed the literature on strategic management in terms of the origins of strategy, the strategic levels, the strategic types, and the strategic classifications. This reviewed has provided the background for meeting the aim of this chapter i.e. to relate strategic management to the drug discovery process.

Although the classifications discussed above provide frameworks for understanding and studying different strategic types they do not allow the comparison of the strategic configurations that they represent. This is because the strategies that are included in these classifications are in a conceptual form i.e. they are not related to organisational strategies or specific organisations. Therefore, it is not possible to directly compare the effectiveness that these strategic types offer. Some of these classifications have been developed into classifications of manufacturing systems (e.g. see Fernendez, 2002, and Leseure, 2001). Yet, there exist no classifications of drug discovery strategies. The creation of such a classification is a key objective of this thesis and as it will be shown in chapter 6, is achieved using an evolutionary technique *cladistics*.

4.6. Factors that influence the change of business strategies

The aim of this section is to identify and justify the factors that influence the change in organisational strategies. These factors will be used in this chapter, to develop a working definition of drug discovery strategy. Furthermore, they will be used in chapters 7 and 8 to search and select the data needed to construct a classification of drug discovery strategies.

The strategies discussed in the above classifications cover a wide spectrum of the strategic literature. These strategies vary along the continuum of *entirely deliberate*

to *entirely emergent* (Mintzberg and Waters 1998). A key difference between the two ends of the spectrum is how strategists conceive and achieve strategic planning and strategic thinking. Supporters of the deliberate strategy view support the idea that strategic thinking is based on analytical frameworks (e.g. Porter's five forces of analysis). At the other end of the spectrum strategists believe that strategic thinking and strategic planning are two distinct thinking modes, and strategic thinking should precede strategic planning (Mintzberg 1994a, Mintzberg 1994b).

A common theme of these strategic types is the desire to align the organisational configuration with that of the environment. Central to this alignment are (i) an organisation's environment, (ii) an organisation's formal and informal structure and processes, and (iii) the resources of an organisation (Farjoun, 2002). A change in these factors leads to a change in the resulting strategy. Depending on the strategic type that is adopted the change could be seen as the result of either careful design or reaction to the new environmental status. For instance, change of imposed strategies would imply that changes of the environment have not favoured certain organisational strategies.

The first factor, the organisation's environment, is the pattern of all the external conditions and influences that affect the organisation's life and development (Andrews, 1980). The environment consists of other organisations and their strategies, technologies, and knowledge (Farjoun, 2002), the market, and possibly legislation. The relationship of an organisation with the environment depends on the interactions of the organisation with the environment's elements. Baden-Fuller and Stopford (1998) argue that this interaction also shapes the environment and thus the organisation's task is to recognise the economic signals and recognise the potential opportunities to shape and harness tastes, technology, and competitor behaviour.

Understanding the dynamics of the environment is a focal point in all the strategy types discussed in the previous section. With planned strategies the environment comprises of threats and opportunities and thus strategy making involves the identification of these and the design of appropriate action (Boseman and Phatak, 1989, Learned et al., 1965, Porter, 1980). With entrepreneurial strategies the environment changes quickly and therefore a responsive and flexible approach to strategy is more appropriate. According to the imposed strategies the environment imposes constraints such as legal and fiscal barriers, incomplete information, etc. Therefore, strategy making is unable to avoid environmental pressures (Hannan and Freeman, 1977, Aldrich, 1979).

The second factor, organisation structure and process, represents the people involved in the implementation of a strategy, and the mechanisms for allocating and coordinating organisational resources i.e. the organisational routines. These mechanisms can be both formal (e.g. governance structure) and informal (e.g. culture, politics, control) (Farjoun, 2002). The organisational actions and routines depend on the history of prior resource allocation and on the nature of the political coalitions (Hannan and Freeman, 1989). Therefore, the formation of organisational routines depends on the history of an organisation. Stinchcombe (1965) suggests that the social structure of an organisation is also a function of its history ....*for example, textiles have been manufactured in the United States much longer than have automobiles. It turns out that textiles (and other industries developed about the same time) have quite a different social structure in their social firm than do automobile plants (and other industries founded during the twentieth century)...(Stinchcombe, 1965, p. 230).* The structure of an organisation depends on the devices employed for

the allocation of the resources essential to their purpose. Since these devices differ during the formation of an organisation so are their structures (Stinchcombe, 1965).

The third factor *resources* includes the internal means and developments that can be drawn upon to accomplish the firm's goals, and especially those unique features called *distinctive competencies* (Selznick, 1957). Resources are converted into final products or services by using a wide range of other organisation assets and bonding mechanisms such as management information systems, trust between management and labour etc. (Amit and Schoemaker, 1998). Barney (1986) argues that for organisational resources to hold the potential of sustained competitive advantage they must have four attributes:

1. they must be valuable, in the sense that they exploit opportunities and/or neutralise threats in an organisation's environment,

2. they must be rare among an organisation's current and potential competition,

3. they must be imperfectly imitable, and

4. there cannot be strategically equivalent substitutes for these resources that are valuable, but neither rare or imperfectly imitable.

Such organisational resources may include the accumulated knowledge (Helfat, 1997, Drew, 1999, Krogh et al., 2001), the technology (Dougherty et al., 1998, Arthur, 1989), and the physical assets (Amit and Schoemaker, 1998).

Figure 4-6 provides a summary form of the elements that influence and shape business strategies.
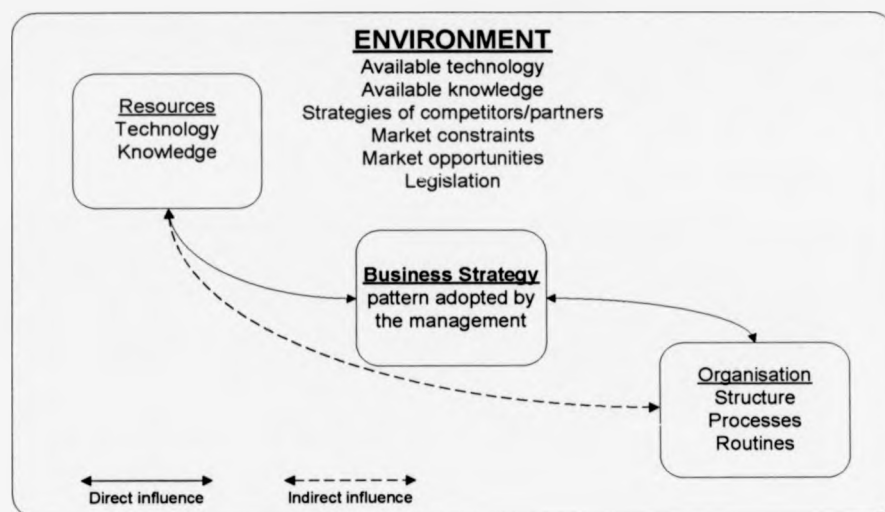
Figure 4-6 Factors influencing business strategy

The following section considers and relates these three factors to the drug discovery process and accompanying strategies.

4.7. *Drug discovery strategies*

This chapter has so far presented a discussion on the origins and diversity and classifications of organisational strategies. The previous section identified three factors that influence the change of organisational strategies. This section will relate these factors to the drug discovery strategies.

The pattern by which pharmaceutical research is being carried out has changed remarkably over the previous century. In the past the focus of pharmaceutical research was on symptomatic relief, while today the focus has shifted towards the treating of an underlying pathology (Ratti and Trist, 2001). As understanding of human biology has progressed, research has shifted from an emergent pattern to a more predictable and less risky behaviour where an organisation can often statistically

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predict the outcome of research and its market potentials. This fact has affected the way organisational strategies have been formed and implemented throughout the history of the pharmaceutical industry. In accordance with chapter 5 it is suggested that these strategies follow an evolutionary pattern.

Organisational strategies are formed according to three factors (see section 4.6): *resources, organisation, and environment*. The resources that have played a key role in the change of drug discovery strategies include technology (FitzGerald, 2000, Henderson et al., 1999, Janzen, 2001, Kniaz, 2000) and knowledge (Henderson, 1994, Henderson et al., 1999, Jensen and Sandstad, 1998, Nightingale, 2000). Naturally, these two resources are tied to the competitive advantage of pharmaceutical organisations (Yeoh and Roth, 1999). Therefore, in the remainder of this chapter, knowledge and technology will constitute two of the factors forming organisational strategies replacing the *resources* factor.

An organisation consists of people and managerial processes that seek to project manage the discovery of new drugs. Finally, the environment of drug discovery consists of characteristics such as diseases, legislation, knowledge and the technology capabilities of competitors (Sedlaceck et al., 1996).

The remainder of this section analyses the following four factors, to justify their selection as the basis for studying drug discovery strategies:

- Knowledge,

- Technology,

- Organisations (structure and processes), and

- Environment.

4.7.1.1. Knowledge

Knowledge has emerged as the most strategically-significant resource of the firm (Grant, 1996 p.375, Janszen, 2000). Scientific knowledge is generated by the social practice of exploring, mapping and mathematically codifying patterns in the behaviour of nature. When these patterns are recognised they can be used for prediction by extrapolating them from known starting conditions to unknown end results (Nightingale, 1998). During the age of botanicals (pre 1800s), scientific knowledge was limited. The discovery of new drugs was based not on scientific exploration, but on a mixture of empiricism and prayer (Lesney, 2000). As civilisation progressed, the information that was available on how the human body functioned and its reaction to various chemical entities generated the foundations of this scientific knowledge.

An organisation's knowledge capital is accumulated through interrelated and independent functions such as R&D, technology acquisition, experiential learning, organisational learning, and network knowledge. These functions are generated both internally and externally to an organisation. Drug discovery requires that knowledge once obtained, is available for decision-making. This is important for two reasons. Firstly, unsuccessful projects should be terminated as soon as possible, and secondly hundreds of individuals should be aware of the reasons (Koretz and Lee, 1998). However, the exponential growth of scientific knowledge and skills, makes the issue of availability of knowledge complex (Liyanage et al. 1999). Therefore, techniques aimed at improving the coordination of research methods, knowledge utilisation and assimilation processes are continuously being developed (e.g. bioinformatics).

Within an organisation two types of knowledge may be distinguished (Janszen, 2000, Helfat and Raubitschek, 2000)

- *Explicit, core or systematic knowledge*. This is knowledge that can be expressed and codified. It relates to the scientific knowledge that is at the heart of and forms the foundation for, a product or service,

- *Tacit, uncodified, intuitive, or integrative knowledge*. That is intangible knowledge that may include personal insights, intuition, hunches and is acquired through informal processes of learning rather than through manuals and procedures (Price and Shaw, 1998). This type of knowledge may be transferred only by interaction and integrates different activities, capabilities, and products in one or more vertical chains (Helfat and Raubitschek, 2000).

An illustration of the use of knowledge as a core competency in pharmaceutical organisations, is the recovery of the European pharmaceutical industry after the Second World War. The war had destructive effects on the capital stock and physical asset investment in European pharmaceutical organisations. However shortly after the War various new products quickly emerged helping to revitalise the industry (Bogner and Thomas, 1996 p.90). The ability of this industry to quickly recover technological and business momentum suggests that the core competencies of the firms were not in their physical plant and technology, but in the collective knowledge they possessed about organic chemistry and the associated techniques of their research laboratories' personnel (Bogner and Thomas1996 p.91).

It has been suggested that the generation of tacit and codified knowledge follows a cyclical path. Most knowledge starts as tacit, but is later codified. Codification is defined as the individual and collective processes through which knowledge and experience may be structured and made explicit (Moenaert et al, 2000). After codification, this knowledge is combined with other previously codified knowledge and is then applied and internalised within an organisation. The codification of

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knowledge happens mainly through the development of prototypes and communication (Nonaka and Takeuchi, 1995 in Janszen, 2000). The development of prototypes allows testing and modelling and therefore enables the codification of knowledge. Communication on the other hand helps articulate and communicate tacit knowledge and thus results in organisational learning. This learning enables organisations to perform their activities in improved ways (Deeds et al., 1999).

The communication channels are not limited to internal activities only. Pharmaceutical organisations establish external strategic links with other organisations and institutions to gain access to a specific set of tangible and/or intangible resources necessary for the development of innovations (Estades and Ramani, 1998). Additional reasons for collaborations between organisations include complementarity, learning, speed, flexibility/reversibility and trust/reciprocity (Senker and Sharp, 1997). Arora and Gambardella (1990) have identified four types of link for biotechnology firms. These are:

- Research and/or joint development agreements with other firms,

- Research agreements with universities,

- Investments in the capital stock of new biotechnology firms, and

- Acquisitions of new biotechnology firms.

Although their focus was on new biotechnology firms (Arora and Gambardella, 1990), these links can be generalised to the wider industry. In their paper they conclude that these four types are complementary to one another and suggest that the development of new knowledge should be thought as a *network of inter-organisational relations*. In addition Yli-Renko et al (2001) have also found a positive relationship between social interaction and network ties and knowledge

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acquisition. To be part of such a network and to be able to effectively exploit the information that circulates in the network has become '*even more valuable than being able to generate new knowledge autonomously*' (Gambardella, 1992). Being part of such a network may depend on something as simple as its location. Organisations that are located close to other organisations in the same industry could reap benefits from *knowledge spillovers* (Deeds et al., 1999). In another research project conducted by Deeds and Hill (1996), it has been suggested that an inverted U-shaped relationship exists between the number of networks or strategic alliances that an organisation is associated with and the number of new products that they develop. Therefore, there is an optimal point of strategic alliances that an organisation may enter before the benefits begin to decrease. This optimal number depends on idiosyncratic organisation-specific factors like the kinds of complementary assets and knowledge that an organisation needs to access through alliances given the nature of its product development efforts and its existing resource base, the quality of an organisation's management, and an organisation's experience at selecting partners and managing alliances (Deeds and Hill., 1996, Graves and Langowitz, 1993). Finally, knowledge transfer in strategic alliances depends on two sets of variables, namely, the knowledge specific variables and partner specific variables (Simonin, 1999). The knowledge specific variables include tacitness and complexity of knowledge while the partner specific ones include prior experience, cultural distance, and organisational distance.

The ability of an organisation to acquire, analyse, store, retrieve, and communicate knowledge is a critical success factor (Jensen and Sandstad, 1998). The ability to value assimilate, and apply new external knowledge to commercial ends has been called *absorptive capacity* (Lane and Lubatkin, 1998, Cohen and Levinthal, 1989,

Cockburn and Henderson. 1998) and it is largely a function of an organisation's level of prior related knowledge (Cohen and Levinthal, 1990). This absorptive capacity can potentially be maximised if the following conditions are met. The organisation that is acquiring the new knowledge (student) and the organisation that provides the new knowledge (teacher) must share some common basic knowledge, whilst having different specialised knowledge. To facilitate the intended transfer, the knowledge holder, or teacher organisation, should be responsible for the codification effort. When scientific knowledge is not or cannot be codified in a meaningful way like a formula of a complex chemical compound, learning from experience and learning by doing in the presence of knowledgeable partners becomes a *sine qua non* for circumventing ambiguity and favouring knowledge transfer (Simonin, 1999). In addition Lane and Lubatkin, (1998) suggest that the ability to assimilate new external knowledge depends partly on the similarity of the student and teacher organisations' compensation practices. The compensation practices of a pharmaceutical organisation provide an indication of the organisation's emphasis on external reputation. Henderson and Cockburn (1994) have convincingly argued that the rate of new drug development increases when the emphasis on the publications and the external reputation increases when evaluating the research staff. The absorptive capacity also depends on the similarity of the structure of the two organisations. The structure of an organisation is important in its learning capacity because it is related with an organisation's problem solving behaviour, it reflects an organisation's perception of the environment and finally represents the codification of an organisation's historic pattern of roles (Lane and Lubatkin, 1998, Stork, 1998). Therefore, absorptive capacity links knowledge with organisational structure, another element of drug discovery strategy.

The link between industrial research and academic or government funded research has been the subject of extensive research (Ward and Dranove, 1995, Cockburn and Henderson, 1998). Academic research is usually concerned with so-called basic or "blue sky" research. Basic pharmaceutical research identifies chemical and/or biological properties of a newly synthesised or previously known substance. Once a pharmaceutical organisation identifies a therapeutic use for the new substance it takes over the research and is now called applied research and development. Ward and Dranove (1995) suggest that these two types of research are linked in such a way that government funded research generates industrial funded one after several years. However, the precise mechanisms by which this effect is driven are not known. The transfer of knowledge from the academia to industry cannot be simply described as a *waterfall model in which the public sector produces knowledge that spills over costlessly to downstream researchers* (Cockburn and Henderson, 1998).

Each organisation has its own set of product groups it is focusing on, or in Porter's (1980) words *a group of segments*. Diversity of therapeutic areas and disease states is often regarded as a means of reducing risk (Tiggemann, 1998). To further reduce risk and increase profitability, organisations have gradually diversified into related and non-related markets such as over the counter drugs, diagnostics, veterinary products, specialised chemicals, and cosmetics and toiletries (Omta et al. 1994). Over time organisations try to develop a competitive advantage over their competitors by specialising in those target segments. Within those segments it appears that there are only four areas in which to build a competitive advantage (Tiggemman, 1998):

- Safety (which incorporates quality of life issues),

- Efficacy (which also incorporates quality of life issues),

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- Patient convenience,

- Economics (which incorporates pharmaco-economics issues).

The demand for pharmaceutical products depends on the uses which drugs are put. Drugs in different therapeutic classes generally are not substitutable in consumption. Even drugs within the same general class are not necessarily interchangeable. The relevant markets are, therefore, determined by diseases or conditions that the drugs are used to treat. Consequently, many organisations choose to focus their efforts on developing competencies in specific therapeutic areas. Prior success in particular fields and programme specific expertise within an organisation can also result in trends in innovation at the organisation level. These innovations are at least partially dependent on the paths that individual organisations may achieve in developing dominant drugs in one or several therapeutic categories (DiMasi, 2000).

In summary, the scientific knowledge acquired by an organisation, is a resource critical to the success of the discovery of new drugs. Such knowledge is generated tacitly, but is then codified and combined with other existing knowledge. The resulting knowledge is then communicated both within an organisation and with other organisations and institutions. The absorptive capacity of an organisation is also critical in the formation of the drug discovery strategy as it reflects the ability of an organisation to use the external knowledge and convert it into new drugs.

4.7.1.2. Technology

The second factor the influences and shapes drug discovery strategy is *technology*. Technology is driving innovation in manufacturing, defence, aerospace, transport, financial services, leisure, education, and of course medicine (Anderson, 1997). The rate of technological change particularly in the pharmaceutical industry is high and is

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constantly accelerating. The more a technology is adopted (or in evolutionary terms "selected" and "retained") the more experience is gained by it and the more it is improved (Arthur, 1989). Technological innovation processes are important because they introduce dynamics into economic growth and impact the wider society (McKelvey, 1996). Technology represents the systematic utilisation of knowledge; it is the application of scientific information (Roman, 1968). Therefore, there is a strong link between knowledge and technology. In fact the role of knowledge in technical change has been the subject of increasing attention in the 1990s (Nightingale, 2000). Recent studies have documented that the most frequent motivation for alliance formation is the development of new technologies (Deeds and Hill, 1996).

New technology has facilitated the development of new drugs through the development of sophisticated instrumentation. Since the WWII the rate of technological advancement in pharmaceutical R&D has been dramatically accelerated. The development of computers and their use into mainstream research has also increased the momentum of technical change. Nowadays, technologies allow pharmaceutical products to be designed by identifying potential drugs at the level of the human genome. In addition, advancements in IT have led to the development of super-efficient tools for the collection, assimilation and analysis of large amounts of data.

The following advancements are considered to be the key technologies of the pharmaceutical industry in the last two decades (Reuters, 2000, Ratti and Trist, 2001, Bellott et al., 1997), genomics, proteomics, rational drug design, combinatorial chemistry, high throughput screening, and pharmacogenomics. These technologies are used by most pharmaceutical companies (Ratti and Trist, 2001). A detailed

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description of these technologies is outside the scope of this thesis. However, a brief

explanation is provided in Table 4-2.

Table 4-2 Key enabling technologies

Technology	Description
Genomics	The study of the genetic instructions that characterise living organisms (Scott and Wendt, 1998). It provides the knowledge on how variations in gene sequence and expression cause disease. Also, understanding the genetic basis of a disease state or even the biochemical processes in healthy individuals helps to build a picture of the cascade of events that lead to illness (Baba, 2001)
Proteomics	The study of proteins and their expression profiles. It is used for identifying the disease specific proteins involved in the generation of disease states. Advances in the analysis of proteoms using robotics and high throughput automated processes have revitalised this discipline.
Rational drug design	Utilises molecular modelling and information gathered from protein structure analyses to design and develop new drugs.
Combinatorial chemistry	This is a method for systematically combining immense numbers of small molecule chemical building blocks together to make all possible combinations according to a specified chemical reaction sequence (Bellott et al., 1997).
High throughput screening	To handle the large number of new drug targets and new chemical entities provided by combinatorial technology *high throughput screening* was developed as a method for running up to 100,000 screens a day (Kniaz, 2000). It consists of the use of automated assays (Lesney and Miller, 2000)
Pharmaco-genomics	Uses the knowledge gained from human DNA sequencing to genetically type potential patient populations for disease susceptibility. The science's strength lies in its ability to link a patient's response to a particular drug with that patient's genotype.

Technical change may require organisational rearrangements, which renders changes

in structures and routines (Thomke, et al., 1998). For example, suppose that a firm

wishes to replace some physical and lab based experimentation methods with

computer simulation methods. To do this it must typically hire or develop people

with new skills and reorganise the relationships between the various specialists who

jointly carry out experiments (Thomke et al., 1998). In fact the adoption of a new

experimental method and technique can serve as a long-term competitive advantage

The reason being, that new methods require (i) the transfer of significant amounts of new skills and (ii) some reorganisation of a firm's R&D activities (Thomke et al., 1998).

The development of scientific knowledge over the last century has resulted partly in the development of new technology. New technology in turn has altered the pattern by which new drugs are discovered. This alteration has influenced both the success rates of drug discovery and the structure of pharmaceutical organisations since new capabilities are now required. Consequently, technology is similar to scientific knowledge in that it constitutes an important asset of a pharmaceutical organisation, and is critical to any drug discovery strategy.

4.7.1.3. Organisation (structure and process)

'This (the pharmaceutical) is a business that's basically driven by people. If you look at the market capital of Pfizer—I think we're the fifth-most valuable company now—it's $250 billion, some mind-boggling number. Our balance sheet assets, the number is less than 10% of that. And so the delta is basically our intellectual property and the expectations of what our people can do.' (Norton, 2002) Senior Vice President, Corporate Human Resources, Pfizer Inc in The Economist 2002

http://www.economist.com/media/audio/eanorton.ram)

The above quote demonstrates the importance that is placed on the management and coordination of people within pharmaceutical organisations. The scientific knowledge required to discover new drugs can be divided into subject areas, which can be composed in a modular fashion to define larger pieces of knowledge. This culture of rationalisation, encourages division of labour amongst individuals into specialised segments of the drug discovery process (Valle and Gambardella, 1993)

The scientific disciplines that underpin drug discovery include molecular biology, physiology, biochemistry, analytic and medicinal chemistry, crystallography, and pharmacology (Cockburn and Henderson, 1994, Stork, 1998). Having individuals from these disciplines working together to ensure that resources from different functions are present is considered one of the most important factors in achieving fast development (Dorabjee et al., 1998). It has been estimated that R&D costs are now $175,000 per person (this figure was calculated by USA's pharmaceutical manufacturers association in 2002 (PhRMA, www.phrma.org)).

Research should be organised with great attention so as to encourage creativity. In the past when new compounds were the result of long screening procedures, the volume of experimentation determined the number of successes. Nowadays however the design of theoretical compounds is possible and creativity is no longer linked with the economies of scale of laboratories (Arrow, 1983). The individuals involved in research teams should be given autonomy to organise their own activities, whilst following their choice of research along the strategic objectives set by the managers (Valle and Gambardella, 1993). Therefore, the management challenge of pharmaceutical organisations is to exercise appropriate control on a research team without influencing its creativity. Omta et al. (1994) have suggested that the arguably greater success of the Anglo-American organisations in comparison to continental European firms is partly due to the greater emphasis on human resources management.

In addition, the trend for mergers, acquisitions and alliances in the pharmaceutical industry has made the issue of managing the individuals even more critical. Organisations with different histories, symbols, ideologies, ways of doing things, and ways of thinking about things have now been joined together. These differences often

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make working together a difficult task to manage (Stork, 1998). This difficulty has led to the development of techniques for managing innovation such as project management. The aim of project management is to develop a sound overall plan that includes contingency plans, rapid identification of bottlenecks, and vigorous resolution of each bottleneck when it appears. This in turn could create an efficient development process (Anderson, 1996).

Formal project management procedures were introduced to the pharmaceutical industry about thirty years ago when workers with limited responsibilities were given the title - project managers (Allen, 1997). According to Allen (1997) the pharmaceutical industry lags behind other industries in implementing true project management. He identifies two reasons for this (i) the high level of specialisation which makes it difficult for people from different disciplines to collaborate, and (ii) the regulation which defines the steps by which drug development progresses. In addition other management techniques such as Total Quality Management which are widely used in other industrial sectors (e.g. automotive manufacturing) have not yet been fully adapted by the pharmaceutical (Rowley and Sneyd, 1996). Anderson (1996) identifies six common sources of inefficiency; lack of motivation; inconsistency of funding; lack of coordination; unproductive research; unfocused development; and slow project termination.

With pharmaceutical project management there are two trends, that of the virtual project and that of the empowered project team (Case, 1998). The former is where the locus of the project and the project work can be off-sight and potentially at considerable distance from functional management. Also, the ownership and responsibility of a project can be shared among several parties either directly or indirectly employed by an organisation (contractors, consultants, and partners). The

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latter is that of a project team that has been given the authority to take most of the decisions, while being allocated significant resources to pursue the project goals (Case, 1998). The more effective form is one that combines empowerment of the project team with relaxation of the traditional ties in favour of more virtual organisations (Case, 1998).

As the availability of scientific knowledge and technology increases so does the need for specialised individuals capable of carrying out the necessary tasks. This has led to the development of organisational teams where scientists from different disciplines and departments come together to develop and bring to bear the appropriate specialised capabilities to develop new drugs. Within each team, data, information and strategic knowledge are widely dispersed across individuals from different functions within an organisation (Bernhardt and McCulley, 2000, Jensen and Sandstad, 1998). Success of these organisations requires much more than 'naming' the team and setting up a regular schedule of team meetings (Clark and Wheelwright, 1993 p. 522). It requires the definition and coordination of the functions that are required for the successful completion of the organisation's goals.

To summarise, the growth of the body of scientific knowledge and technology in the pharmaceutical sector, have created the need for specialisation. This specialisation in turn has created the need for communication interfaces between these individuals and the teams they are part of. The management techniques, which have emerged to address these issues, face the challenge of exercising control without influencing creativity. Over the last century, these techniques together with scientific knowledge and technology have played an important role in the formation of drug discovery strategies.

4.7.1.4. Environment

The fourth factor that affects the formation of drug discovery strategies is that of an organisation's environment. In section 4.3 of this chapter it was argued that drug discovery strategies are located at the business level. Therefore, the elements of the environment that affect the formation of drug discovery strategies are those that are directly associated with the competitive advantage of an organisation i.e. the drug discovery process. The environment of the drug discovery process could be described as consisting of the technology and knowledge of other organisations, the legislation and political situation that directly influence the drug discovery process, and the diseases that are targeted.

The issues of knowledge and technology and their effect on strategy making were addressed in the previous sections. Legislation and political policies affect drug discovery strategy by imposing a set of rules and routines that have to be followed to ensure that the drug is safe and efficient (Drews, 1998). Finally, diseases constitute the most critical part of the environment since the discovery of a successful cure for a disease can provide an organisation with a competitive advantage. The number of diseases that are still uncured and could therefore provide potential targets for research of the pharmaceutical organisations is still high. History has indicated that as one disease is eliminated or controlled another takes its place. AIDS is a recent example of a disease that has emerged, whereas obesity has made the progression from a cosmetic preoccupation to a topic of major concern (Williams and Mallick, 1987). In addition, the increase in the geriatric population will result in an increase of the occurrence of diseases like arthritis, senile dementia, and Alzheimer's (Williams and Mallick, 1987).

4.8. Conclusion

The previous chapter introduced and defined the drug discovery process and summarised that its evolution was characterised by significant change from a relatively unplanned and emergent process, based on scientific enquiry and motivated by curiosity and academic freedom, to a modern, high technology, market targeted, rational and planned business process. Nowadays, the drug discovery process is no longer a '...*random procedure in which inspired scientists, working around the clock, come upon breakthroughs in the middle of the night'* (Henderson, 1994)

To help understand this evolution for the purposes of classification, this chapter has reviewed several schools of strategy and existing strategy classifications, to identify an appropriate framework for researching and classifying drug discovery strategies. The chapter used Mintzberg and Waters' (1998) eight-category strategy classification to understand and define strategy for the purpose of understanding and defining drug discovery strategy. As explained in section 4.5 the reason for this is that this classification provides a well-structured rigorous framework that encompasses the plethora of organisational strategies implemented by organisations and analysed by the scholars. It also provides a categorisation of the different strategies along the continuum deliberate-emergent, which helps justify the evolutionary paradigm that is later presented and adopted by this thesis.

A key element of the resulting framework, and also a stance of this thesis, is that strategy making in the drug discovery context is seen as a process of leaping from one state to another (Mintzberg, 1998). As it will be discussed in the following chapters, drug discovery strategies are patterns of management behaviour that transform due to changes of the four strategic factors technology, knowledge, organisation and

environment. In particular, advances in scientific knowledge and technology have driven organisations to transform their strategic configurations to a more *rational* approach.

The framework is based on the following and summarised in Figure 4-7:

- Drug discovery strategy is seen as a pattern of behaviour rather than a predetermined plan. Viewing drug discovery strategies as plans would not allow for serendipity, a crucial factor in any research activity and particularly in the discovery of new drugs. In contrast, the use of the term *pattern* allows for a more emergent or evolutionary behaviour and therefore complies more with the history of drug discovery that, as it will be shown in chapter 7, has been highly influenced by external factors such as diseases, technology, political, and social circumstances.

- Drug discovery strategies are seen as business rather than a corporate strategies.

- The formation of a drug discovery strategy is achieved using the strategic factors: knowledge, technology, and organisation. The environment within which the drug discovery strategies are formed and executed consists of the corporate strategy, the strategies of the competitors, the available knowledge and technology and finally legislation. Knowledge, technology, and organisation are used to create and protect an organisations' competitive advantage and consequently to meet the goals set by the corporate strategy.
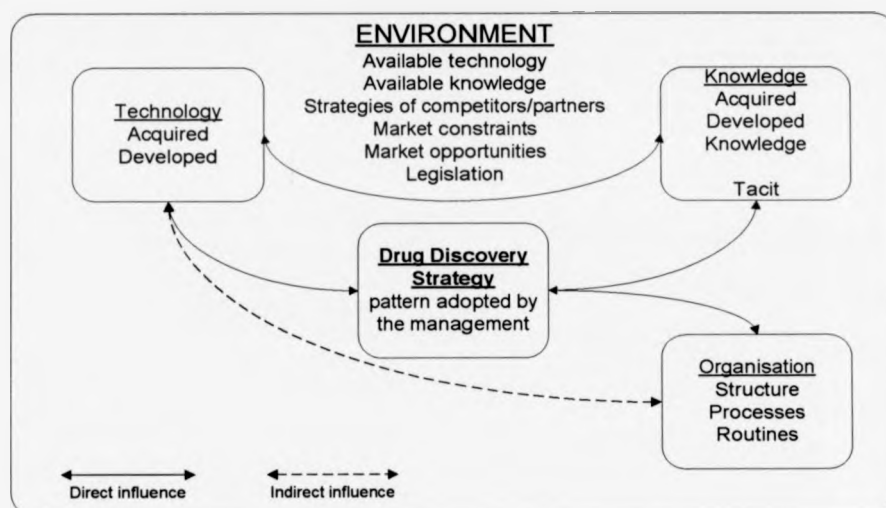
Figure 4-7 Factors influencing the drug discovery strategy

This chapter has provided the background for relating strategic management to the drug discovery process and has therefore addressed the first part of the first research question (How does the discipline of strategic management relate to the process of drug discovery?). It has also identified four factors, knowledge, technology, environment, and organisation that influence and define the change of a drug discovery strategy. It has also addressed the second research question (What are the factors (internal and external) that influence and define different drug discovery strategies?). Finally, the chapter has addressed the second part of the first research question (What is the definition of a drug discovery strategy?) by providing the following definition of the term *drug discovery strategy*:

'A drug discovery strategy is a pattern of behaviour defined or adapted by the management of a pharmaceutical organisation, within a certain environment, to effectively materialise the corporation's goals and policies in order to achieve a

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competitive advantage through the application of knowledge and technology on the discovery of new drugs. '

The following chapter (chapter 5) reviews the concepts of evolution and fitness within the scope of this thesis and develops four hypotheses for the evolution of drug discovery strategies.

5. EVOLUTION REQUIREMENTS, FITNESS, AND HYPOTHESES DEVELOPMENT

5.1. Introduction

The third research question presented in chapter 1 seeks to examine how can an evolutionary and classification approach be used to study drug discovery strategies. To address this it is important to understand the meaning and process of *evolution*. This chapter aims to provide this understanding by undertaking a review of the literature of evolution and identifying and justifying the requirements systems (biological and non-biological) should meet for evolution to explain their change. The four requirements identified are existence in populations, variation, heredity and selection. To address the third research question the requirements are then developed into four hypotheses for the evolution of drug discovery strategies. These hypotheses will be validated in chapters 7 and 8 by using the classification methodology *cladistics* which will be explained and justified in chapter 6.

The fourth research question (What are the characteristics of the fittest drug discovery strategies?) is linked to the concepts of strategy, evolution and the identification of the fittest strategies and their defining characteristics. Prior to addressing this question it is important to understand and define the term *fitness* within the scope of this research. Therefore, the second aim of this chapter is to undertake a review of the literature on fitness and develop a working definition of the term.

It is important to note that even though the theories and analogies presented in this chapter stem from biology, they are still relevant to organisations. However, in

organisational science the use of the terms evolution and fitness is related to, but not the same as the terms used in a biological context. Evolution is often synonymous with change (Leseure, 1998), while fitness is synonymous with success (Venkatraman 1989). This chapter will clarify and define these terms in accordance with the overall research objectives and theoretical stance adopted by this thesis.

In summary, the objectives of this chapter are:

- To review evolutionary theory (biological and organisational) and identify the requirements of evolution for the purpose of classifying drug discovery strategies,

- To develop hypotheses for the evolution of drug discovery strategies based on these requirements, and

- To provide a definition of the term fitness in the context of organisational strategy.

5.2.   Introduction to Evolution

This section describes the process of evolution and develops four hypotheses for the evolution of drug discovery strategies.

Charles Darwin introduced his theory of evolution in 1859 by the publication of his book *The Origin of Species* (Darwin, 1968). Darwin argued that organisms come about by evolution, and provided a scientific explanation of how evolution occurs and why is it that organisms have features, such as wings, eyes and kidneys, clearly structured to serve some features. Darwin defined evolution as *descent with modification* where the word *descent* refers to the way evolutionary modification takes place in a series of populations that are descended from one another. Therefore,

evolution is change in the form and behaviour of organisms between generations and within populations of species (Ridley, 1996). Hence, examining the evolution of species requires the identification of populations they are members of, and this is the first requirement for evolution. A fundamental concept in Darwin's explanation of evolution was natural selection.

The central argument of Darwin's theory of evolution starts from the existence of hereditary variation. Nature's variations occur because they are favourable or useful in some way to an organism in its struggle for existence. Struggle for existence takes place because the number of individuals that are produced is higher than that that can possibly survive. Favourable variations are those that increase chances for survival and procreation. They are then preserved and multiplied from generation to generation at the expense of less advantageous ones. This is the process known as *natural selection*.

Evolution therefore, can be seen as a two-step process. First, hereditary variation takes place; second, selection is made of those genetic variants that will be passed on to following generations. Hereditary variation also entails two mechanisms: the spontaneous mutation of one variant to another, and the sexual process that recombines those variants to form a multitude of variations. The variants that arise by mutation or recombination are not transmitted equally from one generation to another. Some may appear more frequently because they are favourable to an organism; the frequency of others may be determined by accidents of chance, called genetic drift. Therefore, for natural selection and thus evolution to occur it is essential to have variations within a population. Also, a mechanism must exist that allows these variations to be inherited to later generations. Hence, the third and fourth requirements are variation and heredity.

Research in organisational theory has derived considerable inspiration from biological evolution over the last forty years. Several scholars (e.g. Hannan and Freeman, 1977, McKelvey, 1982, Aldrich, 1979, 1999, McCarthy, 2000) have employed ideas and concepts like natural selection and biological classifications to understand the operation and development of organisations and their strategies. Aldrich (1999) has argued that if processes generating variation and retention (or heredity) are present in a system and that system is subject to selection processes evolution will occur (p.21). In an organisational context, the consumer and market forces influence the role of natural selection. Fitter organisations edge out the less fit organisations by reducing their ability to win business contracts and orders. Therefore, the market environment acts as a form of natural selection, linked to the organisations ability to survive and grow in that environment (Nelson and Winter, 1982).

Although these evolutionary approaches have been insightful and have inspired several debates in academe (e.g. Donaldson, 1995) there are important distinctions to be made. For instance, when studying biological organisms evolutionary changes over long periods are easier to observe. Aquatic worms have evolved into mammals, birds, reptiles, amphibians and fish over the last 600,000,000 years, and bacteria have evolved into plants and animals over the last 3,000,000,000 years etc. (Britannica, 2002). In strategic management however, evolutionary changes are a phenomenon less straightforward to observe despite the fact that strategy can be viewed as an evolutionary process (Hannan and Freeman, 1977).

Another difference is the control and motivation of humans. They have long-term objectives, a certain amount of foresight and the ability to plan and administer change. Man and the organisation he creates are to a certain extent the masters of their own

destiny. To a degree humans may shape their own environment, and are not merely shaped by it (Thorelli, 1995).

Allen (2000, 1994) also argues that whereas in biology genetic mechanisms ensure that different possibilities are explored and the offspring spreads them in characteristic space over time, in human systems techniques and behaviours are never passed on exactly. This is because in human systems there are imperfections and subjectivity of existence which leads to curiosity and desire to experiment i.e. human systems are not mechanical (Allen, 1994). Therefore, exploration and innovation are always present as a result of the individuality and contextual nature of experience.

Finally, Penrose (1959) cautioned care in the use of the concept of natural selection to organisations. In biological studies the offspring should have an inheritable variation from the previous population. Penrose pointed out that organisations do not possess genetic material in DNA form, so it is not simply a case of transferring these concepts from biological studies to organisations. Other researchers suggested however that although organisations do not posses DNA, it may be possible to encode this type of information in the form of configurations and routines. For example, Miller (1996) and Maguire (1997a, 1997b) proposed that configurations included the strategy and structures of an organisation. Also, Nelson and Winter (1982) used the term *routine* to refer to a repetitive pattern of activities which are consistent and predictable about business behaviour in an entire organisation. Thus, routines range from specific technical procedures to strategies and policies. In their book, they also suggest that as an organisation grows, it would retain past successful experience in the form of routines. Aldrich (1999) used routines as a generic term that could be used to describe an organisation. Hence, these routines or configurations could be treated as heritable just like the genetic information that an individual has in its DNA.

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Rothschild (1992) compares the role of DNA information with technological information. He argues that as genetic information is the basis of all life in the biological environment, so in the economic environment technological information is the source of all economic life.

As developed by Campbell (1969), the natural selection model for organisations identifies three processes: *variation, selection and retention* that underpin the evolution of organisations. This concept has been further developed by researchers such as Pfeffer (1982) and Aldrich (1999). Aldrich (1999) added a fourth process, the *struggle* for resources.

In accord with the third research question, this thesis examines whether an evolutionary approach can be used to study drug discovery strategies. Therefore, it is important to carefully review such an approach and to propose the requirements that systems should meet for evolution to explain their change, while considering the distinctions between drug discovery strategies and biological organisms. Four requirements are identified and discussed in the following section. These are *existence in populations, variation, heredity* and *selection.*

5.2.1. Requirements for evolution

This section will analyse the four requirements that any species (biological and non-biological) must satisfy for evolution to explain their change i.e. existence in populations, variation, heredity, and selection.

5.2.1.1. Existence in populations

The first requirement of evolution is that of existence in populations (Ridley, 1996, Stearns and Hoekstra, 2000). Changes in biological evolution do not happen to individual organisms, but to populations over long periods (Dawkins, 1986). A

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population is defined as a subset of individuals of one species that occupies a particular geographic area and, in sexually reproducing species, interbreeds (Britannica, 2002). The frequency of this change depends on the members of a population i.e. the species as well as the environment they inhabit. An approximation of the size of a population would be the number of individual organisms that are included in the population (Ridley, 1996 p 146)

Populations of species are relatively straightforward to identify, as living organisms can be easily distinguished from each other. However, such is not the case with organisational strategies, or drug discovery strategies. The configurations of organisational strategies are similar. For instance, the identification of populations of patterns by which pharmaceutical organisations have been applying new technologies cannot be easily distinguished. Existing empirical work found in organisational literature focuses on the distinction of organisational forms and the definition of populations of organisations (e.g. Hannan et al. 1995, Hannan, 1997, Carper and Snizek, 1980), but not populations of organisational strategies. This issue is a research question and area of novelty for this research.

Before proceeding with the argument of populations of drug discovery strategies, it is important to briefly review the literature on organisational forms and organisational strategies. Hannan and Freeman (1977) define organisational forms as *blueprints* for organisational action, for transforming inputs into outputs. Whilst, drug discovery strategy as defined in chapter 4 is a *pattern* adapted by the management of the pharmaceutical organisations. Similar to the organisational form, this pattern is also responsible for transforming inputs into outputs. Within this context the concepts of organisational forms and organisational strategies are interchangeable

In ecology there are three levels of analysis, individual, population, and community. In organisational analysis there are at least five levels i) members, ii) sub-units, iii) individual organisations, iv) populations of organisations, and v) communities of (populations of) organisations (Hannan and Freeman, 1977). Lovas and Ghoshal (2000), on the other hand, defined two units of analysis in their study of evolution in social and cultural systems. These are *strategic initiatives* and *human and social capital*. The former relates to any deliberate effort by an organisation to create or appropriate economic value from the environment, which is organised as an independent project with its own profit and loss responsibility. The latter refers to the knowledge skills and values that are embodied in people and the relations among people which have the potential to facilitate productive activity.

Hannan and Freeman (1977) refer to populations as aggregates of organisations rather than members. The organisations of a population must be similar in their response to exogenous shock. In ecology this response is almost identical. Organisations and their strategies however, are distinctive and thus no two are affected identically by any given exogenous shock. Nevertheless, classes of organisations may be identified which are relatively homogeneous with regard to environmental vulnerability. The nature of a population also depends on the investigation. Therefore, in the case of drug discovery strategies, populations could consist of organisational strategies (or forms), which are located in the pharmaceutical industry. The pharmaceutical industry as a whole could also constitute a population, if the investigation was focused on different industrial sectors. However, this is not the case in this thesis as it focuses on the strategies of the individual organisations.

The formation of populations as well as their size depends on various factors, which include geography, technological competencies, regional market conditions, price

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reductions, and innovations. Carroll and Hannan (1989) argue that the size of a population of organisational forms follow a *concave pattern of growth and decline* (Carroll and Hannan, 1989 p. 524). That is, when the population emerges the number of organisations within that population is small. However, this number increases rapidly in size and then stabilises or declines (Carroll and Hannan, 1989). They identify and test three different causes to this phenomenon, which are discussed in the 'selection' section of this chapter. Furthermore, the size of a population also depends on its *legitimation* (Hannan et al. 1995). Initial increases in the size of a population, i.e. increased density, enhances a population's legitimation, thereby raising its founding rate and lowering its mortality rate (Hannan, 1997). These effects initially induce further growth in the density. However, persistent increases in density eventually generate intense competition, which depresses founding rates and elevates mortality rates. If the effect of competition and legitimation balance, then density is in a steady state (Hannan, 1997).

Organisational and more specifically drug discovery strategies are formed by organisations that occupy a particular area in the competitive landscape. The use of the word *area* is more metaphoric than literal, as it does not refer to a geographic area, but to a symbolic business area whose size depends on the number of organisations that implement the strategies into their system. Therefore, it could be argued that drug discovery strategies form populations whose size depends on the number of organisations that exist within the area of investigation.

To summarise, drug discovery strategies could form populations in an environment, which is described by competitive forces and pressure for introduction to the market of as many new drugs as possible. In addition, the size of a population could be greater or at least equal to the number of organisations that implement similar

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strategies. In contrast to populations of biological species, populations of strategies for drug discovery would not be limited to a geographical area. Although regional variations in strategies do exist, mainly due to factors like local legislation and culture, the strategies that are pursued by pharmaceutical organisations have a global nature. Recent global trends for mergers and acquisitions (O'Reilly, 2001, DiMasi, 2000) also support this view.

Thus, as part of the work that seeks to address the third research question the first of four hypotheses is presented below:

There are similar drug discovery strategies employed by different pharmaceutical organisations to form populations whose (the population's) size follows a concave pattern of growth and decline.

5.2.1.2. Variation

The second requirement for evolution to occur is variation. The infinite variations in life are the fruit of the evolutionary process (Britannica, 2002). Variation may be caused by both genetic and environmental factors. Genetic factors are those factors found inside the organism and include mutation (the accidental introduction of an error in the replication of the parental DNA (Ridley, 1996)) and recombination (the process during which genes are shuffled, Ridley, 1996)). Variation must exist between members of a population, because in its absence evolution would be impossible (Smith, 1993). For instance, if the object of study is body size, then individuals within a population must have different body sizes. This form of variation is called *heritable variation* (Stearns and Hoekstra, 2000). In biological organisms heritable variation exists across various levels. It can be found at the morphology level (e.g. body shape),

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the cell level, the biochemical level and naturally at the DNA level. The more genetic variation that exists in a population, the greater the opportunity for evolution to occur. In addition, variation must exist between the *fitness* of organisms. In evolutionary theory fitness means the degree to which individuals contribute offspring to the next generation i.e. that body of living beings that constitutes the next step in the line of descent (the concept and definition of fitness is addressed in more depth in the next part of this chapter). Therefore, variation between the organisms' fitness means that those individuals of a population that possess certain characteristics are more likely to reproduce than others are. The production of surviving offspring is achieved through the number of offspring born, their survival, the survival of the parents to reproduce again, the number of offspring they have in their second and subsequent breading attempts, the survival of those offspring, and so forth. Variation in reproductive success is made up of variation in all these components (Stearns and Hoekstra, 2000).

The correlation between the two types of variation (between the members and fitness) causes variation. Heritable variation causes the most favourable characteristics to be transmitted to later generations. Following this, reproduction success will ensure that this attribute is reproduced in large quantities to dominate a population over time.

In organisational theory there must be some variation for the environment to select differentially among organisational forms (Aldrich, 1999). Any kind of change is a variation Aldrich (1999) and, as argued by Price and Shaw (1998), it is related to the interruptions of established equilibrium when new patterns of action that threaten, and eventually replace, old ones. The evolutionary process can begin with variations that may be *intentional* or *blind* (Aldrich, 1999). Variation is said to be intentional when an organisation deliberately sets out to resolve problems or exploit opportunities it

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faces. Within organisations, there may be formal programs of experimentation and imitation, such as research and development. Such programs are intentionally created to promote innovative activities that can change the current routine of an organisation to a better functioning or more effective working style. Another source of intentional variation is said to be the incentives provided for innovative employees. Working groups can be created deliberately within an organisation to intensify internal competition and thus promote better functioning. The working groups are then appraised and rewarded when better innovations are created.

Blind variation as cited by Aldrich (1999), occurs independently of environmental or selection pressures. This can include trial and error learning, luck, imitation, mistakes, misunderstanding, surprises, idle curiosity and so forth. It can also take the form of new knowledge or experiences introduced into an organisation by newly recruited employees.

Similar to the identification of populations of drug discovery strategies, the identification of strategic variations within a population is not straightforward. As explained in chapter 4, organisations try different strategies in an endeavour to be successful. Therefore, at any given time it is not easy to distinguish at which strategic state an organisation is. In addition, since the identification of populations of drug discovery strategies is not yet clear, it is not possible to define different strategies that exist within such population.

Thus, the second requirement of evolution is that for the species to evolve they must be different to each other i.e. variation must exist. In social systems it has been argued that for the evolutionary process to function satisfactorily there must be enough variance for the selective forces to operate on (Campbell, 1969). If there is no variance, then no new forms will be selected and the older forms will be retained.

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Biological variation is caused by two factors, environmental and genetic, while it happens along two dimensions, between the members, and between the fitness levels of the individuals. Hence, to assert that drug discovery strategies meet the requirement of variation, the two factors (genetic and environmental) and the two dimensions (between the members and between the fitness) must be explained in the context of drug discovery strategy.

The environmental factors that cause variation are any factor found outside the organism. With regard to drug discovery strategies these factors can be the elements of the environment that surrounds organisations. These would include price reductions, fit to regional market conditions, innovations in the therapeutic areas and the technology (Sedlacek et al. 1996 p. 13), pressure of generic competition, the influence of patient advocacy groups and consumer organisations (Anderson, 1996 p.81), and the changes in the structure of the environment (Prahalad and Bettis, 1996).

The environmental factors may be divided into external and internal industry pressures (Reuters, 2000).

The internal industry pressures exerted on the pharmaceutical industry are:

- Increasing competition,

- The presence of me-too's and generics,

- Quality, efficacy and tolerability issues,

- First to market advantage.

Large pharmaceutical organisations face increasing competition, not only from each other, but also from the biotechnology industry and spin-off groups initiated by academic institutions (Bogner and Thomas, 1996). Me-too drugs are those drugs that

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exhibit similar efficacy and tolerability profiles to their first-to market competitors and because they are separate chemical entities gain patent protection. Generic drugs are those drugs that can only be launched after an innovative drug has lost its patent protection. Competition from generic drugs has become more intense and this results in greater pressures on R&D returns (Gambardella, 1995). These two types of drugs (me-too and generics) have driven pharmaceutical organisations to seek more innovative products, so that they can penetrate a particular market and, once achieved, maintain market share. These innovative products however, must show improved tolerability and efficacy over existing products (DiMasi, 2000). Failure to do so results in the product not being recognised as providing improved therapeutic intervention and therefore is not utilised in preference to existing drugs. Finally, the launch of a novel compound with enhanced therapeutic benefit results in the ability of an organisation to effectively and deeply penetrate the market, thereby ensuring a certain level of sales (O'Reilly, 2001). Any subsequent *me-too* products, which are not significantly differentiated from the first drug, will find it difficult to penetrate the market and achieve significant market share without first reducing their price (Lu and Comanor, 1998, Agrawal and Thakkar, 1997)

Lee and Harrison (2001) also support the view that market competition causes strategic variation or, using their terminology, *industry bifurcation*. The driver for research intensive industry bifurcation is innovation. Short term survival pressures force organisations to seek more innovative strategies and thus cause strategic variation. Baum (1990) adds institutional and environmental forces those that may cause variation. The simultaneous action of institutional, competitive and environmental forces may result in both increasing diversity in some organisational forms and decreasing diversity in some others.

The external industry pressures exerted on the pharmaceutical industry are (Sedlacek et al., 1996):

- Healthcare cost containment measures,

- Pharmaceutical product price controls,

- The introduction of formularies.

Cost containment measures are used by healthcare providers to limit or reduce escalating healthcare costs. Price controls are present in markets where healthcare services are either public or private. In countries such as the UK, where the government predominantly covers the cost of healthcare, strict price regulations exist. The aim of these regulations is to ensure that pharmaceutical organisations do not demand excessive price premiums for their innovative products. Table 5-1 includes a list of UK government policies, which have been implemented in the past.

Table 5-1 Previous UK government policies that may rise again from Earl-Slater (1998)

- Government demands £25m saving on NHS drugs bill, twice in 1983. There is no robust evidence that any such savings were made.
- Government announces agreement on price reductions: NHS drug prices to be reduced by an average of 2.5% in 1993 and the reduction was to hold until September 1996.
- Government switches drugs from being available only on prescription to being available without prescription. Eleven drugs switched between 1983 and 1992, 40 drugs switched between 1993 and 1995. This switching means that the patient or their insurer pays for these drugs
- The increased availability of cheaper drugs from other EU countries (e.g. Spain Portugal and Greece)

In countries where healthcare services are provided predominantly by private insurers such as the US, free market principles exist which result in natural price ceilings. Within those markets there is no single healthcare provider. Instead numerous insurers control the provision of healthcare services. Despite the fact that

there is no single purchaser wielding ultimate power over pharmaceutical drug prices, prices are regulated by internal competition. As the majority of individuals have their healthcare services provided by these organisations, these organisations can exert a level of control over pharmaceutical prices. Finally, the introduction of formularies, the list of drugs physicians are allowed to prescribe, requires new innovative products priced at a premium to offer significant therapeutic benefits over existing products. Failure to do so will result in the drug not being included on the formulary list and thus will not be available for prescription by physicians employed by the particular healthcare payer.

The identification of the genetic factors that cause variation of drug discovery strategies is a more complicated issue. Genetic factors, are those factors that are inside the organism. Chapter 4 identified four factors that influence the change of drug discovery strategies. These are scientific knowledge, technology, organisation, and environment. The first three could be classified as genetic factors and could include, the structure of the research, the position of a team within an organisation, the technology available to the researchers, the culture, the organisation history (path dependence) (Helfat and Raubitschek, 2000), and the sources of new ideas (Lovas and Ghoshal, 2000). Consequently, internal factors are those that affect the organisational structure and organisational capabilities. Genetic factors cause some strategies to be stronger than others i.e. they are fitter for the particular environment and therefore they are more likely to survive.

An illustration of the genetic factors is provided by the work carried out by Cockburn et al. (2000) who suggest that the pursuit of science driven strategies is one reason that certain pharmaceutical organisations achieve a competitive advantage over their rivals especially during the 1980s. However, the positive response to such a

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strategy is '*only half the battle*' (Cockburn et al., 2000). The other half is the original positioning of an organisation in a way that it is able to diffuse the science driven drug discovery more effectively. Although it is not certain whether this positioning is the result of smart strategic moves or luck, it is a reason for internal variation. The initial conditions imposed on an organisation when it was founded, create a unique strategic configuration, which regardless of the changing efforts of an organisation, will be a blueprint of its operation.

Prahalad and Bettis (1996) suggest any element that causes variety, originates inside an organisation and might therefore, be labelled a genetic factor of variation. This factor is the addition of a new business either through internal development or acquisition. In such instances the organisational structure is leveraged by the structure of the new unit.

In addition, internal strategic variation may be caused by the available methods and techniques. At any given time the strategy pursued by one organisation will seek to obtain resources essential to its strategic mission. To achieve this it utilises methods and techniques available at the time. Since these methods and techniques differ between organisations the strategies of the organisations also differ (Stinchcombe, 1965).

So far the causes of variation have been discussed. How it occurs, is based on two dimensions: between the members and between the fitness. Variation between the members in organisational strategies means that the characteristics formulating the strategy (such as plan, pattern, position, perspective, response, stakeholders and contribution to stakeholders, (see chapter 4)) must have different visible characteristics i.e. the characteristics that shape their operation must vary. These characteristics do indeed vary within a population of organisations. Different

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circumstances and different perceptions of the environment cause each strategic attribute of an organisation to be different. *Pattern*, for instance, is an attribute of organisational strategy that is unique to each organisation and hence to each strategy as it is determined by leadership, market, technological, or political forces and so on (Mintzberg, 1996).

The second dimension requires variation to happen across fitness. As will be discussed later in this chapter fitness is '*the condition where the configuration of an organisational strategy matches that of the environment and the frequency of its characteristics appearing in future strategies is high*'. Therefore, this dimension firstly requires the configuration of a drug discovery strategy to match that of the environment. The environment of a drug discovery strategy as described and justified in chapter 4, consists of the technology and knowledge of other organisations, the legislation and political situation that directly influences the drug discovery process, and the diseases that are targeted. Drug discovery strategies utilise an organisation's resources and capabilities, which in turn enhance its sustained competitive advantage in therapeutic differentiation and global NCEs (New Chemical Entities: *the novel chemical or biological compounds, excluding esters or salts unless they conferred a major therapeutic advantage* Jones, (2001) p. 241) (Yeoh and Roth, 1999). Therefore, drug discovery strategies that are more fit to the environment will be the ones that utilise an organisation's resources and capabilities in a way that allows the organisation to develop a competitive advantage and be successful in an environment.

Secondly, for variation to occur across the fitness of a drug discovery strategy, the frequency of its characteristics in future generations should be high. This process of transferring characteristics through strategic configurations over time is addressed in more depth in the next section, *heredity*. That section identifies three correlated

mechanisms by which the transfer of characteristics may occur, *coercive isomorphism*, *mimetic processes*, and *normative isomorphism*.

In summary, variations in drug discovery strategies are caused by two factors genetic and environmental. The genetic factors are those whose origin is inside an organisation, while environmental are those whose origin is external to the organisation. In addition, the resulting variation must exist both between the members and the fitness of drug discovery strategies.

Therefore, the second hypothesis that underpins the third research question is:

Within a drug discovery population, there are strategies that differ to each other in terms of their characteristics and their fitness.

5.2.1.3. Heredity

Heredity is the third requirement for evolution to happen. It is the *inheritance of physical or mental characteristics from parents to offspring* (Simpson and Weiner, 1989). This requirement of evolution asserts that offspring should resemble their parents. In biological systems inheritance is produced by the *Mendelian process* (for a comprehensive explanation of the Mendelian process, see Ridley (1996) pp 35-38, and Smith (1993) pp. 53-75) and it is now understood down to the molecular level (Stearns and Hoekstra, 2000).

Smith (1993) views heredity as a way of transmitting information. He also distinguishes between systems of *limited* and *unlimited* heredity. In systems of limited heredity only a few states can be transmitted. Systems of unlimited heredity are capable of transmitting an indefinitely large number of messages. This distinction is important because the amount of information transmitted from one generation to the next determines the speed of selection. Heredity is also the cause for adaptation. The

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effectiveness of the adaptation depends on how far the differences between individuals which are responsible for their success are inherited by their offspring (Smith, 1993).

In contrast to the previous two requirements, the transfer of characteristics to future strategic configurations has been examined by the strategic management literature. Several mechanisms and theories have been developed to examine and control inheritance of strategic configurations (e.g. Oliver (1988), DiMaggio and Powell (1983)).

In biology, the distinction between generations is clear, but with the evolution of drug discovery strategies it is not. Identifying and understanding these distinctions is a key area of novelty for this research. Drug discovery strategies within the same population may have shorter or longer life cycles depending on their success and the rate of change of the environment they inhabit. In fact, a central problem of evolution in cultural and social systems is the tension between the creation of new variants versus the retention of previously selected variants. The process that best resembles biological heredity is the one that preserves, copies or imitates the strategic configurations or memes of one member in a population (McCarthy, 2002). This process is also known as *retention* (McCarthy, 2002, Campbell, 1969, Pfeffer, 1982, Aldrich, 1999) and as *isomorphism* (Hawley, 1968, DiMaggio and Powell, 1983, Oliver, 1988). Price and Shaw (1998) use the term *meme* to convey an unit of cultural transmission such as a tune, idea, catch-phrase, fashion, recipe, or design.

Retention is said to occur when selected variations are retained, copied or imitated, so that the selected activities are repeated on future occasions or the selected structures appear again in future generations (Aldrich, 1999). Retention can occur at two levels, organisational and industrial. Organisational retention can occur through

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the industrialisation and documentation of successful strategies, and through existing personnel passing on knowledge about strategies to new personnel. Successful strategies that provide organisations with some advantage in the marketplace survive because the organisations survive (Price, 1995). Industrial level retention can take place through the spreading of new strategies from one organisation to another. This can happen through personal contacts, or through observers, such as academics or consultants publishing successful new technologies or management skills.

DiMaggio and Powell, (1983), have identified three mechanisms through which heredity or *isomorphic change* occurs. They call these coercive isomorphism, mimetic isomorphism, and normative isomorphism.

5.2.1.4. Coercive Isomorphism

Coercive isomorphism is the result of formal and informal pressures exerted to organisations. The sources of these pressures are, other organisations they are dependent upon, and cultural expectations from the society within which they function (DiMaggio and Powell, 1983). The form of these pressures may be force, persuasion or an invitation to collude. Examples include the direct enforcement of a new legislation by a government and a scientific breakthrough.

With drug discovery coercive isomorphism can be illustrated by the genetics and molecular biology revolution that began more than forty years ago with the discovery of the double helix structure of deoxyribonucleic acid (DNA) and continued with Cohen and Boyer's techniques of genetic engineering (Henderson et al 1999). These new discoveries marked the beginning of the biotechnology industry, but lay outside the older and established pharmaceutical organisations (Bogner and Thomas, 1996 p.118). Established pharmaceutical organisations could acquire this knowledge either

through acquisition or internal learning. The latter option involved steep and long learning curves to thoroughly understand this technology. Therefore, the common option followed by large organisations was acquisitions or alliances. Hence, pressure forced organisations to adapt alliances as a strategy to develop capabilities in the new era.

Another example of coercive isomorphism in drug discovery is the response of an organisation to a new legislation. New legislation often changes the context within which organisations in the pharmaceutical industry must compete (DiMasi, 2000). For instance, the introduction of the Food, Drug and Cosmetic Act of 1938 by the US congress required the testing of new drugs for safety before being granted approval. It also created a new category of drugs that could only be dispensed to a patient at the request of a physician (Pizzi, 2000). These radical changes forced pharmaceutical organisations to rethink and restructure the methods of discovering new drugs.

5.2.1.5.   Mimetic processes

The second mechanism of isomorphic change is through mimetic (copying) processes. Organisational strategies and processes are reproduced through imitation (Lloyd, 1990). Successful strategies are imitated while unsuccessful ones fall victims to the market. Lloyd (1990) draws on evolution genetics and ethics, to argue that companies are genuine alien form, *'the first our species have encountered'*. Successful organisations frequently set the standard for others to follow, and the characteristics that these organisations possess are responsible for their success. Imitation leads to the relative increase of these more successful characteristics and to the decline of others.

Less successful organisations tend to face an uncertain future, due to a poor understanding of technology, unclear setting of goals, economic and political trends, competitive actions, changes in societal values, and corresponding shifts in consumer preferences (Amit and Schoemaker, 1998). This uncertainty is a powerful force that encourages imitation (DiMaggio and Powell, 1983), even though the imitated organisation may or may not be aware of the imitation or may have no desire to be copied.

The methods employed to understand and copy the desirable characteristics include benchmarking exercises, consultancy reports and surveys, and acquisitions of key people from other organisations. Moreover, the wave of mergers and acquisitions that has dominated the pharmaceutical industry in the last decade could also eventuate to imitation. This trend has been triggered by various factors including the desire to improve the effectiveness of the drug discovery by understanding the operations of the acquired or merged organisation, the acquisition of new knowledge developed in the acquired organisation, and the increase of profits through diversification.

A necessary prerequisite for the successful imitation of a strategy is the clear understanding of the link between an organisation's resources and its sustained *competitive advantage* (Barney, 1991). When this link is not known then organisations that attempt to imitate will not know which resources to copy. In the pharmaceutical industry the characteristics associated with the discovery of new drugs are highly complex and hence difficult to replicate (Yeoh and Roth, 1999). Therefore, drug discovery serves as a competitive advantage.

The imitation of successful strategies however does not suggest that all organisations tend to be the same. If this were the case then there would be no variation. In fact the

process of selecting and implementing the strategies by competing organisations results in variation of realised strategic positions (Deephouse, 1999).

5.2.1.6. Normative isomorphism

The final form of isomorphic change is normative. The source of this form is *professionalisation*. Professionalisation is defined as *the collective struggle of members of an occupation to define the conditions and methods of their work, to control the production of producers and to establish a cognitive base and legitimisation for their occupational autonomy* (Larson (1977) and Collin (1979) in DiMaggio and Powell, (1983)).

Professionalisation has two aspects that provoke isomorphic change namely, formal education and professional networks. Formal education and training provides organisational members with an institutional understanding of the application of the characteristics of the successful strategies. Strategy is conceptualised as an organisation's realised position in its competitive market (Porter, 1980). Although this understanding is only conceptual and the application depends on the individual and the involved organisation, it provides stakeholders with a common basis for strategy making. This basis consists of the best practices of the preceding generation of strategies. The most effective configuration of the strategic characteristics is institutionalised through an iterative isomorphic process (Scott, 1995) and passed on to the next generation as the best (if not the only) way of doing things. Professional networks extend across organisations. New strategic initiatives diffuse across these networks and redefine the norms of organisational behaviour.

Recruitment programs and the careful filtering of new personnel serve as a method for encouraging normative isomorphism. Such programs ensure that those who do

not strike a prospective employer as likely to fit in are not employed (Price and Shaw, 1998). Those who are likely to fit in are those that comply with certain codes conventions and rules accepted by the organisation. This policy helps to increase the speed of diffusion of the ideas and strategies, which are inline with the existing paradigm.

To summarise, the characteristics that underpin organisational strategies are transferred between and within populations over time. The three mechanisms of isomorphic change introduced by DiMaggio and Powell (1983) could provide a framework for understanding the transfer of characteristics and the process of heredity. However, the lack of distinct generations of organisational strategies allows the use of the word *heredity* only metaphorically. Nevertheless, the above discussion has established that mechanisms for the sustainability or retention of the successful strategic characteristics do exist.

Therefore, the third hypothesis is:

Those characteristics of drug discovery strategies credited with successful drug discovery performance are likely to appear in future strategic configurations, while those characteristics that are not are likely to be absent.

5.2.1.7. Selection

The fourth requirement for evolution to occur is *selection* and is derived from the theory of *Natural Selection* as originally introduced by Charles Darwin (Darwin, 1968). Natural selection can be defined as the differential reproduction of alternative hereditary variations. Differential reproduction is determined by the fact that some variations may increase the likelihood of survival and reproduction of some individuals. Natural selection denotes that those individuals that are not suited to

survive in certain environments do not survive (Hutchison, 1974, p127). Selection may be due to variations in survival, in fertility, in rates of development, in mating success, or in any other aspect of the life cycle.

Darwin maintained that competition or struggle for limited resources results in the survival of the most effective competitors. In addition, competition can be either direct or indirect. Direct competition means that individuals struggle with each other e.g. to defend territories. Indirect competition means that they are consuming the available resources first. Competition for survival creates the prerequirement for natural selection to operate (Stearns and Hoekstra, 2000).

Natural selection occurs not only as a result of competition, but also as a result of some aspect of the physical environment, such as inclement weather. Moreover, natural selection occurs even if all the members of a population died at the same time. Natural selection can be directional or stabilising depending on the effect it has on characteristics. When the environment favours a certain characteristic, which is *inheritable*, the number of individuals that possess this characteristic, will increase. At the other end, the number of those that do not will decrease. In this case natural selection is directional. Directional selection also explains adaptation of a population to the environment. Over generations a population adapts to the environment by increasing the frequency of those characteristics which are selected in. Stabilising selection occurs when the environment favours the average form of a population more than the extremes.

With natural selection, the criteria for survival is not consciously selected by the environment or the population. There is no long-term goal or mission statement, because nothing is involved that could conceive of a goal. There is only short-term relative reproductive success, producing both short and long term change.

Characteristics increase or decrease in frequency because of their correlation with the reproductive success of the individuals that carry them (Stearns and Hoekstra, 2000). This in fact is the major difference between living organisms and organisational strategies. Organisational strategies, which are formed and implemented by people, are consciously designed to have long-term objectives. Therefore, special care has to be made when drawing analogies of biological selection in strategic management.

In organisational science, the entities that are selected are organisational routines (Aldrich, 1999). The process of variation creates new routines either blindly or intentionally. New organisational characteristics are selected according to how well they enable an organisation to acquire resources in a competitive environment. Selection is said to occur internally or externally (Aldrich, 1999). Internal selection criteria are set by promotion, incentive systems, imitation, internal diffusion, etc. or any activities that are controllable within organisations. These selections may or may not enhance an organisation's ability to survive. It is possible for new routines to be selected even though they do not conform to existing practices. On the other hand, organisations may link promotion or incentive systems to out-dated criteria. This could promote the selection of old routines, as managers will be more prompt to use the old more established routines. Such measures could reduce the introduction and adoption of new routines. External selection criteria are set by market forces, competitive pressures, the logic of internal organisational structuring, and other factors usually beyond the control of individual organisations. Organisations with maladapted variations in technology, managerial incompetence, misunderstood customers' needs, etc. are less likely to acquire competitive resources and are therefore more inclined to failure. As a result, successful or surviving organisations will have comparable and similar characteristics, which are absent in failing organisations.

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As with biological selection, organisations also compete (struggle) for resources that are limited. This scarcity of resources fuels the selection process faced by an organisation. In new industries, the leading organisations have ample gain and enjoy fast growth. As a population in the industry grows, the resources become more limited, and as a result failure rates increase. This can cause a population to stagnate or decline.

As hypothesised in the previous sections, drug discovery strategies do exist in living populations, and differ to each other (the drug discovery strategies), whilst having the ability to transfer characteristics to future generations. Thus, for selection to occur it is assumed that the environment favours the fittest strategies, while the rest will eventually cease to exist.

Henderson and Mitchell (1997) suggest that the formation and change of strategy follows a cyclic pattern where organisations develop organisational capabilities as they act in the competitive, institutional and cognitive environments. Capabilities arise both by design and as the unexpected by-products of an organisation's actions. The capabilities, managers' understanding of these capabilities, and the historical context that surrounds them, then condition an organisation's responses to changes in their environment. The responses and organisation performance in turn affect the structure of the industry, and all the changes generate new information, which in turn creates new learning opportunities (Henderson and Mitchell, 1997). Therefore, those strategies that create capabilities that cause reactions that are not favoured by the environment will be selected out. This does not necessarily signify the failure or death of an organisation that applies the failed strategy. Rather, an organisation may abandon the strategy in order to create new capabilities.

Carroll and Hannan (1989) also support the view of a cyclical pattern (or concave pattern) on the number of organisations within a population. They also suggest three reasons for this phenomenon. Firstly, organisations exploit ephemeral resources, growing rapidly while the resource abounds and then declining as it fades. Secondly, newer populations with newer technologies emerge and social conditions change. Finally, as the size of a population increases the number of competitive forces and the pressure for legitimation also increase.

However, abandoning a strategy and adapting a new one requires a degree of adaptation and flexibility by an organisation. Hannan and Freeman (1977) have argued that there are a number of limitations in the ability of organisations to adapt. They have called these limitations *structural inertia*. As discussed in chapter 4 the structural inertia depends on both internal and external considerations including, tangible assets of an organisation limited information in decision making (both internal and external), political constraints, established routines or norms, legal and fiscal barriers, and collective rationality.

To illustrate the application of selection forces on drug discovery strategies two examples of change in environmental conditions will be discussed. The first one is the 1962 amendments to the federal food, drug, and cosmetic act of 1938 in the United States (Bogner and Thomas, 1996 p.91). This legislation changed the environment within which organisations in the pharmaceutical industry had to compete. Pre-market regulatory requirements increased as organisations had to demonstrate the efficacy of the new drugs before they were marketed. As a result the scope and expense of new drug development was substantially increased. Those organisations that were better equipped in terms of structure, financial capability, and organisation culture to adapt to the new environment had an advantage in the long run

(DiMasi, 2000). Therefore, it may be argued that those strategic configurations that were favoured by the new environmental condition were sustained while the rest ceased to exist.

The second example comes from within the pharmaceutical industry. The revolution in genetics and molecular biology had an enormous impact on the nature of pharmaceutical R&D and on the organisational capabilities required to introduce new drugs (Henderson et al. 1999). The adoption of biotechnology required organisations to make a transition from blue sky to targeted and market led drug discovery. This transition required both the development of a large body of new knowledge and substantially new organisational capabilities in drug research. These capabilities included a reorganisation of the scientific workforce that was tightly connected to the larger scientific community and an organisational structure that supported a rich and rapid exchange of scientific knowledge across an organisation (Gambardella, 1995, Henderson and Cockburn, 1994). Those organisations that were fortunate enough to have adopted rational modes of drug discovery have been much more successful than those that initially achieved great success with more traditional *random* methods of drug discovery (Henderson, 1994).

In both of the above examples, the organisations that employed strategies favoured by the environment were sustained and served as a competitive advantage. Other organisations had to change and adapt to the new conditions imposed by the environment. The characteristics that those strategies had acquired were not easily replicated and this gave them an advantage compared to the rest.

To summarise, organisational strategies are being continually developed, used, and assessed. The characteristics of the successful strategies are being the subject of imitation, while eventually they become academically institutionalised.

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Consequently, the characteristics that these strategies possess are passed on to the next generation (requirement of heredity). At the opposite end, the least successful strategies cease to exist either because they lead organisations to failure, or because they are abandoned by organisations. With both cases the environment does not favour least successful strategies and this forces them to extinction (selects them out). Therefore, their characteristics are not transferred to the next generation, which is consequently characterised by the characteristics of the successful strategies.

Following this line of argument the fourth hypothesis is:

With a change in the environmental conditions those drug discovery strategies that remain are the ones whose strategic characteristics are favoured by the environment.

5.2.2. Process of evolution: a summary

Based on the above discussion, this section presents a diagram for understanding evolution and its key elements. The diagram is shown in Figure 5-1
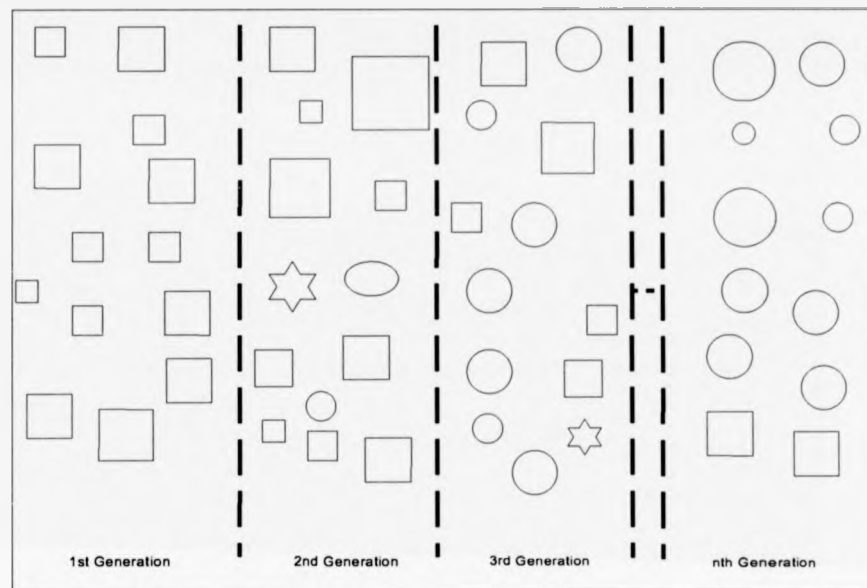
Figure 5-1 Diagram outlining evolution

The column on the left-hand side of the diagram is the population present at the first generation. It consists of species whose main and common characteristic is their square shape. The shape varies in size across the population and like other characteristics such as colour is a potential source of variation between the members. The members of the population interbreed with each other and produce a second generation. As information about the shape is inherited from one generation to the next some errors occur (mutations). These errors result in the production of different shapes like stars, ellipses and circles. At this point an assumption is made about which shape is favoured by the environment (i.e. the fittest). In this example and at the 2nd generation the fittest shape is assumed to be round.

Thus, the second generation again interbreed and generate new members, which tend to have a round shape, or a combination of the two shapes (square with rounded corners). Since the round shaped members are considered by the environment to be

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fittest, they are more likely to reproduce. Therefore, over several generations the dominant species of the population will be the ones with the rounded shape i.e. the rounded species will have been selected in.

5.3. Definition of Fitness

The fourth research question (What are the characteristics of the fittest drug discovery strategies?) revolves around the term "fittest", which has already been mentioned several times in this chapter. To adequately address the fourth research question, it is necessary to define fitness in relation to drug discovery.

Dawkins (1982) identified five definitions of *fitness*, which are widely used in the biological literature. These are Darwin's fitness, population geneticists' fitness, ethologists and ecologists fitness, Hamilton's (1964a, 1964b) inclusive fitness, and Hamilton's (1964a) neighbour modulated fitness. As will be shown the last three definitions treat the subject of interest as a form of agent trying to optimise something (Dawkins 1982). This section will introduce Dawkins' five definitions and will conclude by providing an overview of the use of fitness in strategic management.

The term fitness as used by Darwin and Spencer roughly meant the capacity to survive and reproduce, as they had not provided a precise technical meaning (Gould, 1991). The term 'fittest' however referred to that individual that produces the largest number of offspring to survive to maturity and reproduce. Fitness in this context is known as Darwinian fitness (Allaby, 1999).

The population geneticists made an attempt to link fitness to the relative rate of change of the size of a population, but did not provide a definition of the term fitness (Fisher, 1930). For them fitness is a practical measurement that refers to the number of offspring that a typical individual is expected to bring up to reproductive age, when

all other variables remain unchanged or are averaged out. The focus of this measurement is in the changes in genotype frequencies and gene frequencies that occur in a population. For example, if two populations have different sets of genes and accordingly have a different relative rate of increase, the population which has the larger rate of increase also has greater fitness.

Ethology and ecology are two fields of biology that aim to study the reactions and relationships of a given organism to its environment. Organisms are viewed as integrated systems searching for an optimal solution in an open environment. Fitness, in this context, is seen as a property of the individual organism and is used as a measurement of how successful an individual is in reproducing offspring, or its success in passing its genes on to the future generations (Dawkins, 1982). A practical measurement of this type of fitness is the number of its offspring reared to adulthood as a means of showing the parental care of the organism.

The fourth definition of fitness identified by Dawkins (1982) is the inclusive, as proposed by Hamilton (1964a, 1964b) in an attempt to explain the evolution of altruism. According to Hamilton, close relatives like siblings, parents, and children will have at least 50% of their genes in common. As a result, any sacrifice that could double the genetic benefit of a relative will have an indirect net productive benefit to the genes via the relative's offspring. Inclusive fitness can be defined as *the sum of individual reproductive success and the reproductive success of an individual's relatives, with each relative devalued in proportion as it is more distantly related.* In other words, inclusive fitness is said to be the sum of the individual's own fitness plus half the fitnesses of each brother plus one-eighth of the fitness of each cousin, etc. Inclusive fitness is said to be maximised by the behaviours of the organism over a

lifetime in such a way as to leave as many copies of its genes, or alleles to the coming generations as possible.

The fifth fitness definition identified by Dawkins (1982) as proposed by Hamilton (1964a p. 2-5) is known as the *neighbour modulated fitness* and refers to the expected number of direct offspring produced by an individual. The difference between inclusive fitness and neighbour modulated fitness is that the former tends to concentrate on the effects the individual has on the fitness of his relatives, whereas the latter tends to emphasise the effects that relatives have on the individual's fitness. For this reason, this type of fitness is also known as *personal fitness* (Orlove, 1975). Yet, when used carefully and subjected to certain assumptions, both *inclusive fitness* and *neighbour-modulated fitness* arrive at the same conclusion (Hamilton 1964b)

In another categorisation of fitness definitions, Endler (1986) proposed five contexts in which the term fitness may be applied: Darwinian fitness, rate coefficient, adaptedness, adaptability and durability (Table 5-2).

Table 5-2 Endler's (1986) contexts of fitness

Term	Definition and measurement	Remarks
Fitness	The degree to which there are different rates of survival and reproduction amongst the individual organisms of a population. This is measured by the average contribution to the breeding population by a phenotype, or of a class of phenotypes, relative to the contributions of other phenotypes.	Also known as Darwinian fitness, relative fitness, and selective value. Selection coefficient and selection differential are algebraically related to fitness.
Rate coefficient	The rate at which the process of natural selection proceeds. Measured by the average contribution to the gene pool of the following generation, by the carriers of a genotype, or by a class of genotypes, relative to the contributions of other genotypes.	Similar to the fitness defined above, but also includes the genetic response.
Adaptedness	The degree to which an organism is able to live and reproduce in a given set of environments; the state of being adapted. Measured by the average absolute contribution to the breeding population by a phenotype or a class of phenotypes.	Also known as absolute fitness. Is also applied to species, where it is known as the Malthusian parameter.
Adaptability	The degree to which an organism or species can remain or become adapted to a wide range of environments by physiological or genetic means	The reverse of specialisation.
Durability	Probability that a carrier of an allele or genotype, a class of genotypes, or a species will leave descendants after a given long period of time.	Best expressed for alleles, genotypes, or species by the expected time to extinction.

Adopted from Endler (1986), p. 40

From the above discussion of fitness, an organism's survivability and reaction through adaptability and durability to the changing environment are made clear. Fitness is therefore defined as a measure of prediction of the composition of a population in terms of frequencies of the characteristics in the long term. Such predictions aim at identifying the species that will prevail, or whether many species will remain present, on the basis of the reproductive parameters that could be observed as associated with that type.

5.3.1. Fitness in organisational strategy

The concept of fit in strategic management has its roots in contingency perspectives found in both organisation theory and strategy literatures (Ginsberg and Venkatraman, 1985). The main premise of these literatures is that of *matching* and *aligning* organisational resources with environmental opportunities and threats (Andrews, 1971, Chandler, 1962). In organisation theory the notion of fit is associated with the environment-structure relationship (Donaldson, 1995, Thompson, 1967, Forte et al., 2000). Organisational forms or structures that match the environmental contingencies demonstrate superior performance (Forte et al, 2000). In the strategy literature the concept of matching and alignment is not as clear. The response of an organisation to changing environmental conditions does not necessarily imply a change in organisational strategy (Zajac et al., 2000). However, it should be noted that the use of the term *fitness* in the organisational literature (matching and aligning with the environment) differs considerably to the biological use (forecasting frequency of genes in the future).

Venkatraman (1989) identified six distinct perspectives of fit in strategic management. These are, fit as moderation, fit as mediation, fit as matching, fit as gestalts, fit as profile deviation, and fit as covariation. These perspectives vary along two spectrums as shown in Figure 5-2. The first is the degree of specificity of the theoretical relationships i.e. how precise the functional form of fit is. The second is number of criteria used to specify the concept of fitness.
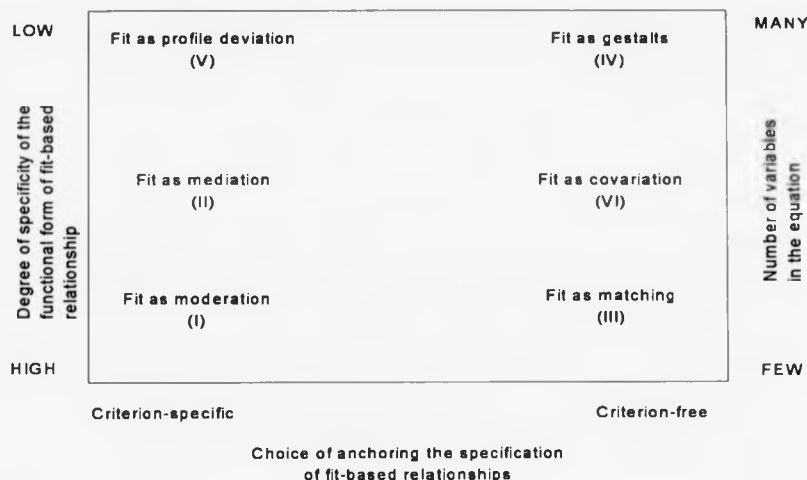
Figure 5-2 A classificatory framework for mapping the six perspectives of fit in strategy research, from Venkatraman (1989) p. 425

Fit as moderation. According to the moderation perspective, the impact that strategy has on a criterion variable is dependent on the level of the environment or *moderator*. The fit between strategy and environment is the primary determinant of the criterion variable.

Fit as mediation The mediation perspective specifies the existence of a significant intervening mechanism (e.g. organisational structure) between strategy and performance.

Fit as matching According to this perspective, a measure of fit between two variables is developed independent of any performance anchor.

Fit as gestalts When many variables are used to conceptualise and specify fitness, the degree of precision must be relaxed. One such multivariate perspective is the identification of *gestalts*, which is defined in terms of the degree of internal coherence among a set of theoretical characteristics.

Fit as profile deviation. In this perspective fit is the degree of adherence to an externally specified profile. This perspective allows a researcher to specify an ideal profile and to demonstrate that adherence to such a profile has systematic implications for effectiveness.

Fit as covariation. According to this perspective, fit is a pattern of covariation or internal consistency among a set of underlying theoretically related variables.

5.3.2. Fitness: Concluding Remarks

Biological fitness is a measure that is used to quantify selection. Therefore, in a biological sense, fitness is the relative probability that a heredity characteristic will be reproduced. Strategic organisational fitness on the other hand focuses on the match of an organisation's characteristics with the surrounding environment. The view of this thesis is that fitness for organisational strategy may be seen as a combination of the two concepts.

With organisations there are mechanisms to achieve intraorganisational transfer of strategic characteristics e.g. isomorphism (DiMaggio and Powell, 1983). The genes or characteristics of successful organisational strategies are more likely to be transferred to later generations with these mechanisms. Successful strategies are those that create configurations that match the environment. Therefore, the frequency of the genes of the successful strategies into the future will be higher.

With this background, the definition given to strategic fitness within the context of this thesis is the following:

The condition where the configuration of an organisational strategy matches that of the environment and the frequency of its characteristics appearing in future strategies is potentially high.

5.4. Conclusions

This chapter had two aims. The first was to provide an understanding on the meaning of evolution, which is important because the third research question presented in chapter 1 requires the examination of how an evolutionary approach can be used to study drug discovery strategies. To meet this aim the chapter undertook a literature review and identified four requirements that systems (biological and non-biological) should meet for evolution to explain their change. These are existence in populations, variation, heredity and selection. The chapter also developed the theoretical background to convert the four requirements into four hypotheses for the evolution of drug discovery strategies as shown in Table 5-3.

Table 5-3 Hypotheses

Requirement	Hypothesis
Existence in populations	*There are similar drug discovery strategies employed by different pharmaceutical organisations to form populations whose (the population's) size follows a concave pattern of growth and decline.*
Variation	*Within a drug discovery population, there are strategies that differ to each other in terms of their characteristics and their fitness.*
Heredity	*Those characteristics of drug discovery strategies credited with successful drug discovery performance are likely to appear in future strategic configurations, while those characteristics that are not are likely to be absent*
Selection	*With a change in the environmental conditions those drug discovery strategies that remain are the ones whose strategic characteristics are favoured by the environment*

If validated, the four hypotheses could define and map the evolution of different drug discovery strategies, which is the aim of this thesis. To do this however, it is important to collect data that will provide insights about the change of drug discovery strategies. Furthermore, it is important to arrange this data in a manner that will allow the comparison of the drug discovery strategies, their populations, and their

characteristics. As it will be explained in chapter 6 such an arrangement may be provided by the classification methodology cladistics.

The second aim of this chapter was to develop a working definition of the term fitness because, as explained earlier in this chapter, to address the fourth research question presented in chapter 1 it is important to understand and define the term *fitness* within the scope of this research. To meet this aim the chapter reviewed the literature on biological and strategic fitness and created the following definition:

The condition where the configuration of an organisational strategy matches that of the environment and the frequency of its characteristics appearing in future strategies is potentially high.

Given this definition chapter 8 will identify those characteristics that define a fit drug discovery strategy.

6. USING CLADISTIC CLASSIFICATIONS TO EXAMINE STRATEGIC CHANGE

6.1. Introduction

Chapter 5 identified four requirements for evolution and created four hypotheses that will be used to address the third research question. To validate these hypotheses it is necessary to select or create a rigorous framework that permits the collection and analysis of data about drug discovery strategies in a concise and consistent manner. This chapter argues that such a framework may be provided by a classification, and in particular an evolutionary classification methodology called *cladistics*. This chapter introduces in detail and justifies the cladistic classification methodology. This methodology is used in chapter 7 to present a classification of drug discovery strategy types (population cladogram) and in chapter 8 to construct a classification of drug discovery strategies of individual organisations (organisation cladogram).

Therefore, the objectives of this chapter are to:

- Examine and justify the use of classifications.

- Examine and justify the use of the cladistic classification methodology.

- Explain the methodology for constructing cladistic classifications.

6.2. Evolution and Classification

A basic problem when applying evolutionary theory to organisational science is understanding the fundamental differences between organisational strategies (Romanelli, 1991). Therefore, a formal (McKelvey, 1982) or informal (Hannan and Freeman, 1989) theory that explains these differences is required. Differentiating

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between the similar and dissimilar has motivated and helped the quest for knowledge across all academic disciplines (McCarthy and Ridgway, 2000). Using a theory of differences and similarities could help identify the nature and degree of organisational differences that arise over time. Such a theory could be provided by taxonomy, i.e. the development of theories and methodologies for classifying entities (McKelvey, 1982), and is central to this thesis, which seeks to define and map the evolution of different drug discovery strategies. It could therefore provide the framework for identifying populations of strategies (1st hypothesis developed in chapter 5), studying variation (2nd hypothesis), and for understanding the processes of heredity and selection (3rd and 4th hypothesis respectively).

The development of classifications, i.e. the action of arranging entities into formally recognised groups, is a common process that helps people to order and store both tangible and intangible entities. In addition, classifications provide a system for storing and communicating knowledge. Carper and Snizek (1980) argue that *the most important and basic step in conducting any form of scientific inquiry involves the ordering, classification, or other grouping of object or phenomena under investigation* (p. 65). In a similar view, Ulrich and McKelvey (1990) argue that all successful sciences are supported by a general classification that allows scientific development. Organisational strategies and management systems are best understood in terms of overall patterns, rather than in terms of analyses of narrowly drawn sets of organisational properties (Rich, 1992).

The creation of classifications could place organisations into homogeneous populations. Identifying such populations is central to this thesis as it is related to the first hypothesis developed in chapter 5 (*There are similar drug discovery strategies employed by different pharmaceutical organisations to form populations whose (the*

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population's) size follows a concave pattern of growth and decline). Furthermore, these populations could allow the generalisation of findings in a narrow population to a broader population. In other words, scientific findings from one population can be generalised to all the members of that population (McKelvey, 1975 and 1982, Haas, et al, 1966, Sanchez, 1993, Rich, 1992).

The process of developing a classification allows examination of the variation between entities within a population. The collection of data needed for the development of a classification could allow conclusions to be drawn about the nature and the sources of variation. This issue is the essence of the second hypothesis presented in chapter 5 (*Within a drug discovery population, there are strategies that differ to each other in terms of their characteristics and their fitness)*.

The third hypothesis developed in the previous chapter is related to heredity (*Those characteristics of drug discovery strategies credited with successful drug discovery performance are likely to appear in future strategic configurations, while those characteristics that are not are likely to be absent)*. A classification that is transparent and includes data about the historical development of drug discovery strategies should allow the development of conclusions that could support or reject this hypothesis. For instance, such a classification could allow the comparison of mature configurations with those of more modern drug discovery strategies. If this comparison leads to the identification of patterns of evolution then there should be evidence to support this hypothesis.

The final hypothesis developed in chapter 5 is related to selection (*With a change in the environmental conditions those drug discovery strategies that remain are the ones whose strategic characteristics are favoured by the environment)*. Similar to the third hypothesis, a classification that allows a diachronic comparison of drug discovery

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strategies could provide evidence to support or reject this hypothesis. For instance, if only a small number of drug discovery strategies have survived a major historical development, such as the world wars, it could be argued that the characteristics of these strategies are favoured by the new environmental conditions.

Classification has always been an important issue, especially for biologists and thus, most of the formal taxonomical tools have been developed within this science. Consequently, organisational and management scientists (McKelvey, 1982, Goronzy, 1969, McCarthy et al., 1997, McCarthy, 1995, McCarthy and Ridgway 2000, Leseure, 1998, and Tsinopoulos and McCarthy, 2000) have borrowed taxonomical tools from biology to build classifications. The application of biological taxonomic tools to organisational science could be regarded as useful since biological scientists have spent many years developing taxonomic theories and accompanying tools to create rigorous and robust classifications. The following section reviews some of the theories of classification.

6.2.1. Theories of classification

Theories of classification can be categorised into two broad types, special classifications and general classifications. Special classifications are created to formulate knowledge about a given problem and therefore are narrower in scope whereas general classifications are created based on the assumption of the natural order of things and offer a broader scope (Leseure, 1998).

Mayr (1969), while reviewing the history of systematics in zoology, identifies five theories of classification. These are: essentialism, nominalism, empiricism, evolutionism and cladism. Based on Mayr's theories, McKelvey (1982) presented the following groups of theories: essentialism and typologies, nominalism; empiricism,

numerical phenetics and numerical taxonomy; and phyletics, evolutionism and cladism. The two first theories are categorised as special classifications and the second two are classified as general classifications (Leseure, 1998). These reviews cover the spectrum of available classification theories and thus, the review in next section will be based on them (i.e. McKelvey 1982 and Mayr 1969). The analysis that is presented helps to identify which is an appropriate taxonomic tool for processing and presenting data (i.e. creating a classification of drug discovery strategies) to validate the four hypotheses developed in chapter 5.

6.2.2. Essentialism and Typologies

Essentialism finds its origins in Aristotle and Plato's thinking. It is based on the philosophical foundation that two objects are classified in the same group if they share the same essence. Essence is defined as the reality that dictates observed properties. Hull (1974) identified three things that can be known about an entity: its essence, its definition and its name. Thus, the foundation is that the name describes the essence and the definition describes the entity. Essence, in the biological world, is defined as "*a hidden reality which can be defined, and* (as a consequence) *this reality dictates the organism's observed properties*" (McCarthy, 1995; pg 6). The resulting classifications of this approach are called typologies (Leseure, 1998).

Typologies have been dismissed from the biological world because they oversimplify reality. Living organisms are compounded by many different characteristics and therefore an essentialist approach does not help to create useful groupings.

As shown in chapter 4, the area of strategic management has created many typologies (e.g. Mintzberg and Waters, 1998, Whittington, 1993, Miller, 1991), but a

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common drawback is that just a few characteristics are selected as the classification variables. As a consequence, strategies (like biological organisms) are considered to be composed of many characteristics rather than just a few and therefore, more characteristics should be taken into consideration to make the classification robust. Leseure (1998) extends the criticism of this approach by arguing that two typologies cannot be merged because of the essences of each typology, thus replication of results are rarely achieved.

On the other hand, typologies offer some advantages. According to McKelvey (1982), the strength of this approach lies in the fact that everything is classified into "*a or non-a or b or non-b, and so forth*" (pg. 40), generating thus, mutually exclusive groups that create specificity.

6.2.3. Nominalism

Three basic arguments underline the philosophical approach of nominalism. These are: (1) only individual objects exist; (2) living and inanimate objects can be classified together and; (3) human minds are the generators of the groupings. Because the groups are created by human minds, nominalists do not recognise natural groupings. In biology, natural grouping is a principle that is accepted and therefore, nominalism was never seriously considered (McKelvey, 1982).

In organisational science, there have been no attempts to use nominalism to classify organisations. Moreover, McKelvey (1982) suggests that nominalism should be avoided because natural groupings of organisations exist (i.e. restaurants; schools or car assemblers) and thus nominalism is an inappropriate classification philosophy.

6.2.4. Numerical Taxonomy and Phenetics

Phenetic classifications are created by collecting large amounts of data that are related to characteristics that typify the entities under study. Once data has been collected, it is processed and presented using numerical taxonomy methodologies such as cluster analysis (Kauffman and Rousseeuw, 1990). Cluster analysis aims to group a sample of elements in such way that the statistical variance among elements grouped together is minimised while variance between groups is maximised (Hartigan, 1975). The main advantage, of this approach, is that large numbers of characteristics are used to study the entities and thus, the classification is considered to be more robust. Also, researchers in this field claim that subjectivity is avoided since the collection of data is led by an influencing theory or pre-notion

The main criticism to this approach concerns the relevance of the characteristics selected for the classification. Since large numbers of characteristics are used, there is the potential to include characteristics that do not help to understand differences.

Cluster analysis has also been used in studies of strategic management in an effort to identify groups of similar organisations (Ketchen and Shook, 1996). There are however three concerns about its effectiveness. Firstly, in contrast to the use of cluster analysis in biology there is extensive reliance on researcher judgment. As argued by Ketchen and Shook (1996), cluster analysis lacks a test statistic that would validate a set of results for a hypothesis of interest, and thus relies on a researcher's judgment for the interpretation of the results. Secondly, as noted by Thomas and Venkatraman (1988), the clusters identified through empirical analysis may not be a significant research result unless they can be related to the expected grouping structure through extant theory. In other words, most applications of cluster analysis lack an underlying theoretical rationale. Finally, as argued by Barney and Hoskisson

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(1990), cluster analysis guarantees the identification of clusters and thus, it cannot be used to test the existence of such clusters i.e. there is a tautology.

6.2.5. Cladistics

Cladistics is a form of evolutionary taxonomy that seeks to determine phylogenetic relationships between entities, but also considers a degree of subsequent divergence, and presence of similar phenotypic characteristics (the observable physical characteristics of an organism) to create classifications. The core concept of cladism or phylogenetic systematics is the use of derived characteristics (apomorphies) to construct common ancestry relationships. Through the creation of these relationships groups or classes are generated (Wiley *et al.*, 1991). In other words, entities are classified according to characteristics they share with other entities, using the relation with common ancestors as the basis for the creation of the groups.

Henning first introduced the concept of phylogenetic systematics in his book "*Phylogenetic Systematics*" (Henning, 1966). The methodology he proposed is now called *cladistics* and the evolutionary diagrams that this methodology produces are called *cladograms*. This methodology was first developed by linguists to classify the evolution of languages and it was later adopted in biological science. Nowadays, cladistics has emerged as a powerful analytical tool in comparative biology (McCarthy and Ridgway, 2000), that provides more information than any other set of biological observations and the results are displayed in a consistent test table and a reproducible framework.

For some researchers, cladistics is considered to be superior to other schools of classification (Ridley, 1996; Wiley *et al.*, 1991 and Lipscomb, 1998). However, much debate accompanies the decision to use any classification methodology.

One of the most important advantages of cladism is that unlike other classification approaches, such as cluster analysis previously discussed, it does not rely on intuition to construct the classifications. This helps to avoid subjectivity when choosing the relevant characteristics for the classifications. Cladistics focuses on the phylogenetic or genealogical hierarchy, which exists independently of the methods used to discover it and is therefore relatively unique and unambiguous in form (Ridley, 1996). Hence, the main advantage of cladistics is the relative objectivity achieved through the empirical methodologies employed to reconstruct phylogenies (genealogical tables showing the racial evolution of a type of organisations).

There have been attempts to construct organisational classifications using cladistics (e.g. Leseure, 1998 and McCarthy et al., 1997, Lord and Price, 2001), and the advantages claimed in these cases, indicate that cladistics is both appropriate and valuable as a methodology for creating classifications of drug discovery strategies to validate the four hypotheses presented in chapter 5. The following sections explain in detail the methodology used for constructing cladograms and how the resulting classification will be used in this thesis.

6.2.6. The cladogram Explained

A cladistic classification is depicted using a tree like diagram, which is called a *cladogram*. There are several possible ways of drawing a cladogram (each is topologically the same), the most popular of which are shown in Figure 6-1 (trees with diagonal branches or trees with square branches (Maddison and Maddison, 1992)). In Figure 6-1 the two cladograms represent exactly the same classification. A cladogram consists of taxa (a group of individuals that is given a name (Wiley et al., 1991)), branches (a line connecting a branch point to a terminal taxon),

characteristics, (a feature or characteristic of an individual) and nodes (points where branches meet and represent speciation events i.e. the event during which a species splits into two (Ridley, 1996, p.16) as shown in Figure 6-1.

Considering three taxa B and C are more closely related to each other than either is to taxa A. This is because B and C share a common ancestor 'x' (which lived at time t_2) that is not shared with A or any other taxon. The group that consists of the taxa B and C is called the *ingroup* and refers to the group studied by the investigator (Wiley et al. 1991, p. 4). Similarly taxon A is more closely related to the group B + C because A, B and C together share a unique common ancestor 'y' which lived at an earlier time (t_1). The group B and C are called sister groups, while the A is the sister group of the combined group A+B+C. The aim of cladistics is to establish sister group relationships and the concept of two taxa being more closely related to each other than either is to a third is fundamental to cladistics (Kitching et al., 1998). In Figure 6-1 taxon D is also called the outgroup and refers to any group used in an analysis, but not included in the taxon under study (Wiley et al., 1991, p. 5). As will be explained later in this chapter, the outgroup is used for comparative purposes.

Determining which type of cladogram layout to use depends solely on practical issues, such as ease of drawing and visual interpretation. The layout adopted by this thesis is the tree with a square branching structure (shown on the right of Figure 6-1) because it is the easiest to draw using the cladistic software available (MacClade).
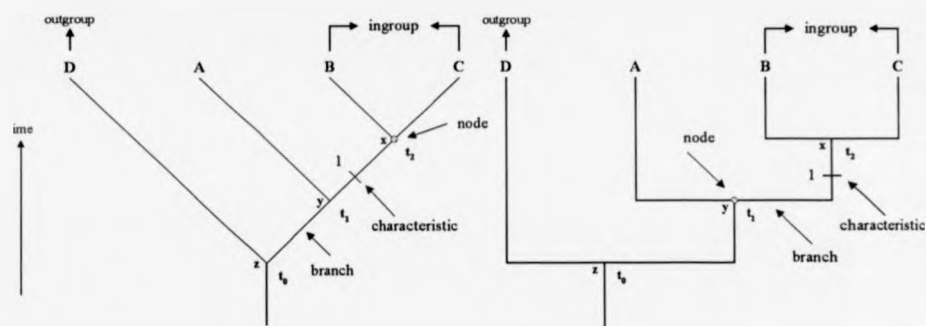
Outgroup - The ancestral configuration used to help resolve the polarity of characters

Ingroup - A set of configurations considered to be more closely related to each other than any are to the outgroup

Branch - A line connecting a branch point (node) to a terminal point

Node - A branch point on a cladogram representing a speciation event

Figure 6-1 Example of tree with diagonal branches and tree with square branches

6.2.7. *Methodology for constructing cladograms*

Kitching *et al.* (1998) suggest that cladistic analysis consists of three processes "*inextricably interlinked*" (pp. 19): the identification of characteristics and entities; the characteristic coding; and the determination of the optimal cladograms (i.e. the cladogram that best explains the relation between characteristics and entities). Similarly, Lipscomb (1998) suggests a five-step methodology for constructing a cladogram. The steps proposed are (i) selection of taxa; (ii) selection of characteristics; (iii) analysis of characteristics to reconstruct the relationship among the taxa, (iv) translation of the tree into a formal classification system, and (v) use of the tree to test various hypotheses about evolution in the group.

McCarthy et al. (1997) and Leseure (1998) proposed a set of seven steps for constructing cladograms for the classification of manufacturing systems. However, these steps do not coincide exactly (Fernandez, 2002) as shown in Figure 6-2.

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a) Leseure's (1998) methodology

b) McCarthy et al's. (1997) methodology
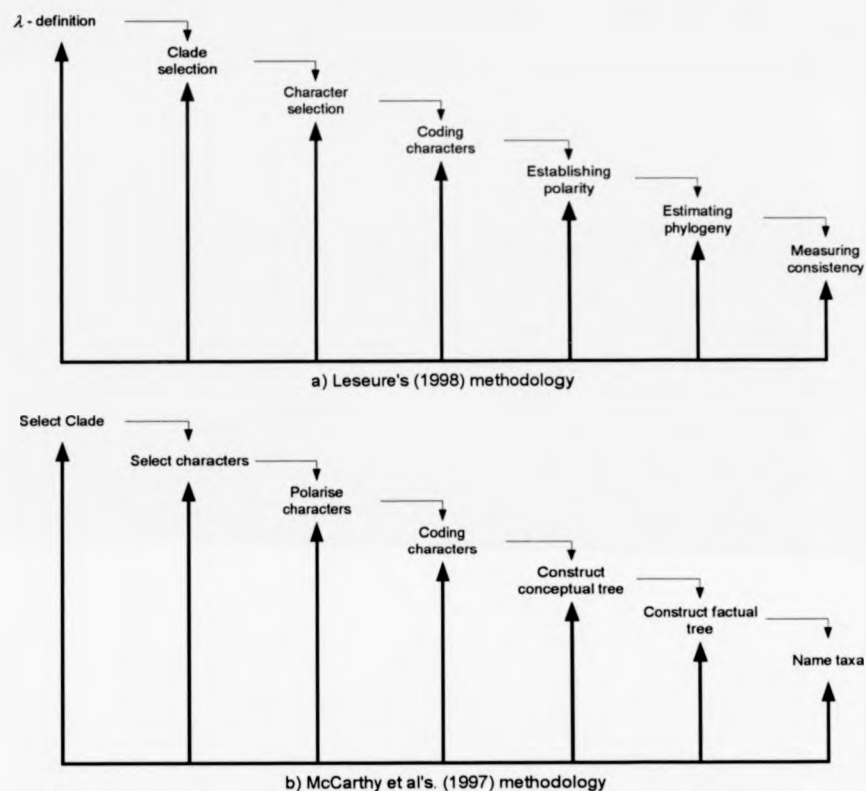
Figure 6-2 Methodologies for building cladograms

Fernandez (2002) in a study that explored the mass customisation strategies of electronics manufacturers proposed an alternative and hybrid methodology based on Lipscomb (1998), McCarthy et al. (1997) and Leseure (1998). This methodology was used successfully to classify individual organisations (Fernandez, 2002). As will be explained later in this chapter, to meet the aims of this research, it is proposed to construct a cladistic classification of drug discovery strategies of pharmaceutical organisations. Therefore, the methodology that will be used is the hybrid methodology developed by Fernandez (2002) as shown in Figure 6-3. This section

introduces this methodology while it shifts the focus from manufacturing

organisations to organisational strategies.
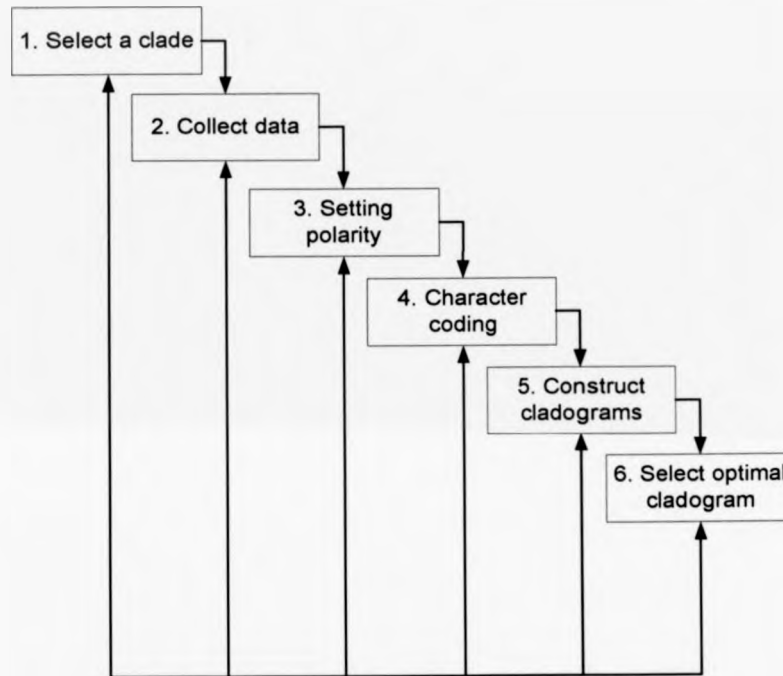
Figure 6-3 Process of constructing cladograms

6.2.7.1.   Step 1: Select a Clade

Wiley *et al* (1991) define a *clade* as a *monophyletic group*, which is a group of

entities discovered to be descendants of the same common ancestor. Defining the

clade establishes boundaries of the group that will be analysed and in a certain way,

this step could be considered as a pre-classification since the selection is based on an

a priori definition of the area of interest.

6.2.7.2.   Step 2: Collect data

When a clade (the monophyletic group) is selected the entities under study and the relationships between them are not known. This step involves the collection of data that consists of the identification of the entities and the selection of the characteristics that will establish the relationships between them.

When the entities under study have been identified it is recognised that they all share a common ancestor. This condition is known as a *polytomy* and is shown in Figure 6-4. The aim of the cladistic classification is to transform the polytomy (Figure 6-4(a)) into a *phylogenetic model* (Figure 6-4 (b)) i.e. to establish the ancestral relationships between entities. To achieve this, the *characteristics* of each entity have to be explored.

(a) Polytomy   **(b) Phylogeny**
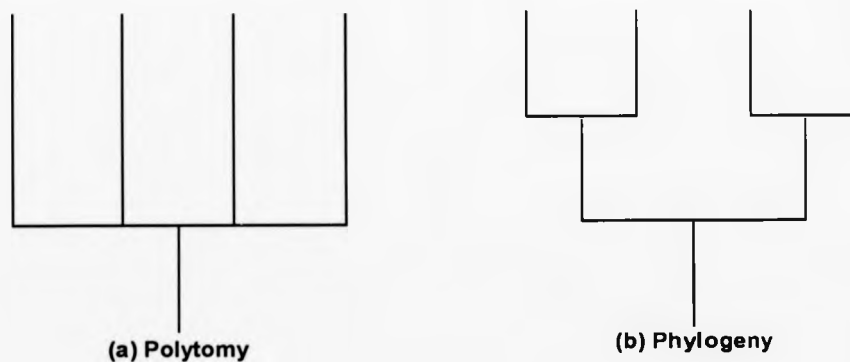
Figure 6-4 Phylogeny and Polytomy

A characteristic is defined as an observable feature or characteristic of an individual (Lipscomb, 1998 and Wiley *et al.*, 1991). Characteristics may be listed in the form of their presence or absence, as binary variables expressing different characteristic states or as multistate characteristics. The final result of a cladistic analysis depends on the

selection of these characteristics. Therefore, the process by which characteristics are selected is one of the main concerns in cladistics.

Fernandez (2002) has suggested three features that any data has to embody to qualify as characteristics for cladistic analyses (Table 6-1).

Table 6-1 Characteristic features for cladistic analyses

Feature	Explanation
Discrete	Logical representation of the characteristic with integer numbers
Qualitative	Characteristics that do not need mathematical expressions or quantifiable features to be expressed
Present large characteristic state changes	Characteristics which represent large clear cut changes from one state to another state.

In spite of these generic recommendations, selecting characteristics is a difficult and sometimes subjective task, since a good cladistic characteristic is a value judgement. In addition to these recommendations, Leseure (1998) proposes a procedure to aid the process of selecting characteristics. This procedure is depicted in Figure 6-5 and it consists of the four following steps:

- Identification of the characteristics that can potentially explain the differences and similarities between the species in the selected clade,

- An informal search for characteristics i.e. the collection of data from sources like books and articles or the expert opinions,

- Decide whether the selected characteristics are *analogies* or *homologies* i.e. decide whether these characteristics are shared between species, but were not present in their common ancestor (an analogy) or are shared between species

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that were also present in their common ancestor (an homology) (Ridley, 1996), and

- Provide the final list of characteristics relevant for the study.
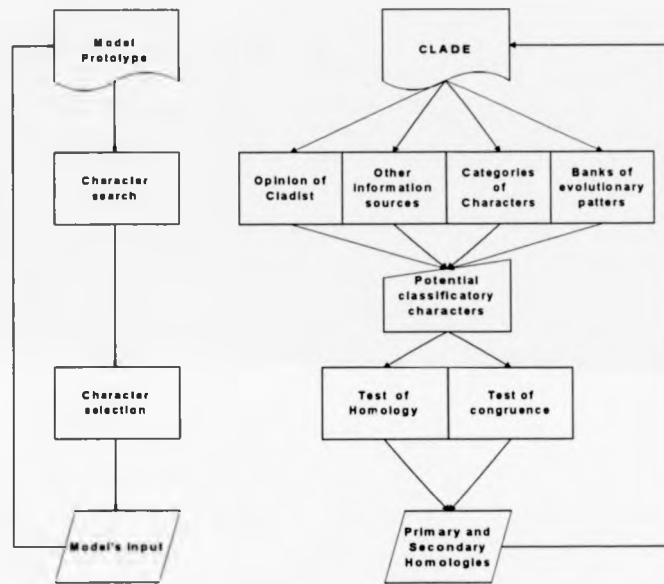
Figure 6-5 Process for Selecting Characteristics (adapted from Leseure, 1998)

In addition to the methodology for selecting characteristics, Leseure (1998) suggested three guidelines for determining the required number of characteristics for a cladistic analysis. Although the number of characteristics selected does not play a crucial role in cladistic analysis, it is important to be aware of these guidelines:

- The number should not be less than the number of branches.

- There should be at least three characteristics per branch to gain more confidence.

- No theoretical maximum

As McCarthy et al. (1997) stated, *"characteristic selection is not a process of choosing available characteristics from a reference list, it is a process of discovering which characteristics are responsible for evolutionary change, the role of individual characteristics in the change"* (pp. 278). The methodology and the recommendations described above should, however, make the work of the taxonomist more unambiguous.

6.2.7.3.   Step 3: Setting Polarity

Once characteristics have been selected and their states defined, the next step in a cladistic analysis is to identify which characteristic states are derived (i.e. *apomorphic states*) and which are ancestral (i.e. *plesiomorphic*). That is to say, to detect what is the direction of change of the characteristics' states. The process of identifying the direction of a characteristic state change is called *polarisation*. Thus, a characteristic is considered *polarised* when its plesiomorphic state has been distinguished from its apomorphic state. Polarisation consists of determining the primitive and derived characteristics by comparing different groups.

To simplify the process of polarising the characteristics a hypothetical ancestor is attached to the tree, which is called, *outgroup*. The outgroup is added to the cladogram as a new entity or taxon whose characteristic states are all zero (Kitching at al., 1998). The addition of the outgroup simplifies the polarisation process because it provides a taxon which is *designed* to be the ancestral. Therefore, any comparisons between characteristics are made with the outgroup as the common reference.

There are several methods for polarising characteristics. These can be classified according to the source of the data required for the study, into direct and indirect methods (Nelson, 1973). The direct methods are those that require data only from

inside the taxa under study and the *ontogenetic criterion* holds as the principal direct method (Kitching et al., 1998). Indirect methods are those that require data from a source external to the study and the *outgroup comparison* is the principal indirect method (Nelson, 1973).

6.2.7.3.1. The ontogenetic criterion

Ontogeny is defined as the development of an individual from its fertilisation to its adulthood. Nelson (1978) defines the ontogenetic criterion for determining polarity as follows: *"Given an ontogenetic characteristic transformation, from a characteristic observed to be more general to a characteristic observed to be less general, the more general characteristic is primitive and the less general characteristic advanced"* (pp. 327).

This approach is not generally accepted in the discipline of biology (Alberch, 1985; Kluge and, Farris, 1969, Kluge, 1985 and De Queiroz 1985) because of its over-simplicity. Therefore, alternative methods have been recommended the most popular of which being the *outgroup comarison*.

6.2.7.3.2. The Outgroup Comparison

The outgroup criterion states that *"For a given characteristic with two or more states within a group, the state occurring in related groups is assumed to be the plesiomorphic state"* (Watrous and Wheeler, 1981, pp. 5) In other words, the outgroup criterion states that if one characteristic is found in both the ingroup and the outgroup, this characteristic is then postulated to be the ancestral state (plesiomorphic) (Fernandez, 2002).

6.2.7.4.   Step 4: Characteristic Coding

Once the characteristics, their states and their polarity have been defined, the next step involves their conversion into numerical or alphabetical symbols. These symbols are called the *characteristic codes*. The characteristic codes are inserted into a matrix, which also includes the classifying entities and the characteristics. These matrices are used by the following step to construct the cladogram.

Various ways exist for carrying out this conversion. However, detailed examination of these methods is not within the scope of this thesis and a description only of the more widely used one is provided.

The method used in this thesis uses a binary approach to code the different states of the selected characteristics. The code '0' represents the absence of the characteristic, while '1' represents its presence or otherwise plesiomorphic characteristic state is coded '0' and the apomorphic characteristic state is coded '1'.

6.2.7.5.   Step 5: Construct the Cladogram

Once the characteristics have been selected, polarised and coded, the next stage in the cladistic analysis process is to construct phylogenetic trees (i.e. cladograms). There are several techniques for constructing cladograms including Wagner optimisation, Fitch optimisation, Dollo optimisation, and Camin-Sokal optimisation (Kitching et al. 1998). The differences between these techniques lie in the criteria imposed to find the optimum cladogram. For instance, the Wagner optimisation imposes minimal constraints upon permitted characteristic state changes, while it allows free reversibility of state changes i.e. from 0 to 1 and from 1 to 0. When the sets of characteristic data are small and simple, a cladogram can be constructed manually using one of the methods mentioned. However, when sets of characteristic

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data are more complex, it is almost impossible to construct a cladogram manually and thus it is usually done through computer software specially designed for the cladistic analyses. The following section explains how to manually construct a cladogram using the Wagner optimisation algorithm.

6.2.7.5.1. The Wagner Algorithm

The aim of this section is to explain how to manually build a cladogram using the Wagner optimisation algorithm. Although the construction of cladograms is usually achieved using computer software, it is important to explain the manual technique because it gives an insight into the nature of the data used and helps to understand the conclusions that may be drawn from a cladogram (Wiley et al., 1991).

To better explain the algorithm an example is also described. The example uses the sample data matrix of Table 6-2

Table 6-2 Data matrix for calculating example cladogram

Taxon	Characteristics					
Outgroup	0	0	0	0	0	0
A	1	1	0	0	0	0
B	1	0	1	0	1	0
C	1	0	1	1	0	1

Given a matrix of characteristics the Wagner Algorithm is implemented using the following algorithm:

1. An ancestor or outgroup is specified (as explained in section 6.2.7.3 of this chapter the outgroup may be a new hypothetical taxon).

2. Within the ingroup, the taxon that shows the least amount of difference from the ancestor/outgroup is found. To accomplish this, D for each taxon to the ancestor/outgroup has to be calculated. The metric D is the difference

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between two taxa and is equal to the sum of the absolute differences their characteristics. For instance in the example of Table 6-2 the difference between A and the outgroup (D(A,outgroup)) is given by the formula::

$$D(A, outgroup) = \sum \left| X(A, i) - X(outgroup, i) \right|$$

Where $X(A,i)$ is a particular characteristic (X) of a particular taxon (A) and i the ith characteristic in a vector of i characteristics. A vector of characteristics for a prticular taxon is defined as $\sum X(A, i)$. For instance, the characteristic vector of A is:

$$\sum X(A, i) = 110000$$

The difference $D(A, outgroup)$ is therefore calculated in the following manner:

$$D(A, outgroup) = \sum \left| X(A, i) - X(outgroup, i) \right| \Rightarrow$$
$$D(A, outgroup) = \left|1 - 0\right| + \left|1 - 0\right| + \left|0 - 0\right| + \left|0 - 0\right| + \left|0 - 0\right| + \left|0 - 0\right| \Rightarrow$$
$$D(A, outgroup) = 2$$

Similarly:

$$D(B, outgroup) = 3$$

$$D(C, outgroup) = 4$$

3. An interval (INT) for the taxon that has the smallest D is created. The interval of a taxon is the length of the line between that taxon and its ancestor. For instance' the interval of A (INT(A,outgroup) is:

$$INT(A, outgroup) = D(A, outgroup) = 2$$

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4. The next taxon that has the next smallest difference from the ancestor/sister group is found. This is done by inspecting the original D values calculated in the previous step. If two taxa or more have the same value of D, then one is arbitrarily selected. In the example that would be taxon B since $D(B,outgroup)=3$

5. The interval that has the smallest difference with the taxon selected in step 4 has to be found i.e. taxon B. The taxon is then attached to the selected interval by constructing a hypothetical ancestor of the two taxa. The characteristic vector of the ancestor, and thus its position along the interval, is computed by taking the median value of the existing taxon, its ancestor, and the added taxon. Because there is only one interval, INT(A,outgroup) there is no choice, but to add B to this interval. Therefore, D[B,INT(A)] does not have to be computed. Then B is connected to INT(A) by constructing a hypothetical ancestor (X) whose characteristics are the median of the characteristics outgroup, A, and B, the three taxa involved in the problem at this point. (Table 6-3).

Table 6-3 Data matrix with a hypothetical ancestor (X)

Taxon	Characteristics					
Outgroup	0	0	0	0	0	0
A	1	1	0	0	0	0
B	1	0	1	0	1	0
X(median)	1	0	0	0	0	0

The tree has now a branch, a new hypothetical ancestor, and, three intervals, INT(A), INT(B), and INT(X) (Figure 6-6)

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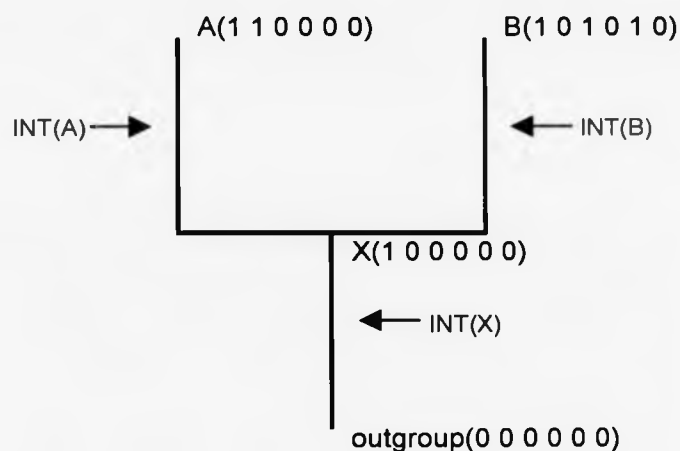
Figure 6-6 A branched tree with a hypothetical ancestor X

6. For each remaining taxon steps 4 and 5 are repeated. The taxon that shows the least difference from outgroup is C. To find the interval that has the smallest interval from C three interval difference values, one for each interval in the tree, have to be calculated. The formula for figuring the difference between a taxon and an interval requires finding the difference between the taxon added and the ancestor of the taxon already in the tree. In this case there are two ancestors. The difference between C and the outgroup has already been calculated and equals to 4. Therefore, the next step is to calculate the differences between A, B, or C and the new ancestor X and the differences between C and A or C and B.

$$D(A,X) = |X(A,i) - X(X,i)| = 1$$
$$B(B,X) = |X(B,i) - X(X,i)| = 2$$
$$D(C,X) = |X(C,i) - X(X,i)| = 3$$
$$D(C,A) = |X(C,i) - X(A,i)| = 4$$
$$D(C,B) = |X(C,i) - X(B,i)| = 3$$
$$D(X,outgroup) = |X(C,i) - X(outgroup,i| = 1$$

Therefore, the distances between the C and the intervals are

$$D[C, INT(A)] = \frac{D(C, A) + D(C, X) - D(A, X)}{2} = \frac{4 + 3 - 1}{2} = 3$$

$$D[C, INT(B)] = \frac{D(C, B) + D(C, X) - D(B, X)}{2} = \frac{3 + 3 - 2}{2} = 2$$

$$D[C, INT(X)] = \frac{D(C, X) + D(C, outgroup) - D(A, outgroup)}{2} = \frac{3 + 4 - 1}{2} = 3$$

Since the difference between C and INT(B) has the smallest value, another hypothetical ancestor (Y) is constructed and C is connected to the tree through this new ancestor to INT(B) as shown in Figure 6-7
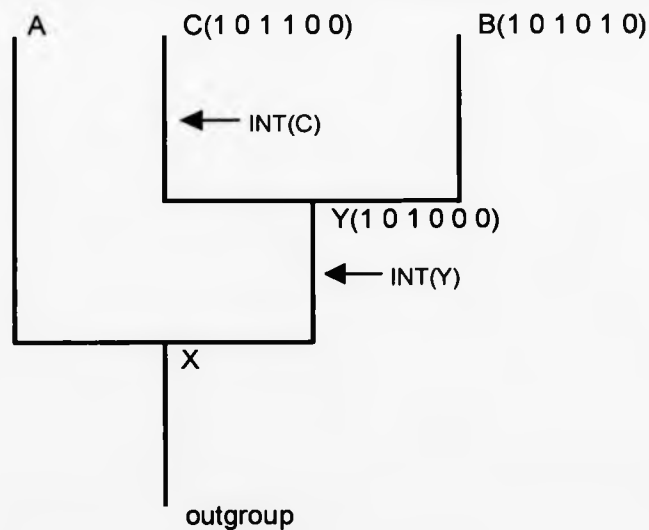
Figure 6-7 Complete tree with two hypothetical ancestors

To calculate the characteristic vector for this new ancestor the median of the vectors of the three appropriate taxa, X, B, and C, have to be used as shown in Table 6-4

Table 6-4 Data matrix with a second hypothetical ancestor (Y)

Taxon	Characteristics					
X	1	0	0	0	0	0
B	1	0	1	0	1	0
C	1	0	1	1	0	1
Y(median)	1	0	1	0	0	0

The construction of the tree is now complete

6.2.7.5.2. Cladistics software

Although the above section provides useful instructions on the manual construction
of a cladogram, the sets of characteristic data used in chapters 7 and 8 are too
complex to be manipulated manually, and thus, computer software has to be used
Two software packages were used for constructing the cladistic classifications in this
research. These are called Phylip and Paup (a third software package called MacClade
is also used to select the optimal cladogram as is explained in the next section). When
constructing cladistic classifications with complex data sets (many taxa and
characteristics) numerous possible cladograms may be constructed (Wiley et al.
1991). As it is explained in the next section several indices exist that aid the cladist to
select the best tree by assessing on which proposed tree the characteristics and taxa fit
better. The advantage of using two software packages is that more cladograms are
developed and therefore it is more probable to find a better cladogram i.e a
cladogram where the taxa and their characteristics fit better.

6.2.7.6. Selecting the optimal cladogram

The final step of the construction of the cladogram involves the selection of the
optimal cladogram. The methodology outlined above may result in multiple
cladograms. This is because given a data matrix the taxa and their characteristics may

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be resolved to produce more than one cladogram in more than one ways. This occurrence is more frequent in situations where the number of taxa and characteristics is large. Consequently, a best tree according to certain criteria is selected. When there are alternative solutions, i.e. multiple cladograms, then the simplest or *most parsimonious* cladogram is chosen (Kitching et al., 1996). The most parsimonious cladogram is referred to as the optimal cladogram and the other cladograms are considered suboptimal. The most parsimonious cladogram is the one where the characteristics and their states arise the least number of times (Kitching at al., 1996). To identify the most parsimonious tree from a technical perspective three descriptive statistics or indices have been developed. These are treelength, consistency index, and retention index. In situations where the number of taxa and characteristics is large it is more practical to use computer software to carry out the calculations of these indices. The software package that is proposed is for this purpose called MacClade (Maddison and Maddison, 1992).

The following paragraphs discuss the descriptive indices used to select the optimal cladogram.

6.2.7.6.1. Tree length

The length of the tree is the total number of characteristic state changes necessary to support the relationship of the configuration of a cladogram. If the state of a characteristic changes more than once on the cladogram then that characteristic may specify overlapping groups and is thus inconsistent. Thus the tree with the minimum length is considered to have less characteristics that specify different and overlapping groups of taxa from other characteristics i.e. there are less inconsistencies in the

selection of groups and thus is the optimal tree (for more information on the calculation of the tree length see Kitching et al., 1998 pp. 92-95).

6.2.7.6.2. Consistency Index

The second descriptive statistic of a cladogram is the consistency index (CI). This assesses the level of difficulty in fitting a given data set to a given tree. The CI serves as a measure of the discordance of the characteristics with a particular cladogram. The consistency index is calculated using the following formula:

$$CI = \frac{M}{S}$$

Where:

- M is the total number of characteristic state changes expected given the data set. In this research each characteristic will have up to two states. It can be either absent (0) or present (1). Therefore, the total number of changes each characteristic could take is one (from absent to present or else from 0 to 1). Thus the value M of the cladogram will equal the number of characteristics of the data set.

- S is the actual number of characteristic changes that occur in the tree.

The best possible fit of a data set on a cladogram will be one where each characteristic arises only once on the cladogram. In such a case M and S would be equal and therefore the consistency index equals 1. In situations where the data matrices are composed of real and complex data (which, as will be shown in chapters 7 and 8, is the case in this thesis) it is likely that the characteristics will appear more than once on a cladogram. Hence, the consistency index will be less than one, which suggests that the data are not 100% consistent with a cladogram.

For more information on the calculation of the consistency index see Kitching et al., 1998 p. 95 or Wiley et al. pp. 72-78).

6.2.7.6.3. Retention index

The last descriptive statistic of a cladogram is the retention index (RI). In contrast to the consistency index that measures discordance of the data set to the cladogram, the retention index is a measure of fit of the data set on a cladogram. The retention index is calculated using the following formula:

$$RI = \frac{(G - S)}{(G - M)}$$

Where:

- G is the greatest number of steps characteristics can have on any cladogram

- M is the total number of changes expected given the data set and

- S is the actual number of changes that occur in the tree

Similar to the consistency index, the best possible fit of a data set to a cladogram will be when the retention index is equal to 1. The main benefit in using the retention index over the consistency index is that the value of the latter will decrease when the number of taxa increases irrespective of any change in data content i.e. irrespective of the fit of the data set. As will be shown in chapter 8 the number of taxa used for the development of the cladogram of drug discovery strategies is large and thus it is more valuable to use the retention index for the selection and evaluation of the cladograms.

For more information on the calculation of the retention index see Kitching et al., 1998 pp. 97-99.

6.2.8. Using cladistics for this research

This chapter introduces cladistics as a methodology for processing and presenting data to validate the four hypotheses developed in chapter 5. This particular section reviews the decision to use cladistics by considering the nature of the four hypotheses and the theoretical assumptions adopted by this research.

In chapter 4 it was argued that the classifications presented (e.g. Mintzberg and Waters, 1998, Whittington, 1993) do not allow comparison of organisational and more specifically drug discovery strategies, because they are not related to specific organisations. Also it was argued that a drug discovery strategy is a pattern of behaviour that changes over time and this change is influenced by knowledge, technology, organisation, and environment. As explained earlier in this chapter, cladistics classifies using phylogenetic relationships between entities, while considers observable characteristics. Therefore, a cladistic classification could provide a classification of drug discovery strategies where the phylogenetic relationships of the strategies are established by considering the four factors, knowledge, technology, organisation (observable characteristics), and the environment of specific organisations.

As explained in chapter 2 a business history methodology (Hendry, 1992) will be used to combine the benefits of longitudinal analysis and case study research. In line with this approach it is proposed that two cladograms be constructed to achieve this aim. The unit of analysis of both cladograms will be drug discovery strategies i.e. patterns of behaviour defined or adapted by the management of pharmaceutical organisations. The first will use historical secondary data derived from existing case studies and research programmes (e.g. Liebanau, 1987, Jones, 2001, Weatherall, 1990, Mann, 1999) to classify types of drug discovery strategies i.e. classes of

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strategies that share a common profile along conceptually distinct characteristics. The drug discovery strategy types classified by this cladogram should correspond to drug discovery strategies adopted by one or more organisations i.e. each taxon shown on the cladogram should represent a population or cluster (Mintzberg, 1998) of organisations. Due to the nature of the taxa of this cladogram it will be referred to as the *population cladogram*.

The second cladogram will use data collected from pharmaceutical organisations to classify drug discovery strategies of individual organisations. The difference between this and the population cladogram will be that the taxa on the branches of the former will be drug discovery strategy types while that of the latter will be organisational strategies. Therefore, the population cladogram will classify drug discovery strategies at a higher level than that of the organisation cladogram. The two levels of analysis (population and organisation) are illustrated in Figure 6-8. Due to the nature of the taxa of this cladogram it will be referred to as the *organisation cladogram*.
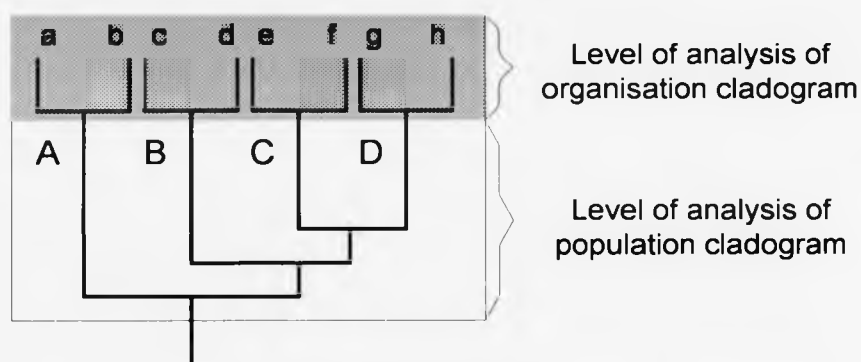
Key:
Uppercase letters: Drug discovery
strategy types
Lowercase letters: Drug discovery
strategies of individual
organisations

Figure 6-8 Levels of analysis of cladograms

This approach has two benefits. Firstly, the construction of the population cladogram provides a test bed for the validation of the hypotheses. It is anticipated that the construction of the population cladogram will be relatively more straightforward than that of the organisation. This is because the data used is derived from literature which has already been processed and aggregated and is therefore more robust and consistent. Thus, the population cladogram will assess and demonstrate how cladistics might help to reveal how an evolutionary and classification approach can be used to study drug discovery strategies, as per the third research question. Secondly, the construction of the population cladogram will provide a provisional list of types of drug discovery strategies and characteristics that will aid the collection of data when constructing the organisation cladogram.

In summary, the construction of the population cladogram will provide the following:

- A list of drug discovery strategy types and characteristics

- A provisional classification of these types

- A framework for assessing and demonstrating the four hypotheses might be validated.

The source of the data that will be used to construct the organisation cladogram is derived directly from the pharmaceutical industry. The entities that will be classified in this case will be drug discovery strategies of individual organisations.

The construction of the organisation cladogram has the following aims:

- *Validate the types of drug discovery strategies classified by the population cladogram:* this will be achieved by identifying groups of pharmaceutical organisations that implement drug discovery strategies similar to the ones classified by the population cladogram. Therefore, the taxa classified by the population cladogram should be the populations of the taxa classified by the organisation cladogram. That is, the drug discovery strategy types classified by the population cladogram will correspond to a number of organisations that have adopted these strategies.

- *Validate the four hypotheses:* the resulting classification should identify groups of organisational strategies. The investigation of these groups should help validate the four hypotheses. For instance, the formation of groups of strategies, which are characterised by the implementation of modern technologies, could denote the selection of technology dominated strategies.

- *Identify the most dominant characteristics i.e. find the configuration of the fittest strategy.* The fourth research question (What are the characteristics of the fittest drug discovery strategies?) requires the identification of the characteristics of the

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fittest strategies. It is anticipated that a selection of characteristics will be more decisive than others i.e. certain characteristics will have a stronger influence on the classification than others. These characteristics will be identified by observing the various cladograms constructed in step 5 of the construction of the cladogram. Therefore, these characteristics will be those that constitute the fittest strategies.

6.3. Conclusions

This chapter set out to explain and justify the use of the cladistic classification methodology in this research. It explained how the four hypotheses developed in chapter 5 could be supported or rejected using a classification. It then presented the key classifications used in biology and justifed cladistics as an appropriate methodology for this research. The chapter then described the methodology for constructing a cladistics classification (a cladogram). Finally, the chapter explained how this methodology will be used in the chapters 7 and 8 to construct a population and organisation cladogram that will address the third and fourth research questions.

7. CONSTRUCTION OF POPULATION CLADOGRAM

7.1. *Introduction*

To address the third research question (*How can an evolutionary and classification approach be used to study drug discovery strategies?*) chapter 5 developed four hypotheses. In chapter 6 it was argued and proposed that to validate these hypotheses two cladistic classifications should be constructed. The unit of analysis of both cladograms will be drug discovery strategies as defined in chapter 4. The first (population cladogram) would use data from available historical secondary sources to identify and classify types or forms of drug discovery strategies. The second (organisation cladogram) would use data from the pharmaceutical industry to identify and classify drug discovery strategies found in individual organisations. As argued in chapter 6 the benefits of this approach are that the population cladogram will provide a test bed for the validation of the hypotheses and that its construction will provide a provisional list and classification that will help the collection of data for the construction of the organisation cladogram. Furthermore, chapter 6 explained the process for constructing a cladistic classification.

The aim of this chapter is to explain the process followed to construct the population cladogram. Also, the chapter will present and analyse the cladogram. Accordingly, the structure of the chapter is based on the process followed to construct a cladogram as explained in chapter 6.

Therefore, the objectives of this chapter are to provide:

- A list of drug discovery strategy types and defining characteristics

- A provisional classification of these types

- A platform for demonstrating how the four hypotheses can be validated

7.2. Step 1: Select the clade

The definition of the clade establishes the boundaries of the group that will be analysed. Hence, this step involves the definition of the study area of interest i.e. drug discovery strategy types. In chapter 6 a drug discovery strategy type was described as a class of strategies that share a common profile along conceptually distinct characteristics. The concept of and a working definition for drug discovery strategy was presented in chapter 4 of this thesis as *'the pattern of behaviour defined or adapted by the management of a pharmaceutical organisation, within a certain environment, to effectively materialise the corporation's goals and policies in order to achieve a competitive advantage through the application of knowledge and technology on the discovery of new drugs'*. Consequently, the clade consists of types of strategies that fall under this definition. As argued in chapter 6 the taxa of this cladogram should correspond to drug discovery strategies adopted by one or more organisations i.e. each taxon shown on the cladogram should represent a population or cluster of organisations. For this reason, this cladogram will be referred to as the *population cladogram*.

7.3. Step 2: Data collection

The second step of the cladistic classification involves collecting data that will establish the relationships between populations of drug discovery strategy types. The source of the data used for the construction of the population cladogram is historical literature i.e. literature that reports the steps that people have taken to understand how diseases occur and how medicine, vaccines, dietary materials, anaesthetics, antiseptics, and other medical materials came to be invented and used (Weatherall,

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1990). The process that was followed to collect the characteristics and identify the drug discovery strategy types is shown in Figure 7-1.
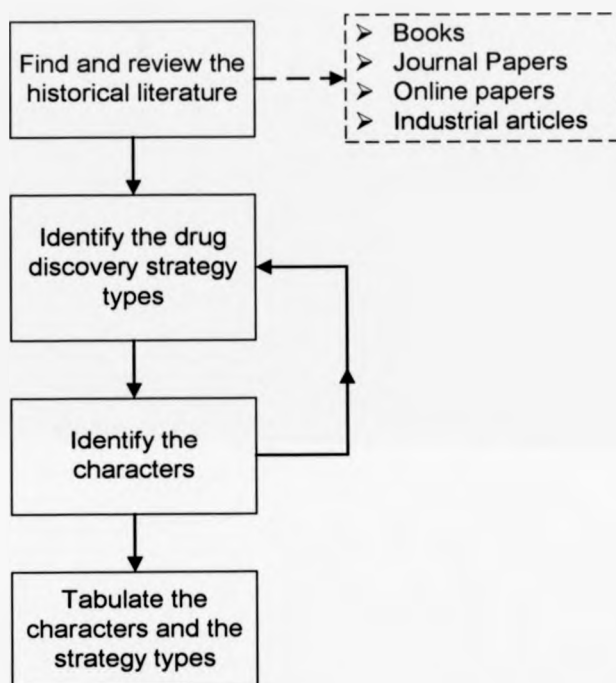
Figure 7-1 Process followed to determine the characteristics of population cladogram

The first step consists of the collection and review of the literature that reports the history of drug discovery. The literature used is listed in Table 7-1.

Table 7-1 Sources used for the construction of the population cladogram

	Reference
A	Danheiser, S, 1997, Laboratory automation and robotics to play a major role in the drug discovery process, *Genetic engineering news*, Issue 10
A	Schneider, I., 1999, Robotic Systems: Adding speed and flexibility to the drug discovery process, *Genetic engineering news*, Issue 15
B	Bogner, W., Thomas, H., 1996, *Drugs to market: creating value and advantage in the pharmaceutical industry*, Pergamon, NY
B	Davenport-Hines, R.P.T., Slinn, J., 1992, *Glaxo: A History to 1962*, Cambridge University Press, Cambridge
B	Gambardella, A, 1995, *Science and innovation the US pharmaceutical industry during the 1980s*, Cambridge University press, Great Britain
B	Liebenau, J., 1987, *Medical science and medical industry*, The John Hopkins university press, Hong Kong
B	Loftus, P., Waldman, M., Hout, R., 1987, Computer-based approaches to drug design, *Drug discovery and development*, (eds) Williams, M., Malick, J.B., pp. 37-96
B	Mann, J., 1999, *The elusive magic bullet: the search for the perfect drug*, Oxford university press, Oxford
B	McKelvey, MD., 1996, *Evolutionary innovations: the business of biotechnology*, Oxford university press, New York
B	Weatherall, M., 1990, In search of a cure: A history of pharmaceutical discovery, Oxford University Press, New York
OP	Cardinal, F, 2002, Abe Lincoln's "Blue Mass" Pills: Was Lincoln a Victim of Mercury Poisoning?, *Sleep disorders*, http://sleepdisorders.about.com/library/weekly/aa072301a.htm
P	Anderson, R.J., 1996, Managing the overall portfolio for Successful Discovery and development, Welling, P.G., Lasagna, L., Banaker, UV, (eds) chapter 4, pp. 79-115
P	Baba, Y., 2001, Development of novel medicine based on genome science, *European journal of pharmaceutical sciences*, Vol. 13, pp 3-47
P	Bellott, E., M., Bondaryk, R., Luther, A.L., 1997, Combinatorial chemistry in the drug discovery process, *Clinical research and regulatory affairs*, Vol. 14, Nos. 3&4, pp. 231-241
P	Deeds, D.L., DeCarolis, D., Coombs, J.E., 1997, The impact of firm-specific capabilities on the amount of capital raised in an initial public offering: evidence from the biotechnology industry, *Journal of business venturing*, Vol. 12, pp. 31-46
P	Frey, R., Lesney, M. S., 2000, Anodynes and Estrogens: The pharmaceutical decade, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society*, pp. 92-109
P	Koehler, C. S. W., 2000, Aids, Arteries and Engineering: Epidemics and Entrepreneurs, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society*, pp. 130-147
P	Lesney, M. S., Frey, R., 2000, Chemistry, Cancer and Ecology: Environments of health, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society*, pp. 110-129
P	Lesney, M. S., Miller, J. B., 2000, Harnessing Genes, Recasting Flesh: Closing the pharmaceutical century, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society*, pp. 148-167
P	Lesney, M., 2000, Patents and Potions: Entering the Pharmaceutical Century, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society*, pp. 18-31

Table 7-1 Sources used for the construction of the population cladogram (continued from page 195)

P   Matraves, C., 1999, Market structure, R&D and advertising in the pharmaceutical industry, *The journal of industrial economics*, Vol. XLVII, No.2 pp.169-194

P   Miller, J. B., 2000, Antibiotics and Isotopes: Swigtime, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society*, pp. 52-72

P   O'Reilly, B., 2001, There's still gold in them thar pills, *Fortune*, Vol. 144, No. 2, pp 78-85

P   Pizzi, R., 2000, Salving with Science: The Roaring twenties and the Great Depression, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society*, pp. 34-51

P   Somberg, J. C., 1996, The Evolving Drug Discovery Process, *The Drug Discovery Process: Increasing Efficiency and Cost Effectiveness*, eds. Welling, P. G., Lasagna, L., Banakar, U. V., Marcel Dekker, New York

P   Tweedy, B. D., Lesney, M. S., 2000, Prescriptions and Polio: Postwar progress, *The Pharmaceutical Century: Ten decades of Drug Discovery Supplement to American Chemical Society*, pp. 72-91

P   U'Prichard, D.C., Pullan, L.M., 1997, The future of drug industry research and the Zeneca response, *Corporate strategy*, November-December, pp. 35-39

P   Williams, M., Giordano, T., Elder, R.A., Reiser, H.J., Neil, G.L., 1993, Biotechnology in the drug discovery process: strategic and management issues, *Medicinal research reviews*, Vol. 13, No. 4, pp. 399-448

Key:
A: Industrial article
B: Book
OP: online publication
P: journal paper

The historical literature used for the construction of the population cladogram and listed in Table 7-1 constitutes secondary data i.e. data that already exists (Hussey and Hussey, 1997). The benefit of using secondary data is that it is published in a form that is easily accessible. Also, there is a huge saving in resources, in particular, time and expenditure. The drawbacks with the use of such data are related to the control of the researcher on the data. Secondary data is collected using a process that a researcher has no control over. This is because the form and the content of secondary data are shaped by the original institute/owner/researchers that gathered the data. This feature can limit the overall scientific value of the secondary data. However,

secondary data can also provide data that might otherwise have been impossible to gather. Such is the case with the construction of the population cladogram. The construction of the organisation cladogram requires data that dates early in the pharmaceutical history and is therefore difficult to collect.

Zikmund (2000) presents a series of questions that should be asked when evaluating secondary data as shown in Figure 7-2. By following this evaluation the data listed in Table 7-1 was considered to be appropriate for the objectives of this research.

As will be explained in the next section, the history of drug discovery starts from very early in human history. However, it is only since the late 1800s when the developments in drug discovery have led to the establishment of the modern pharmaceutical industry. The second and third steps of the data collection involve the identification of the drug discovery strategy types and their characteristics. The final step involves the tabulation of the findings from the previous steps. The table that includes the drug discovery strategy types and the characteristics is Table 7-2 on page 218.

7.3.1. History of drug discovery strategies

The first step in determining the drug discovery strategy types and their characteristics, involves the identification and review of the relevant historical drug discovery literature. Based on the literature sources listed in Table 7-1 the following paragraphs provide a description of the history of drug discovery from the *age of botanicals* (1800s) up to today. This description is structured in chronological order. The account of each period concludes with a discussion of each strategy that dominated that period.
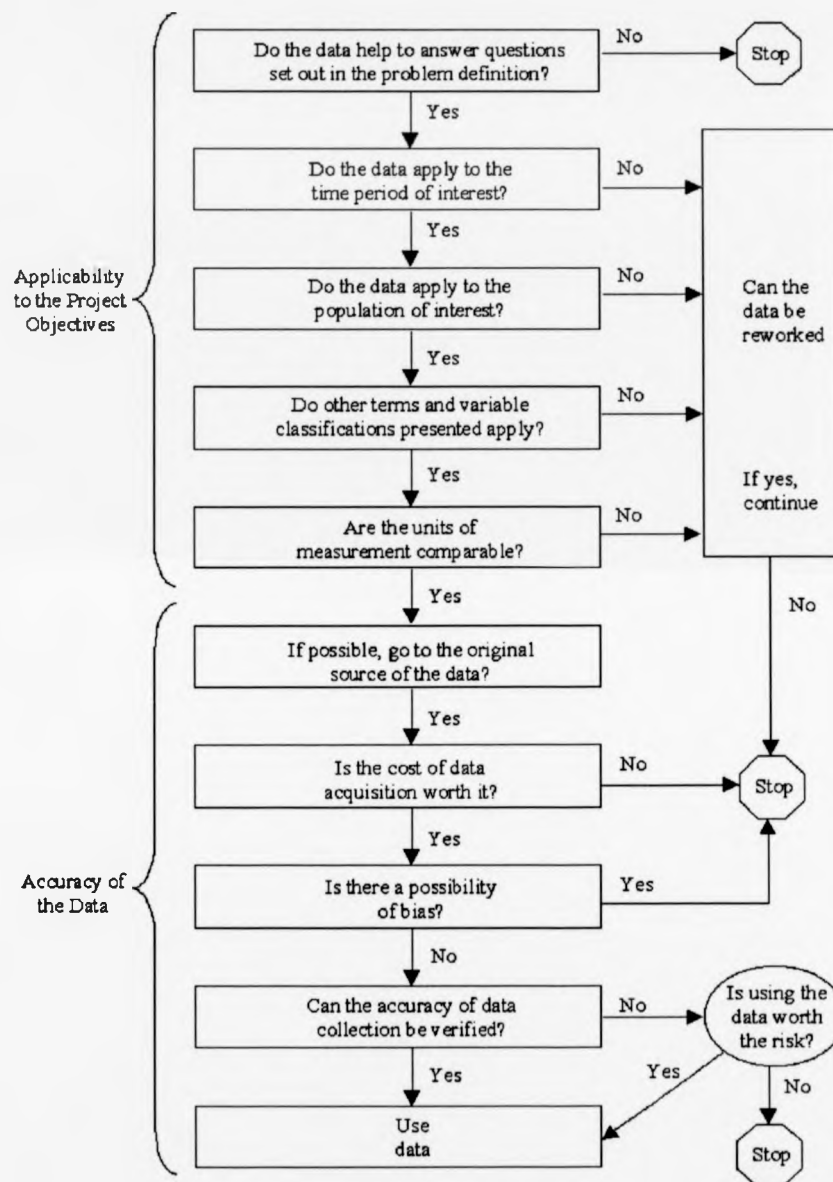
Figure 7-2 Evaluating Secondary Data (from Zikmund 2000 p. 127)

Chapter 4 presented and justified four factors that influence the configuration of drug discovery strategies. These are knowledge, technology, organisation, and

environment. As it will be shown in the description of the history of drug discovery these factors have played a significant role in the evolution of drug discovery. In the next section (7.3.2) a table (Table 7-2) is presented that presents the drug discovery strategy types and their characteristics arranged according to these four factors.

7.3.1.1. The Pre 1800s

The pharmaceutical era prior to the 1800s is called 'The age of botanicals' (Somberg, 1996). Reports exist that prove that man has been making use of herbals from very early in human history. These could be used for foods, items of religious significance and also as medication. The Bible as well as early folklore relate stories of use of medicinal plants and herbs. Also, ancient Greek and Egyptian proofs of pharmacopoeia have been found which include compounding and dosage requirements for various illnesses (Bogner and Thomas, 1996). For instance, the *Ebers Papyrus* lists 811 prescriptions used in Egypt in 550bc (Henderson et al., 1999).

Treatments of illnesses early in human history were inseparable from religious and magical practices. More coherent approaches to treatments have been found in the ancient Greece where Hippocrates (born 460 bc) introduced a more rational outlook basing his practice on observation and experience (Weatherall, 1990). In the following centuries, many medicinal plants were discovered or recognised in the civilisations, which existed round the Mediterranean. In the centuries that followed the decline of the Roman Empire, the study of medicine stagnated under the weight of authority and tradition (Weatherall, 1990). The Arabic speaking world and China also developed medicine independently.

In the 17th and 18th century medical treatment of diseases was based on reasoning. However, such logic started from the dogmas of the time, which had little basis in fact

(Weatherall, 1990). For instance, the yellow colour of saffron showed that it was good for jaundice, the red colour of rust or wine showed that it was good for bloodlessness or anaemia, and the leaves of the plant lungwort, which had some resemblance to the appearance of the lungs, showed that the plant was good for lung disease (Weatherall, 1990). Therefore, any discoveries made during this period were random while there was no scientific justification.

Although the 'age of botanicals' and its unorthodox approach to drug discovery is now long gone, it provided the modern drug discovery era with a significant body of knowledge that led mainly to understanding the biological activity of certain substances found in nature. Even during the 20th century herbals were used during the botanical age were being investigated for their biological activities (Somberg, 1996).

7.3.1.2. The 1800s to 1910s

Early in the 19th century diseases were identified according to the symptom they produced. Therefore, the road to health was to attack the symptom as vigorously as possible (Lesney, 2000). Fever was attacked by bloodletting (fever is hard to be sustained when there is no blood in the body), and stomach pains were attacked by violently cleaning the stomach from poisons (Lesney, 2000). Naturally, these approaches to curing diseases were not effective because attempting to cure people already weakened by a disease often meant that the cure had worse results than the disease itself. Reportedly, George Washington died from *bloodletting*, while Abraham Lincoln died from his constant doses of 'blue mass' (a medication common at that time for depression that was prescribed at a daily dose that contained over 9000 times the amount of mercury that is considered safe by today's standards) (Cardinal, 2002).

Later in the 19th century the patent remedies, usually used without a physician's guidance (Liebenau, 1987), became popular. Homeopaths who developed interesting theories, which related the medicine used to the exact symptoms displayed by the individual patient (Weatherall, 1990), were common. These non-effective, but harmless approaches to curing became the basis for a commodity based medicine industry that gave birth to the pharmaceutical industry. Among the drugs that were developed a few authentic ones were accidentally discovered like quinine, digitalis, and cocaine. These substances were a key part of the modern era of pharmaceuticals (Lesney, 2000).

A significant development in the discovery of new drugs during this decade was the synthesis of the first coal tar dye in 1856. This discovery led to the development of many synthetic dyes, but also to the realisation that some of these dyes had therapeutic effects (Lesney, 2000). Another significant discovery of this period was the microbial theory of disease i.e. the idea that infectious diseases were caused by microscopic living agents. Although initially this theory was not widely accepted (Lesney, 2000), it provided an understanding of the causes and the potential cures for several diseases. The most significant outgrowth of the microbial theory, and one that created the greatest demand for new technologies, was the identification and production of vaccines (a safe source of active immunity) and antitoxins (antibodies isolated against disease organisms and their toxins from treated animals) (Lesney, 2000).

Close to the end of the century two synthesised drugs remarked the birth of the new era, aspirin in 1853 and antipyrine in 1883 (Weatherall, 1990). These two drugs together with the knowledge that was developed about vaccines and microbial pathogens set the scene for the following decades of pharmaceutical development

Another significant development that took place during the last third of the 19th century was the gradual establishment of clinical tests. Horatio C. Wood a physician from Philadelphia was one of the first physicians that conducted experiments to establish the clinical effects of various drugs (Liebenau, 1987). This practice was further enhanced by the development of new technologies such as bacterial cultures, chemical analysis, and clinical thermometers (Lesney, 2000).

One important development that occurred during the final decade of the 19th century is related to the change of the organisational structure of the pharmaceutical century. Up to then the typical structure of the pharmaceutical organisations consisted of direct family control where the efforts of individual scientists resulted in unplanned discoveries. In the course of the decade this changed dramatically with the development of physical departmentalisation and managerial hierarchies (Liebenau, 1987). This development followed the acceptance by the physicians that the drugs produced by pharmaceutical organisations were generally of better quality and more standardised to those produced by individual pharmacists (Liebenau, 1987).

Finally, during the first decade of the twentieth century the American government involved itself in the pharmaceutical industry for the first time. The form of its involvement was the 1902 and 1906 Acts for regulating drug production (Liebenau, 1987). The 1902 Act aimed at controlling the sale and production of biological products and to regulate the sale of viruses, serums, toxins and analogous products. The 1906 Act aimed mainly at controlling the adulteration of food rather than the regulation of drugs (Liebenau, 1987).

The main characteristics and contributions of the 19th century are the microbial theory of disease, the breakthroughs in organic chemistry and biochemistry and the development of new technology. The development of optics together with the

Another significant development that took place during the last third of the 19th century was the gradual establishment of clinical tests. Horatio C. Wood a physician from Philadelphia was one of the first physicians that conducted experiments to establish the clinical effects of various drugs (Liebenau, 1987). This practice was further enhanced by the development of new technologies such as bacterial cultures, chemical analysis, and clinical thermometers (Lesney, 2000).

One important development that occurred during the final decade of the 19th century is related to the change of the organisational structure of the pharmaceutical century. Up to then the typical structure of the pharmaceutical organisations consisted of direct family control where the efforts of individual scientists resulted in unplanned discoveries. In the course of the decade this changed dramatically with the development of physical departmentalisation and managerial hierarchies (Liebenau, 1987). This development followed the acceptance by the physicians that the drugs produced by pharmaceutical organisations were generally of better quality and more standardised to those produced by individual pharmacists (Liebenau, 1987).

Finally, during the first decade of the twentieth century the American government involved itself in the pharmaceutical industry for the first time. The form of its involvement was the 1902 and 1906 Acts for regulating drug production (Liebenau, 1987). The 1902 Act aimed at controlling the sale and production of biological products and to regulate the sale of viruses, serums, toxins and analogous products. The 1906 Act aimed mainly at controlling the adulteration of food rather than the regulation of drugs (Liebenau, 1987).

The main characteristics and contributions of the 19th century are the microbial theory of disease, the breakthroughs in organic chemistry and biochemistry and the development of new technology. The development of optics together with the

development of technologies such as sterilisation, media and methods for growing and staining microbes, X-Ray crystallography, chemical extraction, and the invention of the rotary tablet dominated the growth of the new medical science. Also the industrial revolution provided both the technical capability to respond to the technological challenges, but also a source of public hope for the decades to come.

7.3.1.3. The 1920s and 1930s

The key milestones of these two decades were the discovery of vitamins and the advances in chemistry (Pizzi, 2000). Although the discovery of the vitamins (a vital part of nutritional therapy) was made in 1912 by Casimir Funk (Davenport-Hines and Slinn, 1992) it was not until 1924 that the pharmaceutical organisation *Glaxo* marketed the vitamin extracts by developing vitamin D. Also, many new vaccines and drugs were discovered, most notable of which was penicillin that was accidentally discovered by Alexander Fleming in 1928.

Although this period was characterised by chemists trying to find chemical solutions to the diseases that plagued humankind one of the greater pharmaceutical discoveries of this period did not cure an infectious disease, but the physiological disorder *diabetes mellitus.* This disease is caused by a malfunction of the pancreas and nearly always resulted in death. In 1921 Frederick Banting, a Canadian physician, using the pancreas of a living dog managed to isolate an extract later called insulin and consequently created the first effective treatment of diabetes (Weatherall, 1990). However, insulin was not available until the *pharmaceutical organisation's Eli Lilly* technical development enabled its large-scale production in a state suitable for clinical use.

Infectious diseases however, were still responsible for the highest number of deaths in the 1920s and 1930s. Paul Ehrlich introduced the world to chemotherapy and successfully managed to treat syphilis (Mann, 1999). What was needed however was a drug that would fight pneumonia and septicaemia. In the 1920s bacteriologists started experimenting with dyes that were used to stain bacteria and by the 1930s achieved a breakthrough. This involved injecting an orange-red azo dye called Prontosil. Using this technique Gerhard Farben managed to cure a group of mice infected with streptococcus. This discovery gave birth to a new series of drugs called *sulfa* drugs, which after further development had the ability to stop the growth and multiplication of the bacteria.

Assisting the quest to discover drugs was progress in the area of scientific instrumentation that transformed R&D. The need to invent novel ways of developing new drugs brought for the first time together people from diverse disciplines into teams. Physical chemists and physicists collaborated with biochemists and biologists and instruments were invented such as the electron microscope (1931), the ultracentrifuge (1924), and the pH meter with a glass electrode (1921) (Pizzi, 2000)

Apart from drug discoveries, the main characteristic and contribution of this era was the interdisciplinary thinking that led to the development of new instruments and ultimately the creation of institutions for the regulation of drug discovery such as the USA's Food and Drug Administration (FDA) established in 1927. For the first time knowledge acquired in physics and chemistry was combined to advance the field of pharmaceutical science.

7.3.1.4. The 1940s

This era is more commonly known as the 'antibiotic era'. As defined by Selman Waksman in 1941, an antibiotic is a *chemical substance, produced by a microorganism which has the capacity to inhibit the growth and even destroy other microorganisms* (Mann, 1999, p. 37). During this period drugs started to be discovered in a less serendipitous fashion. Researchers began searching for specific drugs in response to a market need. This resulted in the discovery of numerous drugs, targeting various diseases. For instance, penicillin was developed into an antibiotic for fighting staphylococcal and streptococcal infections, quinine-a complex molecular structure and chloroquine were developed to cure malaria, vitamin B_{12} was developed to help cure pernicious anaemia (the name was inspired by the remorseless progress to a fatal outcome) (Weatherall, 1990).

World War II also played a very important role in the development of the pharmaceuticals. For example, the development and production of penicillin was accelerated by the need to cure infected soldiers. Also, new technology promoted by the war made the production of radioisotopes easy and these were then used for health research. Similarly, the need to fight malaria drove research towards the synthesis of quinine, which was achieved in 1994 when it was synthesised from coal tar

As a consequence of the cruel and inhuman experiments to the Jewish population by the Nazis during the Second World War, the Nuremberg Code was established in 1949. This code requires that individuals enrolled in clinical research give voluntary consent. It also requires that research is undertaken for benefit of the society, must be performed by scientifically qualified persons, and be derived from research on animals that will suggest that anticipated outcome would justify human clinical experiments. By the end of the World War II the technology that was used was

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becoming routinely available for health research as computer aided drug discovery was introduced (Miller, 2000). In the UK the National Health Service, established in 1946 by the labour government, stimulated the industry's development (Davenport-Hines and Slinn, 1992 p. 167).

Another major breakthrough of the 1940s was the design and synthesis of antimetabolites that could destroy cancer cells. In 1948, George Hitchings and Gertrude Elion synthesised and demonstrated the anticancer activity of 2,6 diaminopurine. This development constitutes the foundations of *rational drug design*. (Matraves, 1999, Bogner and Thomas 1996)

In summary, the main characteristics and contribution of this period to the advancement of drug discovery include evidence of a shift from serendipitous research motivated primarily by the academic and intellectual freedom to a less risky more disease focused one. Also World War II and the wartime need for antibiotics marked the industry's transition to an R&D intensive business (Henderson et al., 1999). Finally, the development of numerous antibiotics and their availability created a public expectation of health through drugs and medical intervention. Because of this expectation and the new possibilities, health became a political issue that led the way in the next decade.

7.3.1.5. The 1950s

Following the end of World War II, drug discovery in the 1950s became highly influenced by other world events such as the Cold War, the Korean Conflict, the launch of the first orbital satellite in 1957, mass consumerism, etc. Technologies previously used for pure scientific reasons or for war were now used for civilian life e.g. silicone products, microwave ovens, radar, plastics, computing devices etc. In the

USA a science and technology policy coupled with an anti-Soviet sentiment resulted in large sums of public money being allocated for the discovery and development of new drugs.

Improved mechanisation streamlined production in drug factories and the DNA *(Deoxyribose Nucleic Acid)* era was being born. Understanding of how the human body worked and the progress in computational power helped the development of new technology. The new technology and the understanding of DNA's structure created new windows of opportunity for the development of new drugs. These breakthroughs led to the development of biotechnology. Biotechnology in a scientific sense may be viewed as the application of recombinant DNA technology to create new processes and products (Williams et al., 1993).

The main characteristics and contributions of this decade were the vast amount of knowledge discovered on human biology and chemistry as well as the development of instrumentation.

7.3.1.6. The 1960s

The 1960s was the pharmaceutical decade of the century (Frey and Lesney 2000) when consumers became conscious about drugs in all aspects of their lives and led to the pill taking culture. There were pills for life, leisure, and for love. Prominent drugs for this decade include the pill for birth control, and Valium and Librium for soothing nerves. In terms of drug discovery, technological innovations led to its proliferation. New forms of chromatherapy became available, including HPLC (High Performance Liquid Chromatography), capillary GC (Gas Chromatography), GC/MS (Gas Chromatography to Mass Spectrometry) and the rapid expansion of thin-layer chromatography techniques. By the end of the decade amino acid analysers were

widely used and the centrifuge had become fully developed and integrated to biomedical sciences. Also, analytical chemists and biologists collaborated as never before in the search for new drugs. New technologies were developed, while instruments that were previously designed were adapted to biomedical applications. During this decade the development of new drugs was enhanced by new instrumentation, but also with the introduction of powerful computers that made laboratory automation a new trend.

One of the key developments in drug discovery that would mark the years to follow was the wider understanding of the structure of DNA and the acceptance that it was indeed genetic material (Frey and Lesney, 2000). During this decade the technology necessary for the development of biotechnology in the following decade also proliferated. For instance, in 1964 a simplified technique for protein and nucleic acid synthesis which was the basis for the first such machines, and in 1967 the first specific gene transfer was accomplished.

Finally, breakthroughs in aetiology (the branch of medicine that deals with the causes or origins of disease) strengthened the understanding of diseases and they helped in the development of more science driven strategies for the discoveries of new drugs.

7.3.1.7. The 1970s

During this decade the war against cancer began and the first biotechnology organisation was founded. Treatments for various cancers appeared and chemotherapy joined the ranks of other routine treatments. New drugs that reached the market included cyclosporin used for preventing rejection of organs transplants, rifampicin used for treating tuberculosis, and cimetidine used for treating peptic

ulcers. An important discovery made during the early 1970s was that of reverse transcriptise which in the following decades became critical for the study of AIDS

Computational technology became further integrated with the life sciences and genetic engineering emerged. Genetic engineering allowed scientists to combine bits of DNA. In 1975 two different methods were developed that would allow DNA sequencing i.e. the sequence of bases of DNA with relative ease and efficiency.

In 1976 Genentech (short for genetic engineering technology), the first dedicated biotechnology organisation, was founded by Herbert Boyer, a faculty member of the University of California, San Francisco and the venture capitalist Robert Swanson (McKelvey, 1996). This marked the birth of the biotechnology industry, which saw several entrepreneurs starting new organisations in an effort to capitalise on the new technology.

The 1970s also saw the dawning of a rapid development in information technology as computers started becoming faster, the first microprocessor was invented and Microsoft was founded. The coupling of life sciences with computers was marked by the development of the first microprocessor controlled HPLC by Hewlett-Packard.

The main contributions and characteristics of this decade were associated with the introduction of computing technology into mainstream research and the formation of the biotechnology industry as a new type of drug discovery business. During the 1970s knowledge and instrumentation were put in place that would lead to rational drug design in the 1980s and 1990s.

7.3.1.8.   The 1980s

In addition to further advances in new drug discoveries and application of computational technology, new diseases also appeared during this decade. The most

significant was AIDS (Acquired Immune Deficiency Syndrome). Initially detected as a sexually transmitted disease between homosexual men, AIDS destroys the body's own mechanisms for fighting off infection (Mann, 1999). Those affected by this syndrome die of a host of opportunistic infections such as rare viruses, fungal infection and cancers. The AIDS disease influenced the development of immunology i.e. the study of body resistance to infections (Koehler, 2000). Another phenomenon that triggered novel research was the rise of drug resistance. Diseases that were thought to have been eliminated in developed countries reappeared in the late 1980s, and showed a resistance to multiple drugs previously used for their elimination (Koehler, 2000).

In the area of drug discovery, the developments that marked this decade revolved around the application of computational technology to the design of new drugs and the strategic acquisition of small biotechnology organisations by larger pharmaceutical organisations. Molecular biology and the use of computers gave rise to a new approach to innovation. Before this decade the discovery of active compounds depended on a try and see empirical approach. From now on however, knowledge on body physiology and medical disorder coupled with knowledge on drugs would result in the conceptualisation of the right molecules. The result is ideal design specifications, which are presented to research chemists who search for a close match.

The increased use of computer modelling techniques was influenced by two major factors. The first of these was the availability of low cost, but powerful computer systems. This allowed researchers to perform fast and cost effective computations, which were previously only possible on large and expensive mainframe computer systems. The second factor was the availability of high speed, high resolution,

graphical display systems (Loftus et. al, 1987). The numeric and frequently complex input requirements of many theoretical chemistry programs had long been an obstacle to their acceptance by most chemists. By enabling researchers to build and manipulate chemical structures in a direct and simple manner and to transform the output of theoretical calculations into visual images, graphical display devices provided a powerful interface between the computer and the researcher. The ability to display theoretical results in a visual form, also provided a common means of communication between the fields of theoretical, physical, and synthetic chemistry, thus facilitating the development of effective multidisciplinary approaches to the area of drug design (Loftus et. al, 1987).

Other developments and uses of the computational technology included genetic algorithms and fuzzy logic (Koehler, 2000). Genetic algorithms allow drug designers to evolve a best fit to a target sequence through successive generations until a fit or solution is found (Koehler, 2000). Fuzzy logic formalises imprecise concepts by defining degrees of truth and falsehood. Fuzzy logic has proved useful in modelling pharmacological action, protein structure and receptors (Koehler, 2000).

This decade also saw further commercialisation of drug discovery. Small entrepreneurial biotechnology organisations were founded primarily as a business venture that sought to discover active compounds. However, by the mid 1980s many of these organisations were struggling for survival. Most biotechnology organisations were pursuing a very limited number of potential drug treatments compared to that of pharmaceutical organisations. Also, the industry was based on highly complex and specific knowledge that was still emerging, unlike the mature knowledge structure of traditional pharmaceutical organisations. Therefore, the future of biotechnology organisations was more uncertain than that of large pharmaceutical organisations with

large pipelines (Deeds et al., 1997). This led to their acquisition by big pharmaceutical firms. The acquisition of smaller biotechnology firms a strategy that is still in use by big organisations. It is considered to be beneficial for both the acquired and the acquiring organisations as it provides stable source of funding for the former and expertise in a potentially successful area for the latter.

Finally, another very significant step in the progress of discovery was made in the 1980s and that was the development of *combinatorial chemistry*. This is the simultaneous use of large sets of chemically similar agents to produce thousands of organic compounds, which are then screened for biological activity. One of the factors that led to the development of this technology was the rise of drug resistance, discussed earlier. Diseases that had learnt to resist drugs needed to be confronted with more powerful complex drugs (Bellott et al., 1997).

This decade contributed to the science of drug discovery by further integrating and adapting of computing technology into research, which has since completely changed the environment of pharmaceutical research. The biotechnology sector also flourished with numerous entrepreneurs establishing small dedicated drug discovery businesses across the globe, but most notably in areas such as San Francisco, Maryland, San Diego, Boston, Seattle and North Carolina.

7.3.1.9. 1990s-current

Following computational technology advances made in the 1970s and 1980s and their use in health sciences, the 1990s saw the development and application of robotics and automation to drug discovery (Schneider, 1999, 2000, Danheiser, 1997). Apart from these rapid advances in drug discovery technology, again primarily due to

the computational technology, this decade was also characterised by the reappearance of diseases previously treated.

Continuing the problems that were first observed in the 1980s, old and new diseases were increasingly resistant to the array of drugs fabricated against them. As the decade progressed the number of diseases resisting the treatment increased. Consequently, the researchers had to keep up with the race against bacterial resistance to traditional antibiotics. Bacteria that were previously treatable, but were now resistant include various streptococcal infections, strains of tuberculosis, pathogenic E. coli, and gonorrhoea.

Another front that the pharmaceutical industry had to fight was that of AIDS. Despite the advances in understanding its biology, technology still was unable to master the disease. The viral strains proved to be resistant to any drug or drug-cocktail thrown at them. The drugs available to date can only prolong the lives of patients, while the death rate in Western countries where the expensive drugs were available dropped precipitously (Lesney and Miller, 2000).

For drug discovery the main technological advances that enhanced the process during this decade were combinatorial chemistry, rational drug design, genomics, proteomics and pharmacogenomics. A short description of each of these technologies is provided in chapter 4. The combinatorial methods resulted in an increase in the number of potential drugs. This in turn created a bottleneck in the number of candidates that could be screened for biological activity. To conduct *high throughput screening* new processes and techniques were developed. Finally, *bioinformatics* was developed to achieve computerised storage and analysis of biological data.

During this decade the management aspect of drug discovery also developed. Large amounts of information and scientists from various disciplines had to be effectively managed to increase the efficiency of the drug discovery process and reduce its lead-time. This led to the division labour.

Also the pharmaceutical industry saw the *institunalisation* of mergers, and acquisitions, and the outsourcing of research to medium sized organisations (Lesney and Miller, 2000). This led to the development of large multinational organisations. Another factor that transformed the business during this decade was the Internet, which firstly facilitated the purchase of medicines, and secondly, it allowed to drug producers access to wider range of raw materials.

Another trend popularised during the 1990s was the competition to introduce generic drugs (Anderson, 1996) and the improvement of old drugs (Gambardella, 1995). This trend was the result of the increasing cost and difficulty of finding new blockbuster drugs (O'Reilly, 2001).

The main contributions and characteristics of this final decade of the century are associated with the rationalisation (i.e. more focused, targeted and business like) of the drug discovery process. Also, the biotechnology industry established itself as the discovery arm of the pharmaceutical industry (Baba, 2001). The competitive pressures and the direct link between the number of discoveries and the financial performance of organisations further enforced the quest to discover effective drugs. In addition, new technologies like combinatorial chemistry and high throughput screening helped to create libraries of compounds that would aid scientists with drug design.

The 20th century has seen tremendous advances in the medical sciences resulting in the presence of a multimillion-dollar industry. Particularly during the last two

decades the combination of the advances in computers and the knowledge in human biology has created a wealth of knowledge and resources. Therefore, effective utilisation of these resources became a major issue for pharmaceutical organisations. In the 21st century the technological and knowledge advances coupled with increased cost pressures, more informative, and expensive clinical data require flexible and innovative research (U'Prichard, 1997).

7.3.2. Tabulating the drug discovery strategy types and their characteristics

The previous paragraphs provided a description of the history of drug discovery that aimed at determining the drug discovery strategy types and their characteristics. This section presents a table (Table 7-2) that summarises the drug discovery strategy types (taxa) and their characteristics based on the data gathered, analysed and presented in the previous section. As explained in chapter 6 the strategy types and characteristics included in Table 7-2 will also be used in the second step of the construction of the organisation cladogram, data collection

As explained in chapter 4 a drug discovery strategy is a pattern of behaviour defined or adapted by the management of a pharmaceutical organisation while a strategy type is a class of strategies that share a common profile along conceptually distinct characteristics. From the historical account of the previous section several such types may be identified that populations of organisations have adapted to improve their drug discovery process. Early in the pharmaceutical history (age of botanicals) this pattern was characterised by unconventional or unorthodox techniques, such as use of herbals, which lacked any scientific justification. As knowledge and technology progressed the pattern changed to one where pharmaceutical organisations focused on the development of drugs for specific diseases. For instance, in the 1960s the

breakthroughs in disease aetiology, the enhancement of biomedical instrumentation, and the use of powerful computers assisted organisations to adapt to a more science driven drug discovery strategy. To list the drug discovery strategy types in a table, classes of patterns were identified that were adapted by the management of pharmaceutical organisations over the last century.

The names given to these strategy types depend on the manner by which knowledge, technology, organisation, and environment (the four factors identified and justified in chapter 4) were employed. For instance, the strategy that used herbals with no scientific justification has been named *unorthodox*, while the one that was using science based techniques such as disease aetiology and biomedical instrumentation has been named *science driven*. This process of taxa nomenclature is inline with McCarthy and Ridgway (2000) who argue that the name given to a taxon should act as a vehicle for communication, be unambiguous, and indicate the position of the taxa within the classification.

Chapter 4 presented and justified four factors that influence the configuration of drug discovery strategies. These are knowledge, technology, organisation, and environment. To show that these four factors played a significant role in the evolution of drug discovery strategies Table 7-2 is arranged according to these factors. Also the table sorts the characteristics according to the year of their appearance. A description of each strategy is included in section 7.6.4. In total 15 drug discovery strategy types and 57 characteristics are identified. The numbering of the characters shown in Table 7-2 is the one given to the table of the matrix of the Appendix A.

7.4. Step 3: Setting the polarity

Steps 1 and 2 defined the area of interest and identified potential drug discovery strategy types and their characteristics. The third step involves setting the polarity for each characteristic, to define which state is derived (apomorphic state) and which is ancestral (plesiomorphic state). That is to say, to detect the direction of change of the characteristics presented in Table 7-2. As explained in chapter 6 a new taxon called the *outgroup* (a hypothetical ancestral taxon added to the classification to help resolve any polarity issues) is added at this stage to simplify the process of polarisation. Hence the total number of taxa (strategy types) is now 16.

Chapter 6 explained two methods for polarising the characteristics, the *ontogenic criterion* and the *outgroup comparison*. In the case of the construction of the population cladogram these two methods were not used, because the data presented in Table 7-2 has an obvious and self-determined polarity. This is because for each characteristic shown in Table 7-2 there are two possible states, present or absent. The presence of a characteristic could denote any of the following, the development of a new technology (e.g. computers), a key discovery (e.g. DNA understanding), a new way of thinking (e.g. interdisciplinary), or a change in the environment (e.g. World War II, new regulation). Since the presence of a characteristic is associated with something new it is considered to have a derived state (apomorphic). In line with this argument the absence of characteristic indicates an ancestral state (plesiomorphic).

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Table 7-2 Summary table of strategy types and characteristics

Year	Strategy types	Knowledge	Technology	Organisation	Environment
Pre 1800s	• Unorthodox	2. Random discoveries/no scientific justification	1. Herbals' use		
1800s-1910s	• Individual efforts • Technology dominated	3. Symptom focused 5. Homeopathy 7. Microbial theory of disease 8. Vaccines/Antitoxins 11. Organic chemistry/biochemistry	6. Chemical extraction 9. Synthetic dyes		4. Industrial revolution 10. Government legislation
1920s & 1930s	• Multidisciplinary research	13. Development of antibacterial	12. Insulin 16. Instrumentation development	14. Interdisciplinary thinking	15. Federal regulation
1940s	• Disease focused	17. Antibiotics 20. Vitamins	21. Introduction of computer aided drug discovery		18. World Wars 19. Fight against malaria anaemia
1950s	• Knowledge and instrumentation focused	25. DNA understanding	23. Instrumentation wave 24. Computing Technology		22. Government support
1960s	• Science driven	29. Breakthroughs in disease aetiology	27. Biomedical instrumentation enhanced 28. Powerful computers employed	26. Joined analytical chemistry and biology	
1970s	• Biotechnology • Computer driven I	33. Move for development various chemotherapies for various cancers 34. Reverse trancriptise	30. Genetic engineering 32. DNA sequencing 35. Performance revolution of computers		31. Entrepreneurial trend

Table 7-2 Summary table of strategy types and characteristics (continued from page 218)

Year	Strategy types	Knowledge	Technology	Organisation	Environment
1980s	• Computer driven II • R&D concentration for niche markets • Me-too	37. Immunology 39. Genetic algorithms 40. Fuzzy logic 43. High specialisation in certain field	38. Birth of drug design 42. Computational power		36. AIDS
1990s	• Partnerships acquisitions • Outsourcing • R&D concentration for innovation and competition	52. Generics	45. Genomics 46. Rational drug design 47. Combinatorial chemistry 48. High throughput screening 49. Robotics/automation 50. Proteomics 51. Bioinformatics	56. Division of labour	53. Trend for formation of multinational organisations 41. Limited discovery of biotechnology research 54. Medium organisational size 55. Be the first with generics 57. Internet

When classifying biological organisms this step (setting the polarity) is important and often assumptions are made about the polarity of the characteristics. As explained in the previous paragraph however, this is not the case when classifying organisational strategies at the population level. This is because the absence of a characteristic is an ancestral state, while the presence is a derived state. Yet, due to the importance of this step in the cladistic methodology was explained in this section.

7.5. Step 4: Characteristic coding

So far the characteristics, their states and the direction of change of these states have been defined. Step four involves the conversion of the characteristic states into numerical symbols. The purpose of this step is to construct a matrix, which includes all the identified drug discovery strategy types (taxa), their characteristics and their states. As explained in chapter 6 this matrix is used for the construction of the cladogram.

As described in chapter 6 the method used by this research to code the characteristics is a binary approach with '0' representing an absence (plesiomorphic state) of the characteristic and '1' representing its presence (apomorphic state).

The full matrix listing the drug discovery strategy types, the characteristics, the characteristics' states and codes is presented in Appendix A. The first column of the matrix lists the strategy types that were identified in the historical account. The first row of the matrix of Appendix A lists the characteristic names and numbers. When the value of a cell is 1 then the characteristic shown at the top of the column is present in the strategic configuration shown on the left of that row. When it is 0 the characteristic is not present.

7.6. Step 5: Construct the cladogram

Steps one to four identified and defined strategy types, their characteristics, their states, polarity and codes. The fifth step of the construction of the cladogram involves its actual construction. As opposed to the example given in chapter 6, the large number of characteristics in this study make the construction of the cladogram too complex for the manual method described in section 6.2.7.5.1. Therefore, two computer software packages specially designed for cladistic analyses were used, PAUP and Phylip. Both packages process the data using a variety of algorithms to produce numerous potential cladograms. The key is to select the best fit cladogram by calculating and comparing three indices for each cladogram (treelength, consistency index, and retention index). The computation of these indices was undertaken using a software package called MacClade. The primary functionality of this software is the comparison of various cladograms (Maddison and Maddison, 1992). The following sections present the application of these software packages to construct and select a population cladogram.

7.6.1. Phylip

Phylip stands for 'Phylogeny Inference Package' and the version used by this research is 3.57c. It is a DOS-based software and therefore all the data in the matrix (produced using Microsoft Excel format) needed to be transferred into a text only table (input file). Phylip consists of twenty-eight different algorithms to produce cladograms. These algorithms vary in their abilities, to handle different types of characteristics, to manipulate complex input files, and to compare cladograms. The algorithm used to construct the cladograms for the drug discovery strategies (both population and organisation) is called 'MIX'. As per the discussion in chapter 6, MIX

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is a general parsimony algorithm, which performs the Wagner and the Camin-Sokal parsimony methods. The reason for using MIX is that it estimates phylogenies for discrete characteristics with two states (0 and 1).

The results of the program are automatically written to a file called the *treefile*. The treefile includes data about the best cladograms produced by the algorithm (Camin-Sokal or Wagner). The application of MIX provided two different *treefiles* one for each parsimony principle used (Camin-Sokal, and Wagner). Each treefile contains a set of very similar cladograms. The treefile produced by the Camin-Sokal parsimony method included three cladograms, while the treefile produced by the Wagner parsimony method included five. The cladograms provided by each method are shown in figures Figure 7-3, Figure 7-4, and Figure 7-5. Characteristics 1 and 2 are not drawn on the cladograms because they are the characteristics distinguishing the outgroup branch from the unorthodox branch and are the same for all cladograms.

7.6.2. PAUP

The second software used to construct cladograms was PAUP, which stands for Phylogenetic Analysis Using Parsimony, and is Macintosh based. The main difference between the PAUP and Phylip is that the former allows the user to enter how many different cladogram combinations the program should test. Therefore, a large number could potentially result in the discovery of a better cladogram. The use of this software should validate the cladogram obtained by Phylip by producing a similar branching arrangement. The input file developed for Phylip was inserted in this software. The algorithm that this software uses to develop the cladogram is based on the Wagner method, also used by Phylip.

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After running the program three cladograms were saved in the treefile. The cladograms are shown in Figure 7-6.

7.6.3. *Selecting the optimal cladogram*

So far three sets of cladograms have been constructed (11 cladograms). This stage involves analysing and testing these cladograms to select the optimal one. The optimal cladogram selected from this stage will provide the test bed for the validation of the hypotheses. Also this cladogram will provide a provisional list and classification that will help the collection of data for the construction of the organisation cladogram in chapter 8.

Cladistic software utilises a number of different statistics to assess the quality of the cladograms. The standard measures and the ones used in this thesis are the treelength, the consistency index (CI) and the retention index (RI) (see section 6.2.7.6). This section calculates and compares the three measures for each cladogram. A CI equal to 1 indicates a perfect fit between the characteristics, the taxa, and a cladogram structure where there is no conflict at all. Similarly, cladograms with higher retention indices are preferred, as this metric indicates more evidential support for the resulting groups.

Figure 7-3 Camin Sokal Cladograms

Figure 7-4 (a) Wagner cladograms
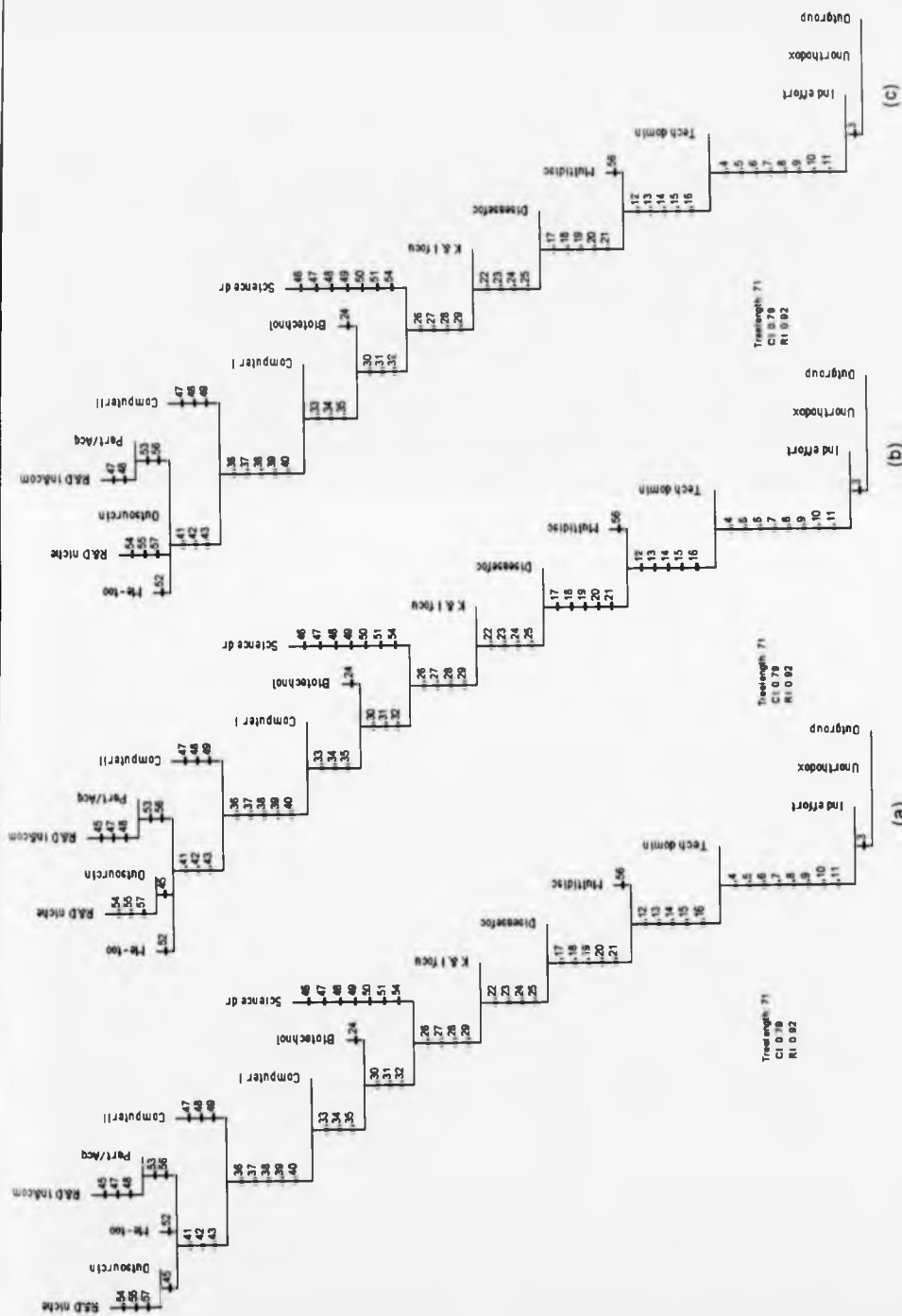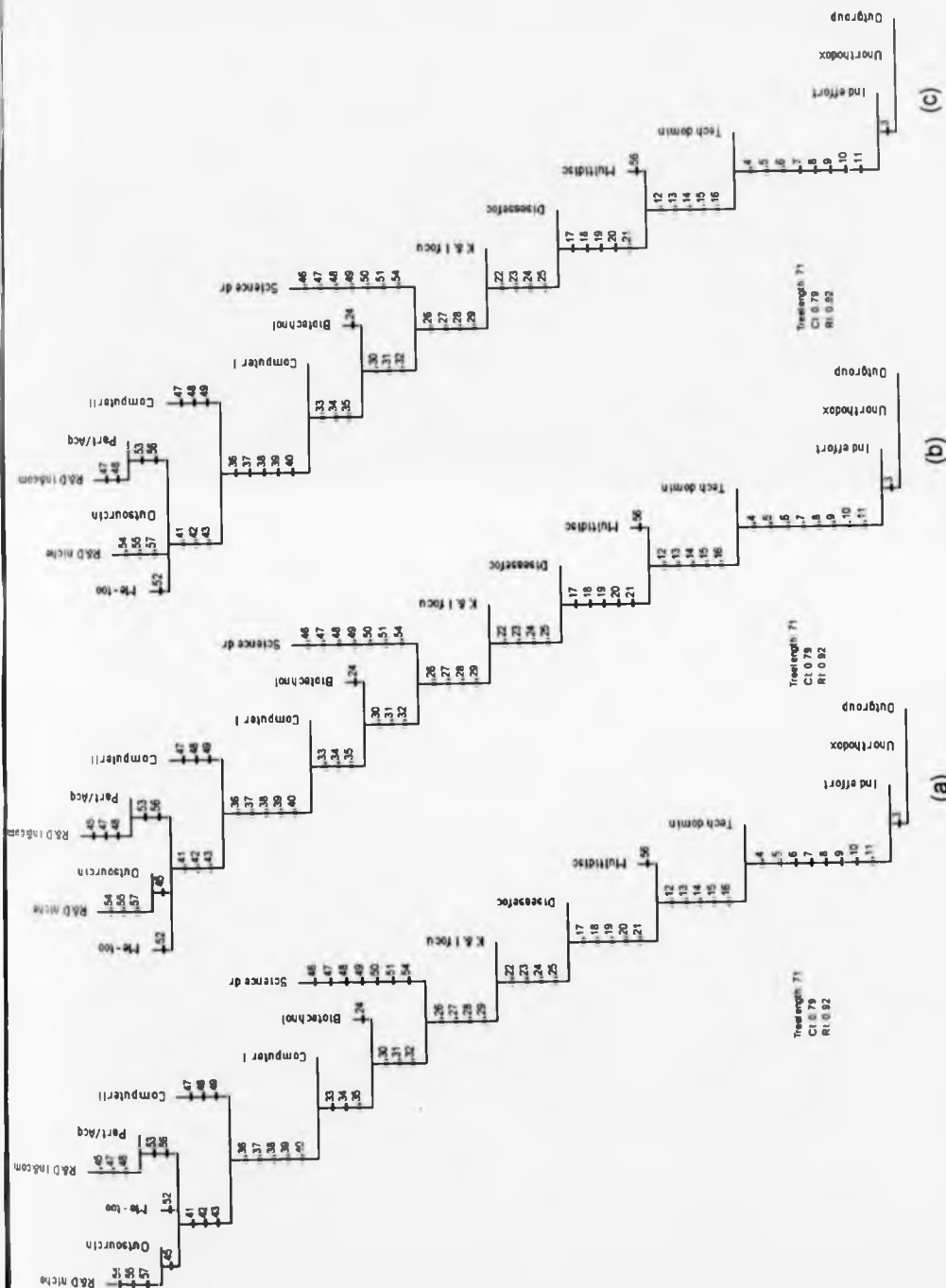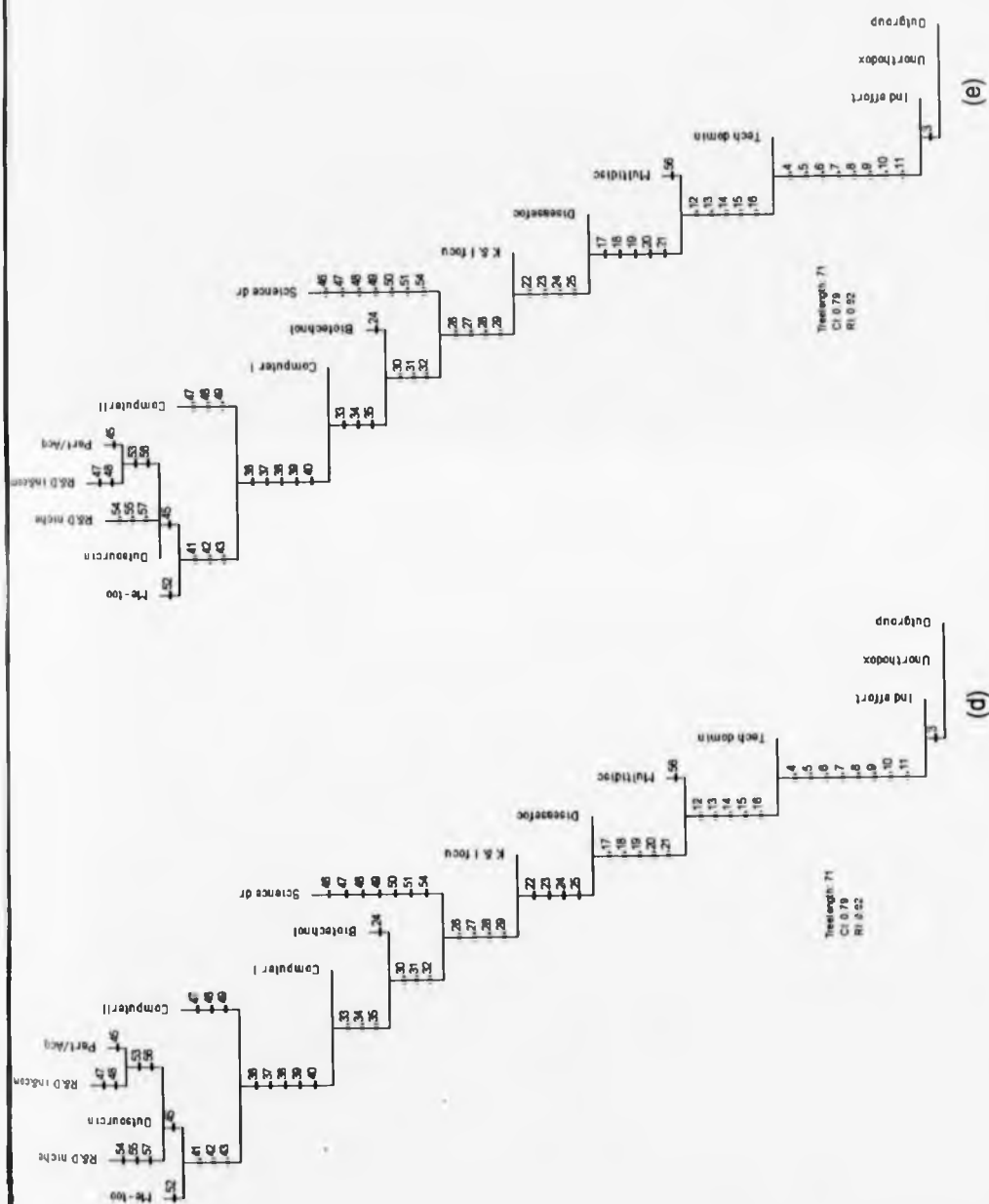
Figure 7-5 (b) Wagner Cladograms
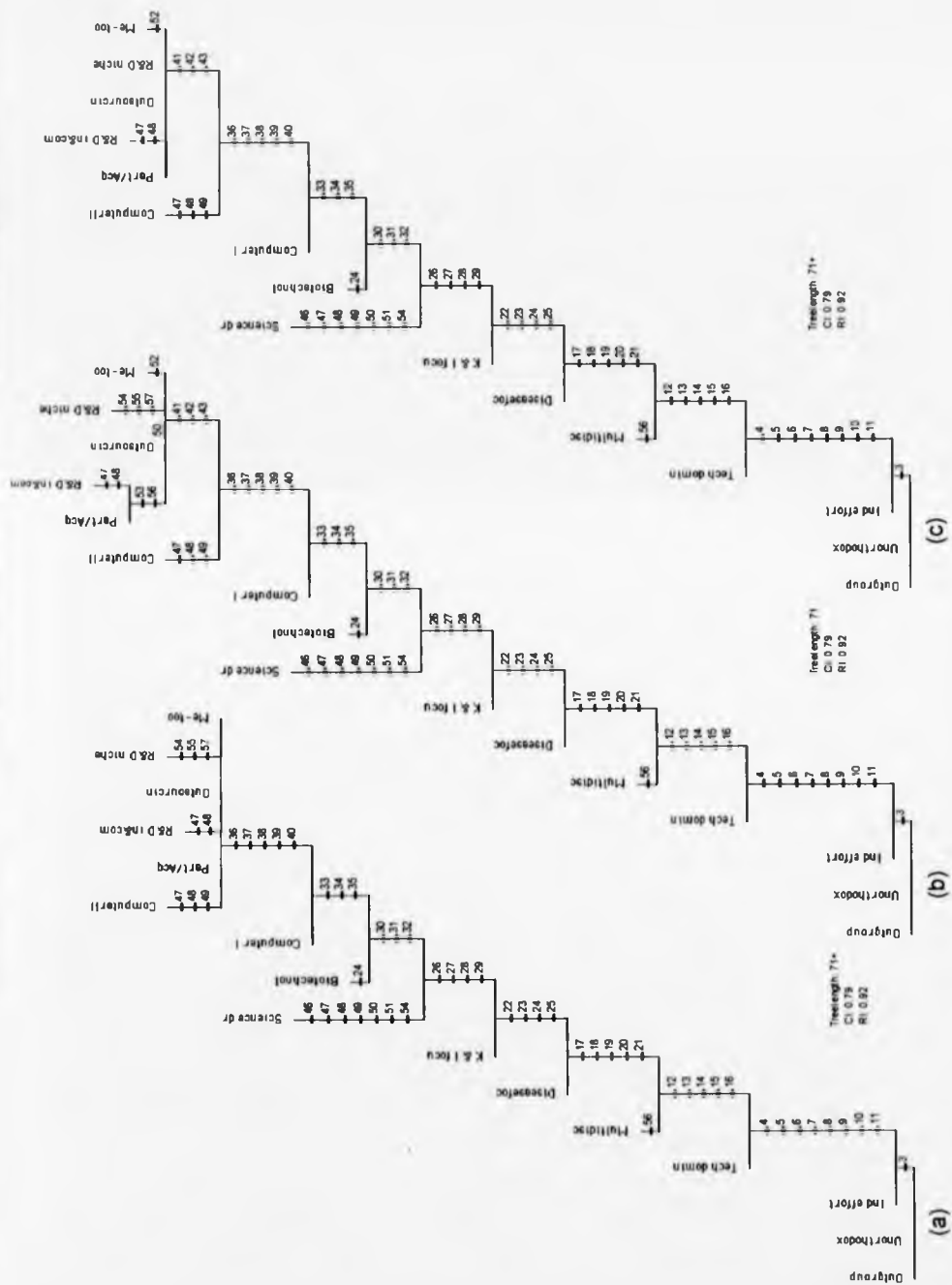
Figure 7-6 PAUP cladograms

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This comparison was conducted by the software package MacClade. MacClade is a Macintosh based program that provides an interactive environment for exploring phylogeny (Maddison and Maddison, 1992). The benefit of using MacClade is that the cladograms may be manipulated by moving the branches and automatically searching for more parsimonious cladograms. As the cladograms are manipulated MacClade calculates the cladogram statistics. It also allows the automatic comparison of two treefiles.

The three treefiles previously constructed were inserted into MacClade and the average indices are shown in Table 7-3.

Table 7-3 Statistical indices of cladograms

Index	Wagner (Phylip)	Camin-Sokal (Phylip)	PAUP
Consistency Index	0.79	0.79	0.79
Retention Index	0.92	0.92	0.92
Cladogram length	71	71	71

The optimal cladogram is the one with the highest consistency and retention indices, and the lowest cladogram length. The first conclusion that may be drawn by comparing the indices of the cladograms shown in Table 7-3 is that their values are identical for all cladograms. This suggests that the data set fits equally for all the cladograms constructed and that the data set is relatively stable. The most parsimonious cladogram would represent the best summary of the data to hand and would thus be the preferred hypothesis of relationships among the study of taxa (Kitching et al., 1998) (in this case drug discovery strategy types). Therefore, the fact that the data fits equally on all the cladograms implies that all the hypothetical relationships depicted on the cladograms of Figure 7-4, Figure 7-5, and Figure 7-6 have equal probability of being correct. However, special care should be taken, as

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this could lead to conflicting results since more than one arrangement could be correct.

Before considering further why all indices have the same value, it is important to review the confidence of the data set. In fact, one of the reasons for the equal values of the different cladograms presented above could be the lack of *significant cladistic structure* (Kitching et al., 1998 p. 118). A cladistic analysis with significant cladistic structure is one where there is confidence that its results are not the by-product of chance. As argued by Archie and Felsenstein (1993), for a given data set, as the length of the most parsimonious cladogram increases, the confidence that one has in both the data and the cladogram decreases. To address this confidence issue Archie and Felsenstein (1993) suggest using the length of random cladograms as an index to make comparisons with the most parsimonious cladograms already constructed. They argue that if the length of the most parsimonious cladogram is significantly smaller than the mean value of the random cladograms then there is confidence in the data set.

The software package MacClade used for the calculation of the cladogram indices also allows construction of random cladograms. Ten cladograms were constructed randomly and their mean treelength (along with the retention and consistency indices) is shown in Table 7-4.

Table 7-4 Mean statistics for random cladograms

Treelength	Consistency Index	Retention Index
204	0.3	0.234

The mean treelength of the random cladograms is 204 (Table 7-4) and is significantly higher than that of the cladograms constructed in the previous section (71 in Table 7-3). Similarly, the values of CI (consistency index) and RI (retention

index) of the random cladograms are lower. Therefore, it can be concluded that there is confidence in the data set and that the cladograms produced are not the product of chance. In summary, it can be argued that the data set contains *significant cladistic structure*.

Having addressed data confidence, the issue of the equal values of the statistical indices must be considered. The cladograms depicted in Figure 7-4, Figure 7-5, and Figure 7-6 are very similar. The difference between them is the arrangement of those drug discovery strategy types (taxa) at the top of the cladogram (see Table 7-5).

Table 7-5 Taxa that create different arrangements

Computer driven II
Partnerships and acquisitions
R&D concentration for niche markets (R&D niche
R&D concentration for innovation and competition
Outsourcing
Me-too

As explained in section 6.2.8, the aim of the construction of the population cladogram is to provide the following:

- A list of drug discovery strategy types and characteristics

- A provisional classification of these types

- A framework for assessing and demonstrating how the four hypotheses might be validated.

The process followed to construct the population cladogram has provided 15 strategy types and 57 characteristics as shown in Table 7-2 (page 218) and therefore the first aim has been met.

With regard to the second and third aims of the construction of the population cladogram, a comparison of the structure of the cladograms reveals that the dissimilarities between the different arrangements are very small. For instance, the taxon *outsourcing* in figure Figure 7-5 (b) (cladogram (e)) is shown as an ancestor of taxa *R&D concentration for innovation and competition*, *R&D concentration for niche markets*, and *Partnerships and acquisitions*, while on the cladogram of Figure 7-6 (b) is shown as an ancestor of *R&D concentration for innovation and competition*, and *Partnerships and acquisitions* only. Such differences could be significant when studying biological organisms as they could trigger philosophical arguments about evolution. However, in the case of this research, where the cladogram is used to classify drug discovery strategy types and not to explore their order of evolution, such small differences are insignificant. Therefore, any of the cladograms shown in Figure 7-4, Figure 7-5, and Figure 7-6 could provide a provisional classification of the drug discovery strategy types and characteristics (second aim), and could provide a framework for assessing how the four hypotheses might be validated (third aim).

To conclude this line of argument any cladogram from those shown in Figure 7-4, Figure 7-5, and Figure 7-6 is considered valid and appropriate within the scope of this research. As it is unpractical to refer to more than one cladogram, the one shown in Figure 7-6 (b) has been arbitrarily chosen and is shown enlarged in Figure 7-7.

One reason for the presence of such differences however, could be the fact that reports for the early evolution of the pharmaceutical industry are concise and consistent and thus, there are no conflicts on the order of appearance of the drug discovery strategy types. However, such is not the case for the more recent periods. Data sources are not yet as clear and sometimes are conflicting. It is therefore likely

that arrangements and hypotheses about the evolution of drug discovery strategy (i.e. the information contained in a cladogram) will also be vague.

Another point to be addressed, is the fact that the consistency and retention indices are less than one. This is because characteristics 24, 47, 48, 49, 54, and 56 appear more than once on the cladogram i.e. their states change more than once. As explained in section 6.2.7.6, in situations where the matrix is complex it is likely that some characteristics will arise more than once on a cladogram. This indicates that the data set is not 100% consistent with the proposed cladogram. In this case, although the multiple appearances of the characteristics reduce the cladogram's technical consistency, it does not necessarily affect its theoretical validity. For instance, the presence of characteristic 47 (combinatorial chemistry) on the *Science driven* and the *R&D concentration for innovation and competition* branches is meaningful. Combinatorial chemistry has been a critical characteristic in the formation of both strategy types (Lesney and Miller, 2000). Therefore, as long as the researcher is aware of this, the cladogram may provide a useful framework for testing and validating hypotheses.
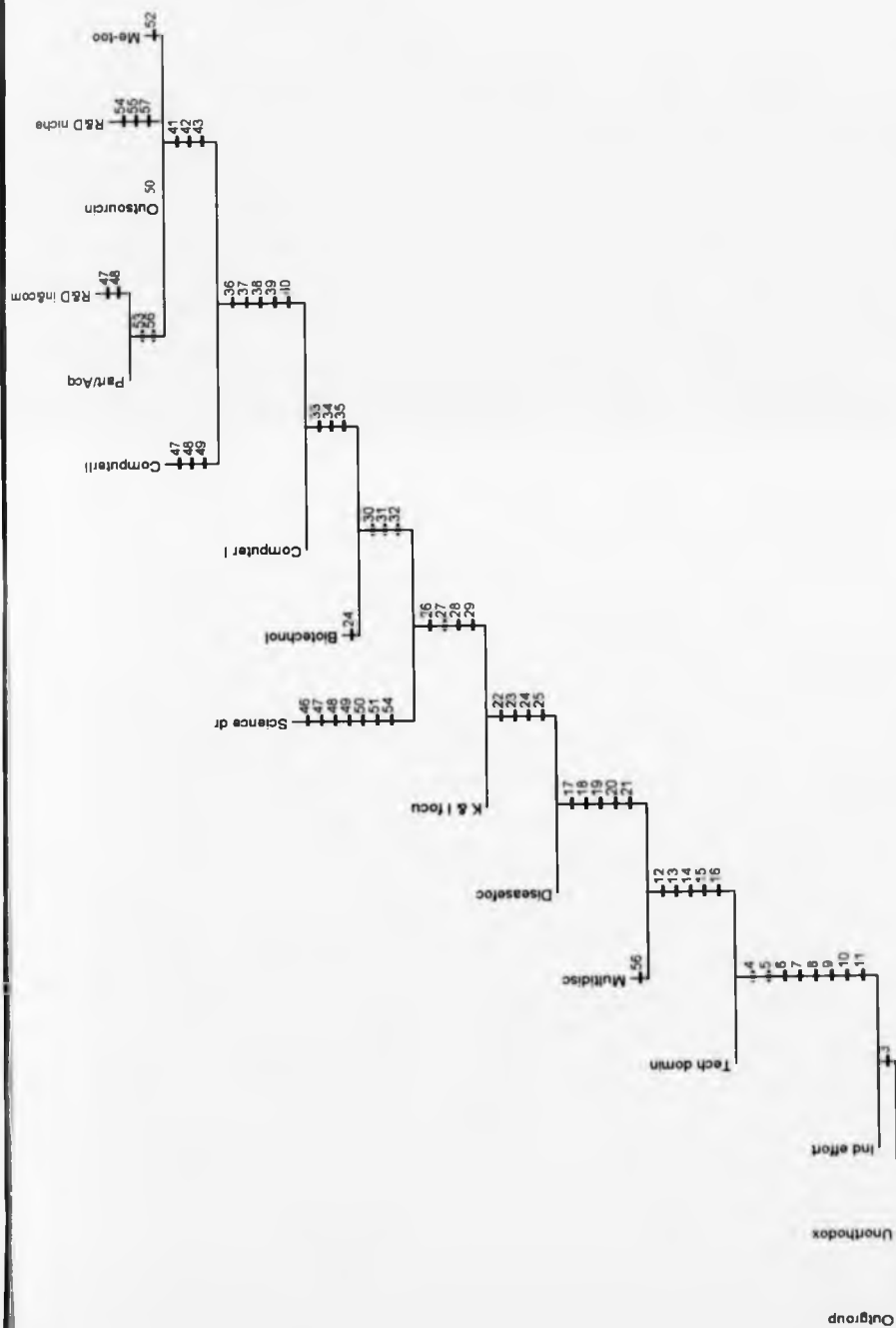
Figure 7-7 Population cladogram

Furthermore, comparing the indices calculated for the population cladogram with indices of other cladograms (see Table 7-6) it may be concluded that the cladogram is relatively consistent. That is, there is not significant difference between other cladograms and the one constructed in this chapter. A more detailed comparison of the cladograms is presented in section 9.4.1.

The following section describes each of the strategy types classified by the cladogram.

Table 7-6 Indices found in the literature

Source	Reference	Consistency index	Retention index
The automotive cladogram	Leseure, 1999	0.89	(not calculated)
The hand tool industry cladogram	Leseure, 1999	1.0	(not calculated)
Electronics industry cladogram	Fernandez, 2002	0.1	0.48
The population cladogram		**0.79**	**0.92**

7.6.4. *Description of the population cladogram*

The aim of the population cladogram is to classify drug discovery types. The drug discovery strategy types classified should correspond to drug discovery strategies adopted by one or more organisations i.e. each taxon shown on the cladogram should represent a population of organisations (hence the label *population cladogram*). The classification provided by the population cladogram will provide a test bed for the validation of the four hypotheses developed in chapter 5. Also, the drug discovery strategy types and their characteristics identified during the construction of the population cladogram provides a provisional list and classification that will help the collection of data for the construction of the organisation cladogram in chapter 8.

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7.6.4.1. Unorthodox (Unorthodox)

Unorthodox drug discovery strategies are those that had no scientific reasoning. The main characteristics of these strategies are 1 and 2 (herbals' use and random discoveries with no scientific justification). These two characteristics are not drawn on the cladograms because they are the characteristics distinguishing the outgroup branch from the unorthodox branch and are the same for all cladograms. Particularly present during the age of botanicals (pre 1800s) the unorthodox drug discovery strategies employed little or no scientific knowledge or technology. The methods to discover new drugs included prayers, and beliefs in tradition. Any successful curing attempts had no scientific justification and were entirely coincidental. Naturally, there was a high degree of emergence present in this strategic type.

7.6.4.2. Individual efforts (Ind effort)

This type of strategy focused on the efforts of an individual. A main characteristic in the formation of this type of strategy is the attack of the symptom (characteristic 3). Researchers did not understand disease aetiology, but began to focus their strategies on phenomena that accompanied disease. Although in this case scientific knowledge and technology are still absent this strategy type is less random than the unorthodox as the researchers were striving for some form of scientific breakthrough (Cause and effect) to cure the disease.

7.6.4.3. Technology dominated (Tech domin)

This strategy type was present when relevant technology was advancing and represents a significant change in type. It is defined by eight new characteristics. The industrial revolution (characteristic 4) and the microbial theory (characteristic 7) of disease are the principal characteristics of this taxon. Microbial theory provided the

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scientists with a fundamental understanding of the diseases. The strategies started to become more focused in that scientists attempted to attack the microbes rather than simply the symptoms.

The industrial revolution and its accompanying innovations in technology led to the development of sophisticated instrumentation, which indicated the path that drug discovery, would follow in the future. Another important characteristic of this strategy was the introduction of government legislation (characteristic 10), which regulated the process of drug discovery. The other defining characteristics, are 5 (homeopathy), 6 (chemical extraction), 8 (infectious diseases/vaccines), 9 (synthetic dyes), and 11 (organic chemistry and biochemistry).

7.6.4.4. Multi-disciplinary (Multidisc)

Scientific knowledge is often divided into subject areas, which can then be composed in a modular fashion to define larger pieces of knowledge (Valle and Gambardella, 1993). The need to combine the various subject areas for the development of new drugs encouraged management of pharmaceutical organisations towards division of labour (characteristic 56) amongst individuals into specialised segments of the drug discovery process. A critical characteristic of this branch is the interdisciplinary thinking (characteristic 14) when for the first time disciplines such as physical chemists and physicists collaborated with biochemists and biologists to explore solutions. The other defining characteristics of the multi-disciplinary drug discovery strategy are the discovery of insulin (characteristic 12), the development of antibacterial (characteristic 13), the introduction of federal regulation (characteristic 15), and instrumentation development (characteristic 16).

7.6.4.5.   Disease focused (Diseasefoc)

This is one of the first strategic types where the discovery of a new drug is clearly influenced by non-planned environmental conditions such as the World Wars (characteristic 18) and the fight against malaria (characteristic 19). Characteristics such as these have driven the management of pharmaceutical organisations to seek research patterns that focus on specific diseases. Also, this strategy type encompasses the introduction of computer-aided design (characteristic 21), while the large-scale production of vitamins (characteristic 18) and antibiotics (characteristic 17), mainly to satisfy the needs of the wars, also began.

7.6.4.6.   Knowledge and instrumentation focused (K & I focu)

Further understanding of human biology together with the discovery of DNA (characteristic 25) and the progress in computing technology (characteristic 24) are the main characteristics of this strategy type. Another key characteristic of this strategy is the instrumentation wave (characteristic 23) where a range of instruments became available to scientists to carry out more effective research.

The implementation of this type of strategy was enhanced by funding for drug discovery provided by the government (characteristic 22) and again by the world wars (characteristic 18). Government funding provided academia with the resources for carrying out basic research (i.e. research that identifies chemical and/or biological properties of a newly synthesised or previously known substance). This research became applied when a pharmaceutical organisation identifies a therapeutic use for the new substance. The two world wars exerted pressure on pharmaceutical organisations to tackle the diseases that affected the soldiers.

7.6.4.7.   Science driven (Science dr)

The *science driven* drug discovery strategies are those strategies that combine the characteristics of the previous strategies with biomedical instrumentation (characteristic 27) and powerful computers (characteristic 28).   In addition, breakthroughs in disease aetiology (characteristic 29) meant that scientists were able to conduct research that focused directly on the disease rather than on the symptom

7.6.4.8.   Biotechnology (Biotechnol)

The *biotechnology* drug discovery strategy type applies the technology characteristics genetic engineering (characteristic 30), and the introduction of computing technology (characteristic 24) supported by DNA sequencing (characteristic 32).   Naturally, these strategies are primarily employed by biotechnology organisations This is also one of the first strategic types where drug discovery is seen as a commercially valuable process.   Small entrepreneurial biotechnology organisations (characteristic 31) such as Genentech, were founded that aimed solely at the discovery of active compounds

7.6.4.9.   Computer driven I (Computer I)

The computer driven drug discovery strategy types developed in two phases This type refers to the first phase that was triggered by the affordability of information technology and the increase in computational performance (characteristic 35). Information technology is used in mainstream research, as most of the drug discovery laboratories are equipped with fast computers This technology enabled researchers to perform complex computations and to build and to manipulate chemical structures in a direct and simple manner

Also, during the development of this strategy chemotherapy joined the ranks of other routine treatments (characteristic 33) and reverse transcriptise was also developed (characteristic 34) a technique which would prove useful in the understanding of AIDS.

7.6.4.10.   Computer driven II (ComputerII)

The second computer driven drug discovery strategy type is differentiated from the first, with the automation of the laboratories and the use of robotics. Following the widespread implementation of this strategy type by pharmaceutical organisations, computers became an integrated part of drug discovery research (characteristic 42). The computational power now available to scientists helped the development of techniques and technologies such as rational drug design (characteristic 47), genetic algorithms (characteristic 39), fuzzy logic (characteristic 40), combinatorial chemistry (characteristic 48), high throughput screening and robotics (characteristic 49).

7.6.4.11.   Partnerships and acquisitions (Part/Acq)

Partnerships and acquisitions is a strategy employed by the management of pharmaceutical organisations to enhance the discovery of new drugs by sharing knowledge and technology with other organisations. Acquisitions imply the take-over of one organisation by another. Partnerships on the other hand are focused on the sharing of knowledge and technology. In fact partnerships could exist both between two competing organisations, but also between organisations and organisations such as research associations and academic institutions. A key characteristic of this strategy is *limited discovery* (characteristic 41). Most biotechnology organisations were pursuing a very limited number of potential drug treatments compared to that of pharmaceutical organisations. This reduced the probabilities of the discovery of new

drugs and forced several small biotechnology organisations to seek funds from larger corporations to help them to survive which in turn encouraged the trend for formation of multinational organisations (characteristic 53). The global nature of this strategy has been strengthened by division of labour (characteristic 56).

7.6.4.12. R&D concentration for innovation and competition (R&D in&com)

The characteristic that primarily differentiates this strategy from previous ones is the trend for the formation of multinational pharmaceutical organisations (characteristic 53). Large pharmaceutical organisations spend large amount of effort and resources to develop the ability to innovate and achieve a sustainable competitive advantage. The introduction of a *blockbuster* drug could provide such an advantage. Technologies such as rational drug design (characteristic 47) and combinatorial chemistry (characteristic 48) allow the management of pharmaceutical organisations to better guide their drug discovery process. The degree of randomness that this strategy encompasses is further reduced as the failure to deliver new products translates into high costs. Therefore, pharmaceutical organisations cannot afford to rely on serendipity as much as they used to.

7.6.4.13. Me-too (Me-too)

Me-too strategies are employed by organisations whose research has not been as effective as their competitors'. In situations like these, organisations imitate their competitors' products, whilst avoiding infringement of patents. The imitation of these drugs can take several forms. Patent laws protect a new product for 17 years. Therefore, the first form of imitation is the production of a drug once its patent has expired. These types of drugs are known as *generics* (characteristic 52). The second

form of imitation is through the reformation of other organisations' rejected research. One organisation's rejected research could be another's success. Several organisations look for opportunities such as these. The third form of imitation is through the production of a drug, which is similar to the drug of another organisation. This form is associated with the development of those new drugs, which in reality are modified versions of existing drugs containing the same active ingredients as those already in the market. In fact, according to a survey conducted by USA's National Institute for Health Care Management (NIHCM) nearly two-thirds of prescription drugs approved in the 1990s belonged to this category.

7.6.4.14. Outsourcing (Outsourcin)

High specialisation in technology fields such as genomics (characteristic 46) and proteomics (characteristic 50) has forced those organisations that cannot cope with the demand of research to outsource all or parts of it. The strategy of partnerships and acquisitions previously discussed focuses on the acquisition of technology and knowledge of other organisations. Outsourcing still focuses on the utilisation of another organisation's capabilities, and high specialisation (characteristic 43), but the difference is that the motivation for using another organisation's capabilities is that the outsourced tasks require less specialisation, but more time and resource.

7.6.4.15. R&D concentration for niche markets (R&D niche)

This type of strategy is adopted primarily by medium sized organisations (characteristic 54). These organisations identify a niche in the market and focus their research and capabilities towards this niche (e.g. Syntex Corporation). This strategy type also applies to those organisations pursuing a generics strategy where they develop a competitive advantage by being the first to introduce to the market a drug

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whose patent has expired (characteristic 55). The degree of emergence of this type of strategy is further reduced as the organisation focuses on a specific aspect of the research.

7.7. *Review of data and results*

This section considers the validity of the data and the resulting cladogram. It is important to note that the construction of the population cladogram (Figure 7-7) has the following potential limitations.

Data exhaustiveness. To construct the population cladogram the chapter explored the factors that have affected the change of drug discovery strategy types and categorised them under the four headings that were identified and justified in chapter 4. These are technology, knowledge, organisation, and environment (see Table 7-2). As argued earlier in this chapter, the complete history of the pharmaceutical industry is long and thus, innumerable characteristics may exist. Although every effort has been made to include the defining characteristics, it is unavoidable that some characteristics will have been omitted. The collection of data for the construction of the organisation cladogram in chapter 8 partly addresses this limitation.

Data collection validity. As explained in chapter 6, the collection of data for the construction of a cladogram is subject to a number of criteria. These criteria should ensure that the collection process is both consistent and objective. These criteria however are not foolproof. Chapter 6 described how the selection of a good cladistic characteristic is often a value judgement guided by research design and objectivity. Therefore, it is expected that the construction of the cladogram is subject to a degree of subjectivity. If however, all or some of the groupings identified on the population cladogram are also present in the organisation cladogram, then the confidence in the

selection process will be increased. This is because any implicit assumptions taken during the data collection process will be validated.

Classification robustness The consistency and retention indices of a perfect cladogram would have a value of one. This is not the case with the population cladogram. Nevertheless, as explained in section 7.6.3, this imperfection does not affect the theoretical validity of the cladogram.

7.8.   Conclusions

The construction of the population cladogram had three aims. The first was to provide a list of drug discovery strategy types and their defining characteristics. In total 15 strategy types and 57 characteristics were identified as shown in Table 7-2 (page 218). These strategy types and characteristics will be used in chapter 8 to help the collection of data for the construction of the organisation cladogram. The second aim was to provide a provisional classification of these populations to assess and demonstrate how cladistics might help to reveal how an evolutionary and classification approach can be used to study drug discovery strategies. The cladogram shown in Figure 7-7 (page 233) provides such classification. The third aim of the cladogram was to provide a framework to demonstrate how the four hypotheses (developed in chapter 5 to address the third research question) could be validated. The discussion provided in this section explains how the population cladogram advances this research towards validating the four hypotheses.

Similar to the classification provided by Mintzberg and Waters (1998) and discussed in chapter 4, it is argued that the strategy types classified by the population cladogram vary along the spectrum emergent to focused. Emergent strategies are those *patterns realised despite, or in the absence, of intentions* (Mintzberg and Waters, 1998 p 20).

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Therefore, within this context, the emergent drug discovery strategies are those that were practiced before and during the early years of the 20th century and shown on the left hand side of the cladogram (e.g. unorthodox and individual efforts). As available knowledge and technology increased, drug discovery strategies became more focused as shown in Figure 7-8 (e.g. science driven and me-too).

Evolution of Strategies
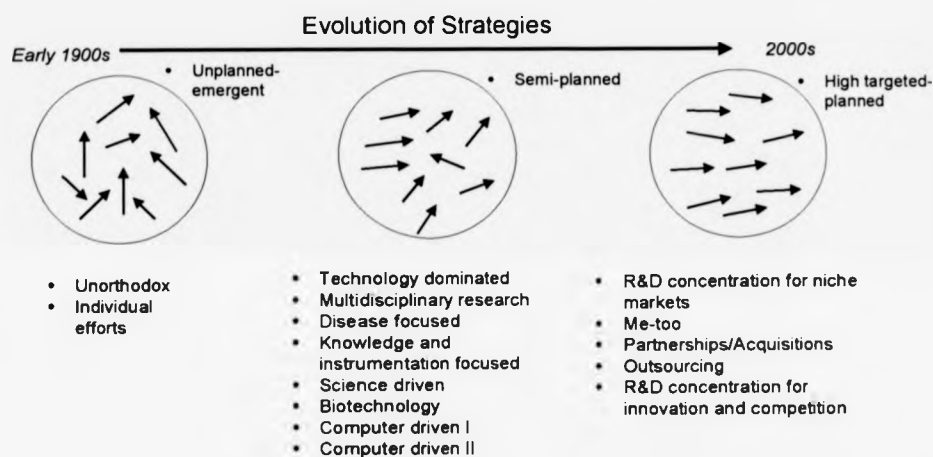
Figure 7-8 Evolution of strategies for drug discovery

It would be delusive to argue that the more focused strategic types discussed above have eliminated any emergence. Although drug discovery strategies still encompass a degree of emergence, advances in technology and knowledge aid scientists to better understand their target and consequently, are better equipped to guide their research. In addition, the escalating costs of research means that pharmaceutical organisations cannot afford to leave their research to chance and continuously seek less emergent strategies.

7.8.1. Hypotheses validation

The first hypothesis states that *there are similar drug discovery strategies employed by different pharmaceutical organisations to form populations whose (the population's) size follows a concave pattern of growth and decline.* The population cladogram is not organisational specific and therefore, it is not possible at this stage to draw conclusions about the drug discovery strategies of individual organisations (this issue is tackled in chapter 8). However, as explained in chapter 6 the drug discovery strategy types classified by this cladogram correspond to drug discovery strategies adopted by one or more organisations and thus, the population cladogram represents populations of drug discovery strategies. Therefore, each drug discovery strategy branch should represent one or more organisations that have implemented that strategy into their system. Consequently, the construction of the organisation cladogram in the next chapter (whose aim is to be organisation specific) should identify groupings of strategies that match all or some of the branches of the population cladogram. If this is true then the first part of the hypothesis (there are similar drug discovery strategies employed by different pharmaceutical organisations to form populations) will be validated. The size of these groupings or populations will be the number of organisations that are included in each branch. If the size of the population is small when the population emerges, then rapidly increases in size and then stabilises or declines, then the second part of the hypothesis will be validated *(the population's size follows a concave pattern of growth and decline)*.

The second hypothesis suggests that *within a drug discovery population, there are strategies that differ to each other in terms of their characteristics and their fitness.* As discussed above the population cladogram is not organisation specific and therefore, it is not possible at this stage to compare the configurations of drug

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discovery strategies of individual organisations as required by this hypothesis. However, each drug discovery branch on the cladogram should represent one or more organisations that have implemented that strategy into their system. As explained in chapter 4 ultimately, each organisation is unique and thus has a unique configuration of characteristics. The construction of an organisation cladogram should allow the comparison of these organisations and conclusions to be drawn about the differences and similarities of their drug discovery strategies and their fitness (i.e. the condition where the configuration of an organisational strategy matches that of the environment and the frequency of its characteristics appearing in future strategies is potentially high).

The third hypothesis suggests that *those characteristics of drug discovery strategies credited with successful drug discovery performance are likely to appear in future strategic configurations, while those characteristics that are not are likely to be absent.* The data collected for the construction of the population cladogram has been arranged in chronological order as shown in Table 7-2. Therefore, it is possible to observe from the cladogram how the third hypothesis could be validated by identifying the presence of characteristics in past and future strategic configurations. For instance, characteristic 14 (first interdisciplinary thinking) first appeared in the 1920s and 1930s. As explained in section 7.6.4.4 the progress of scientific knowledge forced pharmaceutical organisations to think multidisciplinary i.e. to combine scientists from disciplines such as physical chemistry, biochemistry, and biology to collaborate for the discovery and development of new drugs. Since then, interdisciplinary thinking has increased the performance of drug discovery (Harvey, 1995) and is thus present in future strategic configurations such as *biotechnology* and *science driven.* In the contrary characteristic 2, *random discoveries/no scientific*

justification, which belongs at the unorthodox branch, is not present in future strategic configurations. Drug discovery strategies based on dogmas and religious beliefs did not advance the practice of drug discovery. In fact, as explained in section 7.3.1.1, on many occasions this acted as a barrier. Therefore, this characteristic is absent from the future strategic configurations shown on the right hand side of the cladogram.

The fourth hypothesis suggests that w*ith a change in the environmental conditions those drug discovery strategies that remain are the ones whose strategic characteristics are favoured by the environment.* The proposed way of validating this hypothesis is by examining the response of drug discovery strategies following a significant environmental change. The history of drug discovery offers two obvious and distinct events. The first is the two world wars (characteristic 18) and the second is the introduction of drug regulation (characteristic 15). The groupings of the population cladogram do not show any particular change with the appearance of these characteristics. This may be due to the fact that the population cladogram does not group drug discovery strategies of individual organisations. However, this is not the case with the organisation cladogram (presented in chapter 8) that uses data from pharmaceutical organisations to classify their drug discovery strategies. As will be shown on the organisation cladogram these two characteristics do affect the formation of populations of drug discovery strategies.

To conclude, in addition to the first two aims, the population cladogram partly addresses the third aim by providing a framework for demonstrating how the four hypotheses for the evolution of drug discovery strategies developed in chapter 5 could be validated. To complete this aim chapter 8 presents the construction of the organisation cladogram that will identify groups of pharmaceutical organisations that

implement drug discovery strategies similar to the ones classified by the population

cladogram.

8. CONSTRUCTION OF ORGANISATIONAL CLADOGRAM

8.1. Introduction

To address the third research question (How can an evolutionary and classification approach be used to study drug discovery strategies?) chapter 5 developed four hypotheses about the evolution of drug discovery strategies. Chapter 6 explained how cladistics would be used to validate these hypotheses. It was argued that two cladistic classifications (cladograms) would be constructed. The unit of analysis of both would be drug discovery strategies as defined in chapter 4. The first (population cladogram) was constructed in chapter 7 and used data from available historical secondary sources to identify and classify types or forms of drug discovery strategies. The second (organisation cladogram) is constructed in this chapter and uses data from the pharmaceutical industry to identify and classify drug discovery strategies found in individual organisations. As explained in section 6.2.8 the difference between this and the population cladogram is the level of analysis. The taxa on the branches of the former will be drug discovery strategy types (classes of strategies that share a common profile along conceptually distinct characteristics), while that of the latter will be organisational strategies. As argued in chapter 6, which explained the process for constructing cladograms, the benefits of this approach are that the population cladogram will provide a test bed for the validation of the hypotheses and that its construction will provide a provisional list and classification that will help the collection of data for the construction of the organisation cladogram. In addition, as explained in section 7.8.1, the construction of the organisation cladogram will address the following issues that the population cladogram did not. Firstly, the organisation cladogram will allow the comparison of drug discovery strategies and their fitness of

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individual organisations and thus, advance the research towards validating the first and second hypotheses. Secondly, it will allow examining the characteristics that are favoured by the environment and thus advance the research towards validating the fourth hypothesis.

The aim of this chapter is to explain the construction of the organisation cladogram. Similar to chapter 7 the structure of the chapter is based on the process followed to construct a cladogram as explained in chapter 6 (see Figure 6-3).

The fourth research question (What are the characteristics of the fittest drug discovery strategies?) requires the identification of the characteristics of the fittest drug discovery strategies i.e. those drug discovery strategies whose configuration matches that of the environment and the frequency of their characteristics appearing in future strategies is potentially high. As explained in chapter 6 the process of constructing the organisation cladogram will also address this research question.

Therefore the objectives of this chapter are:

- To validate the drug discovery strategy types classified by the population cladogram

- To validate the four hypotheses, and

- To identify the most dominant characteristics i.e. identify the configuration of the fittest strategy.

8.2. Step 1: Select a clade

As explained in chapter 7 this step involves defining the area of interest and unit of analysis. Similar to the construction of the population cladogram the unit of analysis for the organisation cladogram is drug discovery strategies as defined in chapter 4

However, whereas the population cladogram classified drug discovery strategy types (i.e. classes of strategies that share a common profile along conceptually distinct characteristics) the organisation cladogram classifies drug discovery strategies of individual organisations. Therefore, the clade in this case consists of the drug discovery strategies of individual organisations. The construction of the population cladogram has provided a list of drug discovery strategies types. As argued in chapter 6 the taxa of the population cladogram (constructed in chapter 7) should correspond to drug discovery strategies adopted by one or more organisations i.e. each taxon shown on that cladogram should represent a population or cluster of organisations. The construction of the population cladogram (chapter 7), focused on the drug discovery strategy types of the last two centuries. To maintain consistency between the two cladograms, the construction of the organisation cladogram will focus on individual pharmaceutical organisations that have existed (but do not necessarily exist today) over the last two centuries.

8.3. Step 2: Data collection

This step involves the collection of data that will establish the relationships between drug discovery strategies of organisations and the characteristics identified in chapter 7 and listed in Table 7-2. Although the unit of analysis for the construction of the two cladograms (population and organisation) are the same (drug discovery strategies), the type of data and the collection process are not. The data collected in this case focuses on individual organisations as per the aims and objectives of the organisation cladogram.

An exhaustive classification of drug discovery strategies of individual organisations would require the inclusion of all pharmaceutical organisations that have existed

during the last two centuries. However, equally valuable results may be deducted from a well designed sample (Czaja and Blair, 1996, Thompson, 2002). Also, a sample could be more efficient and less expensive than a *census* i.e. an exercise that attempts to include every element or member of a population (Czaja and Blair, 1996). Therefore, to construct the organisation cladogram the data collection process uses random sampling.

Sampling consists of selecting some part of a population to observe or to classify. This permits estimation about something for the whole population (Thompson, 2002). In this case the term population refers to all organisations that have existed in the pharmaceutical industry over the last two centuries.

The size of a sample depends on a number of things such as the research design being used, if hypotheses are being tested, and the size of the differences between two variables. With simple random sampling (as is the case with the construction of the organisation cladogram) an approximate size of the sample n is given by the following equation (Thompson, 2002):

$$n = \frac{1}{\dfrac{d^2}{z^2\sigma^2} + \dfrac{1}{N}} \Rightarrow n = \left(1 - \frac{n}{N}\right)\frac{z^2\sigma^2}{d^2}$$

Equation 8-1

Where:

N is the size of the population

d^2 is the confidence interval and refers to the margin of error that is tolerated. The only way to avoid a sampling error is by including all the members of the population (i.e. n=N).

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σ^2 is an approximation of the population variance i.e. the standard deviation of the population and is usually provided by previous data.

z^2 is the square value of the standard deviation score that refers to the area under a normal distribution of variables. The value of z is set by the researcher and expresses the probability level of the sample results i.e. in how many repeated samples of 100 that total the same size as the sample n, the population value is likely to fall within the specified confidence interval d. One standard deviation includes about 68% of the sample value and its score is 1.0, two standard deviations include about 90% of the sample values and its score is 1.64, and three standard deviations include about 99% of the sampled values and its score is 2.58 (Blank, 1980).

When N is large relative to the sample size, the *finite population correction* $\left(1 - \dfrac{n}{N}\right)$ is close to 1 and thus the sample size is given by:

$$n = \frac{z^2 \sigma^2}{d^2}$$

Equation 8-2

This research is not limited to a geographical area nor to a certain moment in time and therefore it could be assumed that the size of the population is large relative to the size of the sample. Therefore, the size of the sample will be calculated by Equation 8-2.

The values of the variables of Equation 8-2 are estimated as follows.

8.3.1. Confidence interval: d

The only way to estimate a population value without a sampling error (i.e. $d=1$) is to include every element of the population (Czaja and Blair, 1996). As was argued due

to limited time and resources, this is not possible and thus a margin of error to be tolerated has to be defined. As argued by (Czaja an Blair, 1996) this value is set by the researcher. A reasonable confidence interval is 0.1 (Czaja and Blair, 1996). This means that margin of error tolerates is set at $\pm 10\%$.

Therefore,

$$d = 0.1$$

8.3.2. Population variance: σ^2

This value is the standard deviation of the population and is usually provided by previous data when available (Thompson, 2002). Due to the originality of this research no such data is available in the literature other than that used of the construction of the population cladogram and presented in chapter 7 of this thesis. Therefore, to obtain an approximation of this value the standard deviation of the matrix constructed for the population cladogram (included in Appendix A) will be calculated.

The standard deviation σ is given by:

$$\sigma = \sqrt{\frac{n\sum x^2 - \left(\sum x\right)^2}{n(n-1)}}$$

Equation 8-3

Therefore, the standard deviation σ of the values included in the data matrix of Appendix A is:

$$\sigma \approx 0.499$$

8.3.3. Probability level: z^2

As argued by Czaja and Blair (1996) the values of z is also set by the researcher. To ensure that the population values are included in the sample, the probability level is set at 90% (which is also a reasonable probability level as argued by Czaja and Blair, 1996). That is to include the population value in 90 out of every group of 100 samples of the same size. Thus,

$$z = 1.96$$

Therefore, the sample size is:

$$n = \frac{z^2 \sigma^2}{d^2} \Rightarrow n = \frac{(1.64)^2 (0.499)^2}{(0.1)^2} \Rightarrow n = 66.9 \Rightarrow$$
$$\Rightarrow \underline{\underline{n \approx 67}}$$

Therefore, the required size of the sample is 67 organisations.

8.3.4. Selection of organisations

As explained earlier the organisations which are eligible for this research are not limited to one geographical area nor to a moment in time. Therefore, there is a plethora of organisations to choose from. The only limitations for the inclusion of an organisation in this research were that they should carry out research in the area of drug discovery.

The next task in the selection of organisation is to find the *sampling frame* i.e. the lists of resources that contain the elements of the defined population (Czaja and Blair, 1996). Three pharmaceutical specific directories were used for this purpose and listed in Table 8-1. The reason why three directories were used was to overcome the following problems arisen when the frame is a list as reported by Czaja and Blair (1996).

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- *The list could contain units that are not members of the defined population.* The use of multiple directories allows the cross reference of information.

- *Information about individuals or units on the list may not be accurate.* The use of multiple directories allows the validation of the information.

- *Information about individuals or units on the list could be missing.* Missing information of one directory may be filled in with information from another directory.

Table 8-1 Pharmaceutical directories

Directory name	Web address	Description
Drug Info Net	www.druginfonet.com	Drug InfoNet contains information to healthcare and pharmaceutical topics on the Internet. It provides a wide range of healthcare information. It is a free service that aims at providing education as consumers and healthcare professionals.
InPharm	www.pharmweb.net	Pharmweb is an online community of pharmaceutical and healthcare-related professionals with approximately 25,000 self-registered users.
Pharmaceutical and medical abbreviation directory	www.pharma-lexicon.com	This directory provides medical search tools needed to find information on the Internet.

The selected organisations are listed in Table 8-2.

Table 8-2 List of organisations

Abbot Laboratories	Advanced biotechnology ltd
American Home Products	Amgen
AstraZeneca	Bayer
Aventis	Schwarz pharma
Baxter International	Bene-Arzneimttel
Bristol Myers Squibb	Biogen
Ciba Geigy	Datex-Ohmeda
Eli Lilly	Vertex Pharmaceuitcals
Fujisawa	Britannia pharmaceuticals
Genentech	Celltech
Genetics Institute	ICN pharmaceuticals
Glaxo	Glaxo Holdings
GlaxoSmithkline	Glaxo Wellcome
Marion	Astra
Merck	Zeneca
Miles Laboratories	Johnson & Johnson
Mylan Laboratories	Tanox
Novartis	Aegis pharmaceuticals
Novo	Alliance pharmaceutical
Pfizer	SmithKline Beecham
Pharmacia	Wellcome
R.P. Scherer	Upjohn
Roche	Takeda
Rorer Group	Menarini
Roussel Uclaf	Orion Pharma
Sandoz	Zila Pharmaceuticals
Sankyo	Remington
Sanofi-Synthelabo	King pharmaceuticals
Schering-Plough	Gate pharmaceuticals
Searle	Ferring pharmaceuticals
SmithKline Beckman	Drogsan
Sterling Drug Inc.	Cadila pharmaceuticals
Syntex corporation	Dimethaid
Axcan Scandipharm	

The process followed to collect the data for the construction of the organisation cladogram is outlined in the flowchart of Figure 8-1.
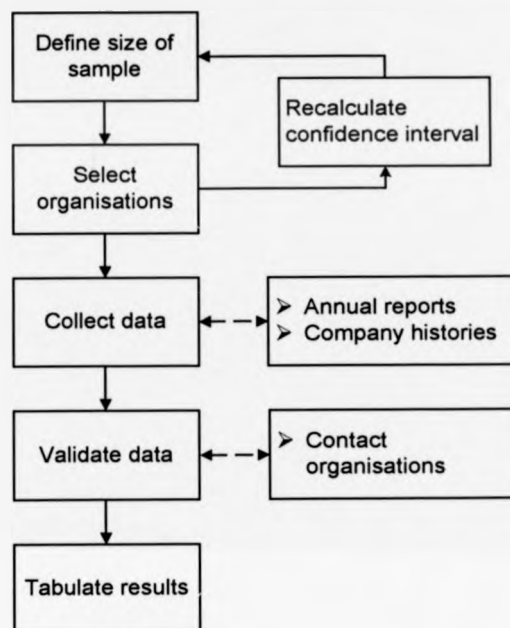
Figure 8-1 Process for determining characteristics

All surveys are limited by time and resource constraints and thus consistent data for 36 organisations were found. This means that the margin of error increases. If all the variables are left constant in Equation 8-2 the margin of error for a sample of 36 organisations becomes:

$$n = \frac{z^2 \sigma^2}{d^2} \Rightarrow d = \sqrt{\frac{z^2 \sigma^2}{n}} \Rightarrow d = \sqrt{\frac{(1.96)^2 (0.499)^2}{36}} \Rightarrow \underline{d = 0.16}$$

Therefore, the confidence interval now becomes ±16%.

The organisations that data was collected from are shown in table Table 8-3.

Table 8-3 Revised list of organisations

Abbot Laboratories	Mylan Laboratories
American Home Products	Pfizer
AstraZeneca	Upjohn
Aventis	Bristol Myers Squibb
Baxter International	Searle
Ciba Geigy	Sanofi-Synthelabo
Eli Lilly	Wellcome
Fujisawa	Sankyo
Genentech	Smithkline Beckman
Genetics Institute	Pharmacia
Marion	Takeda
Merck	Miles Laboratories
Novartis	Schering-Plough
Roche	GlaxoSmithkline
Rorer Group	R.P. Scherer
Roussel Uclaf	Novo
Sandoz	Sterling Drug Inc.
Syntex corporation	Glaxo

8.3.5. Selection of characteristics

The process of constructing the cladogram in chapter 7, allowed the working definition of drug discovery strategy (presented in chapter 4) to be developed into a classification of strategy types and the relationship between the types, and their defining characteristics. To ensure research consistency, the characteristics used to construct the population cladogram form the basis of the data collection for the organisation cladogram. As discussed in sections 8.1 and 8.2 the unit of analysis is the same for both cladograms, the difference is the source of data and the level of analysis. The population cladogram (chapter 7) used historical literature (i.e. literature that reports the steps that people and organisations have taken to understand how diseases occur and how medicine, vaccines, dietary materials, anaesthetics, antiseptics, and other medical materials came to be invented and used (Weatherall, 1990)) to classify drug discovery strategy types. As will be explained the

organisation cladogram uses data about pharmaceutical organisations to classify drug discovery strategies of individual organisations.

The construction of the population cladogram in chapter 7 provided 57 characteristics of 15 drug discovery strategy types. The manner by which the characteristics are used for the construction of the organisation cladogram is by linking them with organisations during the data collection process (outlined in Figure 8-1). This means that the collection of data for each organisation will focus on identifying whether an organisation has acquired the characteristics used for the construction of the population cladogram and listed in Table 7-2, or not.

Although the above process should reveal the drug discovery strategies of the organisations within the context defined in this thesis, it is anticipated that the collection process will identify several more characteristics. This is due to two reasons. As explained in chapter 4, each organisation tries to achieve competitive advantage by developing idiosyncratic capabilities (Barney, 1991, Porter, 1980). Therefore, characteristics unique to each organisation should exist which are not necessarily included in the list of characteristics of the drug discovery population cladogram. The second reason is that, as explained in chapter 7, the list of characteristics is not exhaustive. Therefore, the collection of data about individual organisations should reveal more characteristics. This is also supported by McCarthy et al (1997) who argue that characteristic selection is not a process of choosing available characteristics from a reference list, it is a process of discovering which characteristics are responsible for evolutionary change, and the role of individual characteristics in the change. Hence, the list of characteristics in Table 7-2 will serve as a very good starting point for the collection of data for the construction of the organisation cladogram.

A note should be made at this stage with regard to the point in time when the data was collected for the drug discovery strategy of each organisation. As explained in chapter 4, this thesis adopts an evolutionary perspective for examining strategic change. In accordance with this perspective a strategic configuration at any point in time depends on the evolutionary and co-evolutionary paths an organisation has followed throughout its history (Teece et al. 1997, Eisenhardt and Martin, 2000, Spanons and Lioukas, 2001). As will be explained the data included for each organisation spans from the moment it was introduced until either the date of its death (usually due to a merger or acquisition) or the date the data collection took place. Therefore, the configuration of the organisations' drug discovery strategies included on the cladogram should take account of the organisations' evolutionary and co-evolutionary paths and the point in time when the data was collected should not affect the research.

The data collected was principally from two publicly available sources, historical archives (Kepos, 1995), and organisation annual reports. The historical archives provided data about the main milestones on the history of organisations. The organisation annual reports provided information only on the therapeutic areas organisations are undertaking research on. In addition, several other sources were obtained including the history of Glaxo reported in two books by Davenport-Hines and Slinn (1992) and by Jones (2001), and the history of Pfizer reported in a book by Rodengen (1999). A list of the organisation literature used is shown in Table 8-4.

Table 8-4 List of organisation literature

Organisation Name	Name of literature	Contacted during validation
AstraZeneca	A-Z: evolution of a medicine Annual report, 2001	Yes
Glaxowellcome	Key Facts, 1999 Annual report, 2000 Jones, E., 2001, *The business of medicine: the extraordinary history of Glaxo, a baby food producer that became one of the world's most successful pharmaceutical organisations*, Profile books, London Davenport-Hines, R.P.T., Slinn, J., 1992, *Glaxo: A History to 1962*, Cambridge University Press, Cambridge	Yes
Novo Group	Charter, 2001 Annual report, 2000	No (Group of organisations)
Roche	Roche in brief, 2001 Annual report, 2000	Yes
Schering Plough	Product pipeline, 2002	Yes
Abbott Laboratories	Annual report, 2001	Yes
Wyeth (AHP)	Annual report, 2001	Yes
Aventis	Annual report, 2000	Yes
Baxter	Annual reports, 1996-2000	Yes
Bristol Myers Squibb	Annual report, 1999	No
Genentech	Annual report, 2000	No (biotechnology)
GSK	Product development pipeline, 2001	Yes
Elli Lilly	Annual report, 2000	Yes
Merck	Annual report, 1999	Yes
Mylan	Annual report, 2001	Yes
Novartis	Annual report, 2001	Yes
Pfizer	Annual report, 2001 Rodengen, 1999 (ISBN: 0945903375)	Yes
Pharmacia	Annual report, 1998	Yes
Sankyo	History, 2001 Innovative new drugs, 2001 Review of operations, 2001	Yes
Sanofi-Synthelabo	Annual report, 2000	Yes
Takeda	Annual report, 2001	Yes
Fujisawa	Annual report, 2001	Yes
Miles laboratories	Annual report, 2001	No (Generics)

The International directory of histories (Kepos, 1995) was also used for the construction of the organisation cladogram

To ensure that there were limited inconsistencies, (e.g. omitting therapeutic areas) in the selection of the characteristics from these sources, the following criteria were imposed in addition to the criteria suggested by Leseure (1998) and Fernandez (2002) and presented in chapter 6:

1   Drug discovery strategies were described in chapter 4 as business strategies. Therefore the selected characteristics must be such that have a direct effect on the business level of strategy. This criterion was imposed, because on many occasions the future of pharmaceutical organisations has been influenced by factors such as political occurrences and strategic financial investments by senior management in areas such as manufacturing and marketing. Unless these factors have influenced the drug discovery process of an organisation they were not included in the cladogram. For instance, the world wars have been a crucial factor in the formation of drug discovery strategies (a detailed description of the effect of the wars on drug discovery is included in section 8.8.1.1). Therefore, the wars have been included as a characteristic where appropriate.

2   Their effect must influence the evolutionary paths of drug discovery strategy. That is, the characteristics must have altered the way drug discovery strategy in a particular organisation is being employed i.e. it does not only have short-term effects, but also long term.

3   They must fall under the four categories: knowledge, technology, organisation, and environment as discussed and justified in chapter 4.

As explained in chapter 7 the construction of the population cladogram provided a list and classification of strategies and characteristics, which helps specify the

collection of data for the construction of the organisation cladogram. Therefore, the next task in the selection of characteristics is the identification of individual organisation specific characteristics and determining how they relate to the characteristics in the population cladogram. A review of the historical archives for each organisation identified a list of key milestones that were included in the study as characteristics. Several characteristics were present in more than one organisation, several were found solely in one organisation. This latter point was expected, as it is known that each organisation tries to achieve competitive advantage by developing idiosyncratic capabilities (e.g. Barney, 1991, Porter, 1980).

As per chapter 7, the characteristics identified have been classified according to the four factors that shape the drug discovery strategy. These factors are *knowledge, technology, organisation*, and *environment*. The following sections present, discuss, and justify the reasoning for each characteristic category. The full list of characteristics is shown in Table 8-5.

8.3.6. Technology

There is plenty of evidence to suggest that the pharmaceutical industry is a technology-dominated sector (Deeds et al., 1997, Ratti and Trist, 2001). The scope of this thesis is to identify the key factors that influence the change of the drug discovery strategies. The construction of the population cladogram, and more specifically the historical account provided in chapter 7, has demonstrated that there are some technologies that have affected the drug discovery process more than others, e.g. combinatorial chemistry and genomics. Therefore, it is within the scope of this thesis to identify the most influential technologies, which are at the disposal of the drug discovery scientists.

Chapter 4 identified five key enabling technologies. These are *genomics, proteomics, high throughput screening, combinatorial chemistry, and pharmacogenomics.* Since these technologies have been credited with driving the pharmaceutical drug discovery process (Reuters, 2000), they are included as technology characteristics in Table 8-5. Additional technologies that are selected include fermentation technology, procaine development, blood collection etc.

8.3.7. Knowledge

Chapter 4 argued that the scientific knowledge acquired by an organisation, is a resource critical to the success of the discovery of new drugs. Such knowledge is generated tacitly, but is then codified and combined with other existing knowledge. Accordingly, the characteristics that fall under the category *knowledge* have been divided into two subsections; tacit and codified. Tacit knowledge is *intangible knowledge that may include personal insights, intuition, hunches and is acquired through informal processes of learning rather than through manuals and procedures.* It includes the mechanisms that an organisation may use to acquire and/or manage the codified knowledge. The acquisitions of these mechanisms by an organisation denote the ability of an organisation either to acquire external knowledge or develop new knowledge internally. For instance, characteristic 25 of Table 8-5, *acquisitions*, denotes that an organisation has acquired another organisation and that it has developed the ability to acquire knowledge. Naturally, the fact that an organisation has gone through an acquisition or even a merger (characteristic 24) does not on its own imply that an organisation has developed the ability to acquire external knowledge. If however, an organisation has acquired more than one characteristic from the list it is reasonable to deduce that such ability has been developed.

The second area of knowledge, codified, is the *scientific or technological knowledge that is at the heart of and forms the foundation for a product or service*. In drug discovery, core knowledge is associated with the areas of research that develop new products i.e. new drugs. Therefore, codified knowledge in a pharmaceutical organisation is linked with therapeutic areas of interest e.g. cardiovascular, oncology, immunology.

Research within a certain therapeutic area requires a pharmaceutical organisation to acquire a degree of expertise within that area (Henderson and Cockburn, 1994). As noted a number of times in this thesis, the discovery of new drugs is a process that requires time, resources, and the dedication of a number of people from diverse disciplines. Therefore, the fact that an organisation is conducting research within a certain therapeutic area means that they have developed a capability within that area. This argument is supported by Henderson and Cockburn (1994) who argue that drug discovery productivity is an increasing function of *component competence*, i.e. knowledge and skills, in particular disease areas.

There are two means by which an organisation may acquire a capability within a therapeutic area. The first one is through the acquisition of another organisation that may already be expert in the field. The second is by slowly acquiring the necessary knowledge. Thus, the importance of the therapeutic areas is such that they have been identified and listed as characteristics for this study.

The therapeutic areas were identified from the annual reports of the sample organisations (Table 8-3). To ensure that the data collected was reliable the data was cross-referenced with related commercial publications (e.g. Financial Times, Drug Discovery and Development Magazine, American Chemical Society Publications).

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To achieve data compatibility and consistency, the diversity of the report formats is considered. Due to variations in both the organisations' locations and the principles used to construct such a report, the data was not in the same format. The required data existed in the following formats:

- *Therapeutic areas.* This was the simplest form to handle as the therapeutic area was explicitly stated e.g. infectious diseases, cardiovascular etc.

- *Diseases.* The name of the disease was stated instead of the therapeutic area. This was less straightforward to handle, as most of the diseases (e.g. Alzheimer's disease, AIDS, angina, hyperlipenia) specified were not known to the author and thus could not be categorised under therapeutic areas.

- *Name of drug.* This was the most difficult format to translate to a therapeutic area as only the name of the drug under development was stated e.g. Pfizer's Cardura.

To achieve data compatibility, the following format was adopted. For the diseases, they were compiled into a list, which was in turn forwarded to a medical practitioner. The medical practitioner then identified the therapeutic area where each disease belongs (e.g. *Alzheimer's* disease belongs to the therapeutic area *neurology*). For the drugs, the *British National Formulary* of the *Royal Pharmaceutical Society of Great Britain* (Mehta, 2001) was used. This publication is used by doctors, pharmacists and other healthcare professionals to provide sound, up to date data about the use of medicines. It includes key data on the selection, prescribing, dispensing and administration of medicines. It is considered a valuable and reliable source for obtaining descriptions and data about drugs. Each drug was found in the formulary (which sorts drugs in both alphabetical order and according to the therapeutic area

they treat) and then from the data provided the therapeutic area was identified (e.g. Pfizer's *Cardura* belongs to the *cardiovascular* therapeutic area).

8.3.8. Organisation structure and process

Chapter 4 discussed and justified organisation structure and process as the second factor that influences the change of drug discovery strategies. This factor includes the structure and process related with the management of the diverse scientific disciplines required for the development of new drugs.

As argued in chapter 4 the advances in scientific knowledge and technology have created the need for specialisation of individuals in different sections of the drug discovery. This in turn has created the need for communication interfaces between these individuals and the teams they are part of. Also the challenge faced by project management techniques is to exercise control without influencing creativity. Over the last century, these techniques together with advances in scientific knowledge and technology have played an important role in the formation of drug discovery strategies.

The characteristics listed in Table 8-5 under the heading organisation include those practices that are associated with the management and coordination of these individuals such as division of labour and centralised management. The historical archives used to obtain data about the organisations of Table 8-3 provided information about this category.

8.3.9. Environment

This factor consists of those elements that are directly associated with the competitive advantage of a pharmaceutical organisation i.e. the drug discovery process. The environment of the drug discovery process was described as consisting

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of the technology and knowledge of other organisations, the legislation and political situation that directly influences the drug discovery process, and the diseases that are targeted. The diseases targeted by organisations depend on the therapeutic area in which they have developed an expertise on. Therefore, data about the diseases that each organisation is targeting, is included in the list of characteristics under the heading *codified knowledge*. For instance, an organisation that undertakes research on endocrinology may be targeting diseases such as diabetes, acromegaly, etc.

A detailed description of all characteristics is included in the Appendix B of this thesis.

As explained earlier the starting point for the development of Table 8-5 is Table 7-2. An examination of the two tables reveals that there are a number of differences. Firstly, Table 7-2 lists 57 characteristics, while Table 8-5 lists 77. This is expected because the level of analysis and the process of collecting data for organisations revealed more detailed characteristics several of which were unique to individual organisations. Secondly, several characteristics, such as *herbal's use*, included in Table 7-2, are not included in Table 8-5. This is because these characteristics correspond to strategies that were present at the beginning of the pharmaceutical history and thus, they are not found in the strategic configurations of the organisations included in this chapter. Also, the characteristics of Table 7-1 correspond to generic strategy types. For instance, the characteristic *introduction of computer aided drug design* (included in Table7-2) represents a technology that influenced the formation of populations of drug discovery strategy and not simply one single organisation. Finally, the numbers given to the characteristics of the two tables are different. In both cases the numbers are the ones used in the tables of the Appendix.

Table 8-5 Categorisation of characteristics

Technology	Knowledge		Organisation	Environment
	Codified Knowledge	Tacit Knowledge		
1. Computational power	49. Synthetic dyes	13. Diversification	15. Focus on pharmaceuticals	39. World wars
2. Instrumentation development	50. Alkaloids	14. Reduction of diversification	16. R&D focus	40. Cyclamates
3. Disposable devices development	51. Antibiotics	21. Limited discovery	17. Increase in R&D expenditure	41. Enforced price reductions
4. Biotechnology	52. Nutritional therapy	22. Dependence on strangers' research (generics)	18. Cost cutting R&D	42. Intense competition
5. Fermentation technology	53. Vitamins	23. Reformation of others' rejected/ unfinished research	19. R&D performance	43. Community aid
6. Combinatorial chemistry	54. Insulin	24. Merger	20. R&D concentration	44. Price reductions through competition
7. Rational drug design	55. Apothecaries	25. Acquisitions	29. Focus on cost effective analysis and treatment	45. Government support
8. High throughput screening	56. Chemical enzymes	26. Collaboration with academia	30. Centralised management	46. Government legislation
9. Proteomics	57. Neurology	27. Collaboration/ joint ventures	31. Research units	47. Patent protection laws
10. Genomics	58. Infectious diseases/vaccines	28. Marketing	32. Globally organised research	48. Nationalisation
11. Procaine Development	59. Haematology	35. Management innovations	33. Reorganisation (restructuring)	
12. Blood collection	60. Musculoskeletal	37. Niche Market establishment	34. Division of labour	
	61. Oncology		36. DNA marketing	
	62. Immunology		38. Individual efforts	
	63. Transplant			
	64. Gynaecology			
	65. Metabolic diseases			
	66. Cardiovascular			
	67. Gastroenterology			
	68. Genitourinary			
	69. Opthamology			
	70. Endocrinology			
	71. Psychiatry			
	72. Respiratory			
	73. Paediatrics			
	74. Anaesthesia			
	75. Surgery			
	76. Orthopaedics			
	77. Dermatology			

8.3.10. Validation of data

To increase the confidence of the collected data, those organisations from Table 8-3 that are still in existence today were surveyed to validate the characteristics listed in Table 8-5.

The survey used a structured questionnaire and was distributed by email, telephone interviews, and post mail. The questionnaire was directed to the research and development departments of the surveyed organisations. The contact person within the departments was identified through the company website or the business directories.

Once a contact with each organisation was established, the aims and scope of this study were explained and the characteristics identified for each organisation were confirmed. As shown in Table 8-4 nineteen pharmaceutical organisations were contacted.

The characteristics shown in Table 8-5 is the final validated list. The characteristics not validated, were omitted. The final data matrix (organisations V characteristics) for building the organisation cladogram is presented in Appendix C.

8.4. Step 3: Setting polarity

The polarity of the characteristics (in most cases) was derived by observing the sequence of appearance of the characteristic states in history. For instance, characteristic 13, *Diversification*, has two states. The first, is that of the absence of diversification, i.e. an organisation focuses on its original line of research. The second, is that of the presence of diversification i.e. an organisation attempts to enrich its research portfolio by developing new lines of research. Historically, organisations

diversified when their own line of research brought no results or was considered obsolete. Therefore, the absence of diversification precedes its presence. Thus, the absence of diversification is considered a plesiomorphic or ancestral state, while the presence of diversification is considered an apomorphic or derived state.

Similarly, the characteristics representing the codified knowledge may only be present or absent. That is an organisation is either undertaking research in a certain therapeutic area or it is not. Therefore, the absence of the characteristic will be the plesiomorphic (ancestral) state while the presence will be its apomorphic (derived).

Although this rule was applied to most characteristics, it cannot be generalised to all the characteristics of the cladogram. This is because there are some characteristics, where it is not possible to distinguish which characteristic states came first historically. One such example is characteristic 23, *Reformation of others' rejected/unfinished research*.

8.5.   *Step 4: Characteristic coding*

So far the characteristics, their states and the direction of change of these states have been defined. This step involves the conversion of the characteristic states into numerical symbols. The purpose of this step is to construct a matrix, which includes all the studied organisations, their characteristics and their states. This matrix is used in the next step for the construction of the organisation cladogram.

The matrix summarising the data and used for the next step of the construction of the cladogram is shown in the table of the Appendix C. The first column of that matrix includes the names of the organisations that were included in the study. The names of the organisations denote the drug discovery strategy of that organisation i.e. it is not the organisation that is classified, but the configuration of its drug discovery strategy

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The first row includes the characteristics. Similar to the matrix constructed for the population cladogram, the boxes that include the number 1 denote that the characteristic that is shown at the top of the column where the box is included is present in the drug discovery strategy of the organisation shown in the first box of the row. Similarly, the boxes that include the number 0 denote that the characteristic that is shown at the top of the column where the box is included is not present in the drug discovery strategy of the organisation shown in the first box of the row.

8.6. Step 5: Construct the cladogram

So far the characteristics, their states, polarity and codes have been defined and all the acquired data has been summarised in a matrix shown in Appendix C. The final step of the construction of the cladogram involves its actual construction. Similar to the construction of the population cladogram the software packages Phylip, Paup and MacClade were used.

8.6.1. Phylip

The treefile produced by the Wagner parsimony method included forty cladograms while the Camin-Sokal provided forty-nine different cladograms.

Figure 8-2 and Figure 8-3 each show the three most parsimonious (i.e. the ones with the shortest treelength and highest values of consistency and retention indices) cladograms found in the Wagner and Camin-Sokal treefiles respectively

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Figure 8-2 Wagner sample cladograms
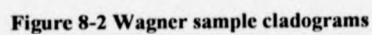
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Figure 8-3 Camin Sokal sample cladograms

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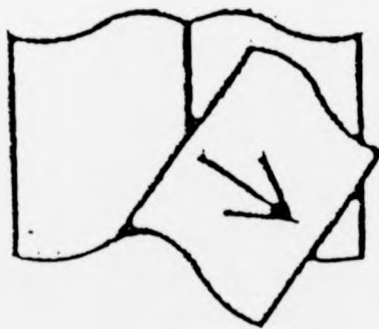
8.6.1.1.1. PAUP

The number of cladograms produced by PAUP was eighty-four. Figure 8-4 includes the three most parsimonious cladograms. The + sign included in the statistics of Figure 8-4(c) implies that the cladogram includes an unresolved polytomy (for an explanation of the polytomy see section 6.2.7.2 of chapter 6). The unresolved polytomy is encircled.

8.7. *Determining the optimal cladogram*

The three treefiles previously constructed were processed using MacClade and the average indices are shown in Table 8-6.

Table 8-6 Indices of organisation cladograms

Index	Wagner (Phylip)	Camin-Sokal (Phylip)	PAUP
Consistency Index	0.26	0.25	0.26
Retention Index	0.49	0.46	0.50
Tree length	296	311.67	296

The optimal cladogram is the one with the highest consistency and retention indices and the lowest tree length. The first conclusion is that the three sets of cladograms are relatively similar, but not as similar as these listed in Table 7-3 for the population cladogram. The second conclusion is that the longest cladograms (least parsimonious) are the ones provided by the Camin-Sokal method. Similarly, the shortest cladograms and the ones with the highest consitency indices were provided by PAUP. Consequently, the optimal cladogram should be one of the 84 cladograms provided by PAUP.

Figure 8-4 PAUP cladograms with best indices

The selection of the best cladogram was carried out in two stages. First the three tree statistics (treelength, consistency index, and retention index) were used. Three of the 84 cladograms produced by PAUP had slightly higher consistency and retention indices (0.26, and 0.51 respectively). The three cladograms are shown in Figure 8-4. A comparison of the branching arrangement of the three cladograms reveals that all three of them group the drug discovery strategies in 2 groups and 5 subgroups (these groups will be presented and explained in detail in the following section). The differences between the cladograms are in the order of the drug discovery strategies within each group. To illustrate this, these differences have been encircled on Figure 8-4. From the comparison of the encircled parts of Figure 8-4 it may be concluded that the only difference between them is indeed the order by which the drug discovery strategies appear in each grouping.

As explained in section 7.6.3 such differences could be significant when studying biological organisms as they could trigger philosophical arguments about evolution. However, in the case of this research, where the cladogram is used to classify drug discovery strategy types and not to explore their order of evolution, such small differences are insignificant. Also, as explained in section 6.2.8, the aim of the construction of this cladogram is the identification of such groupings (populations) while the order that the taxa appear within each grouping is not important for this research. Therefore, any of the cladograms shown in Figure 8-4 are correct within the scope of this thesis. However, as it is not practical to refer to more than one cladogram, cladogram (a) of Figure 8-4 has been selected and will be used for further discussion and testing of the four hypotheses developed in chapter 5.

Similar to the construction of the population cladogram, the confidence of the data set should be considered i.e. to establish the *significance of the cladistic structure*

(Kitching et al., 1998 p. 118). To address this confidence issue the process proposed by Archie and Felsenstein (1993) and explained in chapter 7 is followed.

MacClade was used to construct random cladograms and calculate their mean statistics (see Table 7-4).

Table 8-7 Mean statistics for random cladograms

Treelength	Consistency Index	Retention Index
456	0.17	0.15

The mean treelength of the random cladograms is 456 (Table 7-4) and is significantly higher than that of the cladograms constructed in the previous section (292 in Table 8-6). Therefore, it can be concluded that there is confidence in the data set and that the results of the cladistic analysis presented above are not the product of chance and it can be said that the data set contains *significant cladistic structure*.

8.8.   *Analysis of the cladogram*

In this section the selected cladogram (Figure 8-5) is analysed. The section presents, explains and labels the major groups identified on the organisation cladogram. Also, an aggregated version (Figure 8-6 Aggregated organisation cladogram) of the organisation cladogram is presented. The aims of the aggregated organisation cladogram is to demonstrate the groupings identified in this section along with the defining characteristics, and to bring the organisation cladogram to the same level as the population cladogram. As explained in section 6.2.8 the drug discovery strategy types classified by the population cladogram correspond to a number of organisations that have adopted these strategies. Therefore, by identifying classes of organisations that have adopted such strategies, the organisation cladogram can be elevated to the level of the population cladogram. This will help compare the two cladograms.

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As explained in the previous section 2 groups and 5 subgroups of organisations were the same in all 84 cladograms constructed by Phylip. These groupings are shown on the aggregated organisation cladogram of Figure 8-6.

Figure 8-5 Selected cladogram

Treelength 296
CI 0.26
RI 0.51
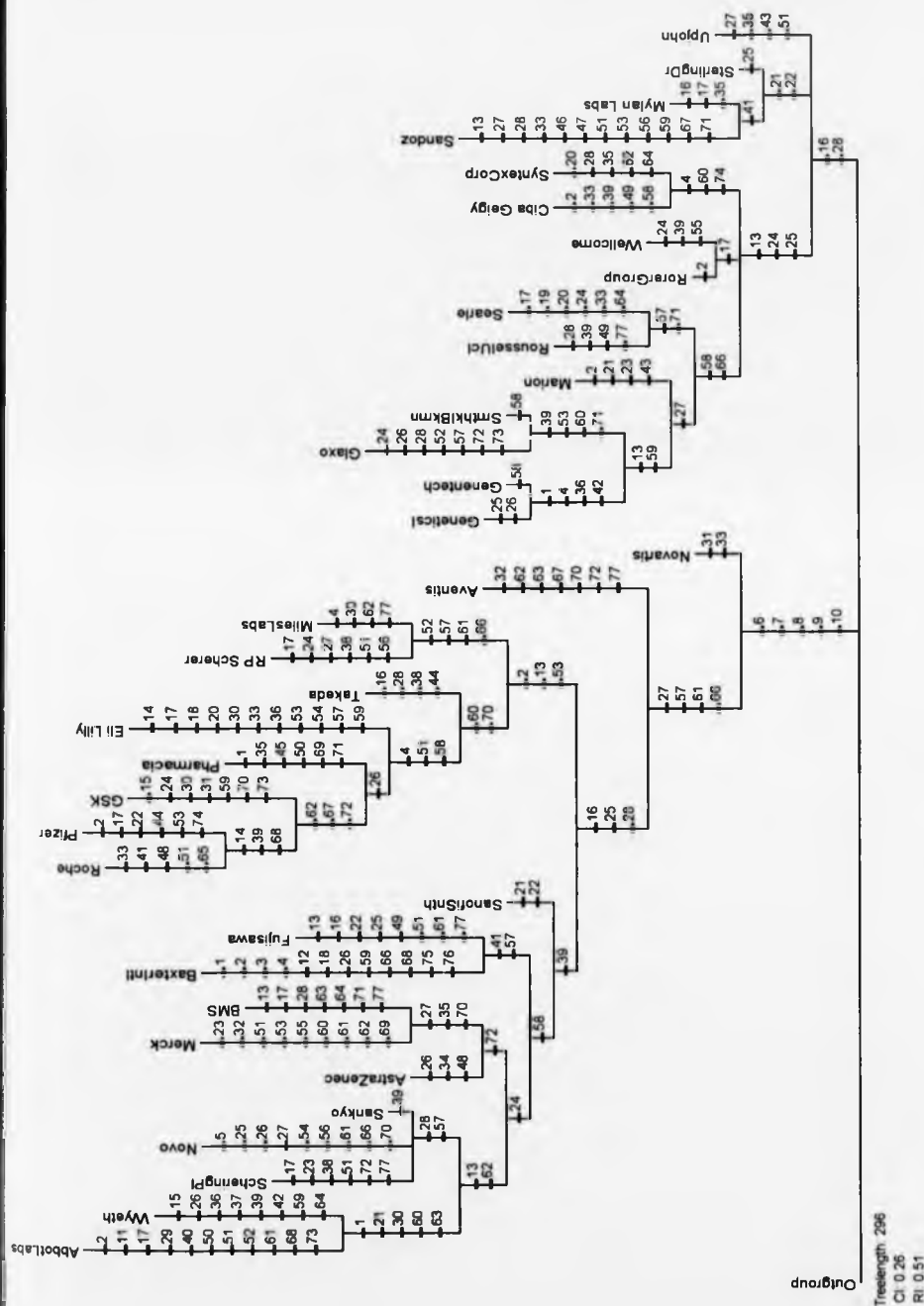
Two major groups of drug discovery strategies were identified at the same level. The first is defined by characters 16 and 28 and the second by characters 6, 7, 8, 9, 10, 16, 25, 27, and 28. These have been named the *technology driven*, and the *alternative strategies* respectively. The two groups can be divided into five subgroups, which have been named *knowledge and instrumentation focus*, *externally enforced management pattern*, *me-too*, *biotechnology*, and *partnerships and acquisitions*. The names given to these branches are in line with the names of the population cladogram and they depend on their defining characteristics.

The following sections describe each branch.

8.8.1. Technology driven

The main characteristics of the first group are 6 7 8 9 and 10. These characteristics are *combinatorial chemistry (6), rational drug design (7), high throughput screening (8), proteomics (9), and genomics (10)*. These characteristics were considered and discussed in chapter 4. Most of the drug discovery strategies that are present in this branch belong to those organisations that are still in existence today and have therefore adopted the new technologies to remain competitive. In line with this argument the name given to this branch is *technology driven*.
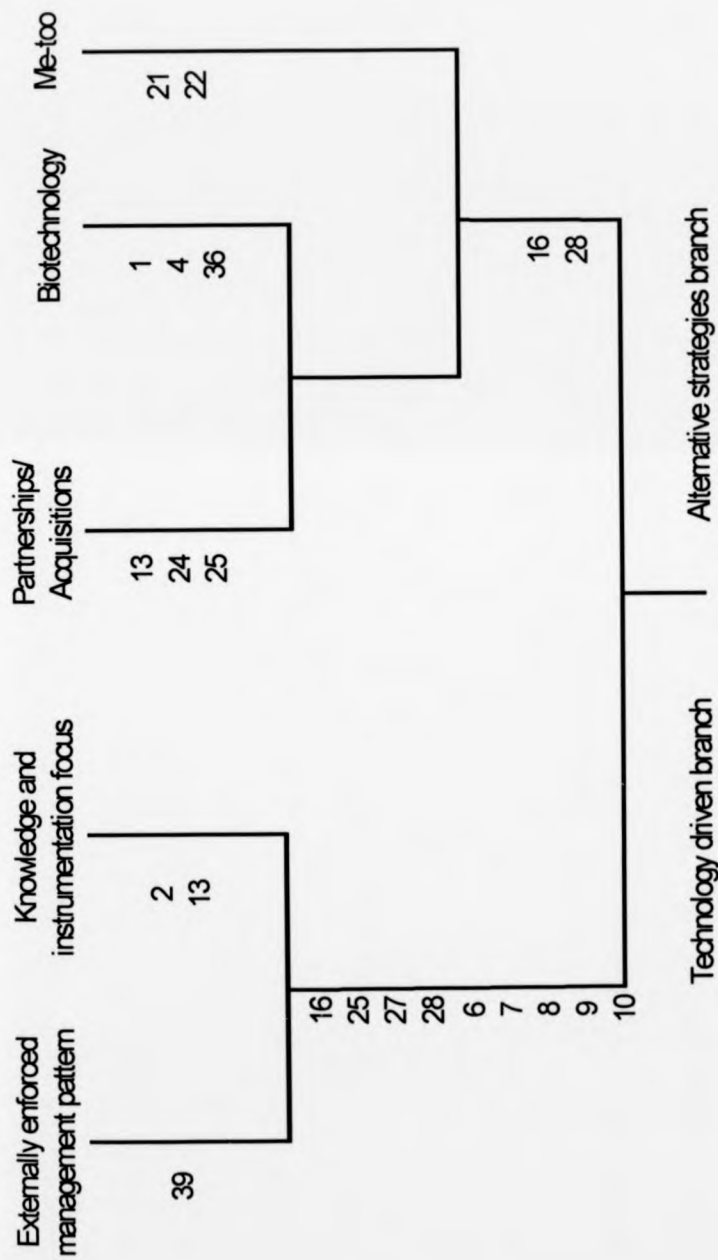
Figure 8-6 Aggregated organisation cladogram

Another important characteristic present in the drug discovery strategies of this branch is the characteristic *collaboration and joint ventures (27)*. An analysis of the cladogram reveals that drug discovery strategies that do not belong to the technology driven branch have also implemented this characteristic. The need for collaboration and joint ventures was identified in chapter 5 as an important aspect of the development of new knowledge. It is therefore anticipated that this characteristic will be present in more than one branch. Finally, the characteristics *R&D focus (16), acquisitions (25), and marketing (28)*, are also present in most of the drug discovery strategies of the technology driven branch.

The technology driven branch is split into two sub-branches. The first one is that of the drug discovery strategies that have acquired the characteristic *world wars* (39) and the second is that of the drug discovery strategies that have acquired characteristics *instrumentation development (2)*, and *diversification (13)* as explained in the following sections.

8.8.1.1. Externally enforced management pattern

This branch was not present on the population cladogram. This strategy type is traced back in the 1940s and is associated with the political control enforced to pharmaceutical organisations during the world wars (39).

The strategic configurations that have been affected by the wars revolve around three issues. The first is associated with the transfer of the research of German organisations to their American competitors after the Second World War (e.g. Abbott Laboratories, Schering-Plough, Sterling Drug Inc.). The second is associated with the wartime restrictions on imports and the boycott of German products. The restrictions on imports meant that many pharmaceutical organisations faced shortages of

ingredients (e.g. Ciba Geigy was unable to secure raw materials and chemical intermediaries for the production of dyes from German suppliers in 1914). These shortages upset the equilibrium that had existed before the wars between German and other pharmaceutical organisations. The boycott of the German pharmaceutical products had a twofold result. Firstly, the German organisations had to organise themselves for anti-German sentiments both during and after the war (e.g. Merck turned over a sizable portion of its stock to the Alien Property Custodian of the United States). Secondly, the European organisations that had either established research plants in Germany or were supplying drugs to Germany also had to be prepared for a change in the political structure. The final issue is associated with the increasing necessity of certain therapeutic products for the war like blood collection, antibiotics, anaesthetics, and vitamin supplements.

The rest of the drug discovery strategies included in these branches are differentiated by the type of codified knowledge organisations have acquired an expertise on.

8.8.1.2. Knowledge and instrumentation focus

This strategy type is present on the population cladogram. The characteristics that differentiate this branch to the *externally enforced management pattern branch* previously discussed are *instrumentation development (2)*, and *diversification (13)*. Instrumentation development is a technology characteristic, while diversification is a tacit knowledge characteristic.

The acquisition of the instrumentation development characteristic implies that a drug discovery strategy does not only focus on the discovery and development of new drugs, but also on the development of medical instruments. As explained in chapter 7 the emergence of this branch was enabled with the development of computing

technology, when large computers became widely used in pharmaceutical laboratories, and the understanding of DNA, hence its name.

The acquisition of the diversification characteristic on the other hand implies that an organisation has entered new market segments by introducing new products. The decision for a diversification strategy is usually coupled with a merger with or an acquisition of another organisation.

These two characteristics are usually triggered by the need of an organisation to increase their product portfolio. Both the development of instruments, and diversification have a similar aim, the introduction to the market of new drugs.

8.8.2. *Alternative strategies*

The second main group of the cladogram is the one whose main characteristics are *R&D focus (16)* and *Marketing (28)*. Although these characteristics are important and are possessed by most of the drug discovery strategies in that branch, they are also present in the first branch. Therefore, the main difference between the two branches (technology driven and alternative strategies) is the lack of the technologies (characteristics 6, 7, 8, 9, and 10). Most of the drug discovery strategies which are included in this branch belong to organisations that do not exist any more mainly because they have merged or been acquired by other organisations. Hence, they have not adopted these technologies into their drug discovery process.

8.8.3. *Partnerships/Acquisitions, biotechnology,* and *me-too*

Within the *alternative strategies* branch three smaller groups were identified. The first is the partnerships and acquisitions branch and is differentiated by characteristics, *diversification (13), merger (24),* and *acquisitions (25)*. Within this branch several smaller groups of drug discovery strategies may be identified. The principal

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differentiation of these groups is the core knowledge that they possess i.e. the therapeutic areas. The second is the biotechnology and is differentiated by characteristics *computational power (1)*, *biotechnology (4)*, and *DNA marketing*. The third is the me-too branch and is differentiated by characteristics *limited discovery (21)*, and *dependence on strangers' research (22)*.

Diversification is a characteristic that was acquired by many organisations particularly during the 1960s and 1970s and it was a result of the lack of major breakthroughs in drug discovery (e.g. Marion Laboratories spent little on original research while they invested on reformulating and developing products discovered, but rejected by other companies) and the establishment of an organisation in a foreign country (e.g. Roussel-Uclaf was established following a merger between a French and a German organisation). Mergers and acquisitions are two characteristics that have been present in strategic configurations throughout the pharmaceutical history. However, their popularity has significantly increased during the 1980s and 1990s as explained in chapter 7. This was the direct result of the escalating costs of drug discovery. Smaller research organisations needed the financial support of larger organisations while larger organisations needed the flexibility and technology breakthroughs of smaller organisations.

The drug discovery strategies that belong to the second branch, biotechnology, are associated to those entrepreneurial organisations that were established following the development of technology that allowed scientists to combine bits of DNA in the 1970s.

The drug discovery strategies that are included in the third branch, me-too, are the ones that belong to organisations that belong in the generics industry. Limited discovery and the escalating costs of drug discovery forced several organisations to

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pursue different approaches to survive in the market. As it was previously discussed one of those approaches was diversification. Another less popular approach was that of the manufacturing of generics (e.g. Mylan Laboratories). Generics are those drugs that are manufactured once their original patent has expired. The difficulty associated with this approach is that as drugs come off the patent, competing organisations quickly manufacture their own generic versions. Due to the nature of the strategies grouped in this branch that advocates imitation of drugs of other pharmaceutical organisations the branch has been named *Me-too*.

8.9.   Discussion on the four hypotheses

This section of this chapter discusses how the population cladogram, constructed in chapter 7 (Figure 7-7), and the organisation cladogram (Figure 8-5) address the four hypotheses developed in chapter 6.

8.9.1. 1st hypothesis

There are similar drug discovery strategies employed by different pharmaceutical organisations to form populations whose (the population's) size follows a concave pattern of growth and decline.

As explained in the previous section of this chapter the organisation cladogram classified drug discovery strategies into five groups; me-too, biotechnology, partnerships and acquisitions, knowledge and instrumentation focus, and externally enforced management pattern, as shown in the aggregated organisation cladogram of Figure 8-6. With these branches there are variations of drug discovery strategies implemented by different organisations. Four of these groups match four of the groups of the population cladogram. Therefore, it may be argued that the first part of

the hypothesis that requires the drug discovery strategies to form populations is validated.

As explained in section 5.2.1.1 the size of a population is the number of entities that exist within that population. Therefore, the size of each population aggregated on the cladogram of Figure 8-6 is the number of the organisations included in the corresponding groups of the cladogram of Figure 8-5. For instance, the population *externally enforced management pattern* includes the organisations (1) AbbotLabs, (2) Wyeth, (3) ScheringPlough, (4) Novo, (5) Sankyo, (6) AstraZeneca, (7) Merck, (8) BMS, (9) Baxter International, (10) Fujisawa, and (11) Sanofi Synthelabo. Therefore, the size of that population is 11.

Table 8-8 summarises the sizes of the 5 populations of drug discovery strategies identified in the cladogram of Figure 8-6.

Table 8-8 Size of populations

Drug discovery strategy	Number of drug discovery strategies in population
Me-too	3
Biotechnology	2
Partnerships and acquisitions	9
Knowledge and instrumentation focus	8
World wars	11

Although four of the branches of the population cladogram match the branches of the organisation (me-too, biotechnology, partnerships and acquisitions, and knowledge and instrumentation focus), constructed and explained in chapter 7, there are another 11 (one of the taxa is the outgroup which was included only for simplifying the polarisation process, as explained in chapter 6) that do not. There are two possible reasons for this. The first is that in line with the second part of the hypotheses two of the drug discovery strategies found early in the pharmaceutical history, *unorthodox*

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and *individual efforts*, do not exist anymore. Unorthodox strategies are not pursued anymore due to their inefficiency and thus this population could be extinct. Also the need for combining knowledge from different disciplines could have also eliminated the population of *individual effort* strategies. The elimination of this strategy type shows that populations of drug discovery strategies may follow a concave pattern of growth and decline as suggested by the second part of the 1st hypothesis. If this line of argument is correct then the second part of the hypothesis is also validated, since the size of these older strategies reduces, while the size of the newer increases i.e. the size of the population follows a *concave pattern of growth and decline*. However, the cladogram does not provide strong evidence to support this argument. This is because patterns of change for population size are not clearly depicted on the cladogram.

The second possible reason for the smaller number of branches on the organisation cladogram, is that both the number of organisations and the process of collecting the characteristics has not covered the complete spectrum of the drug discovery strategies classified by the population cladogram. Although this may be considered a limitation of the methodology, it does not affect the overall conclusions and findings of the cladogram constructed in this chapter. The aim of the population cladogram was to provide a platform for demonstrating how the four hypotheses could be validated and not an exact match with the organisation cladogram.

8.9.2. 2nd hypothesis

Within a drug discovery population, there are strategies that differ to each other in terms of their characteristics and their fitness.

The organisation cladogram (Figure 8-5) classifies drug discovery strategies that individual organisations implement. The configuration of an organisation's drug

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discovery strategy can be different to that of another's because, as explained in chapter 4, it is a function of its idiosyncratic processes such as, strategic decision-making, creating alliances, and its interpretative flexibility (the degree to which users of a technology are engaged in its constitution during development and use (Dougherty et al. 1998)).   In addition, competitive advantage depends on the organisational processes, shaped by an organisation's asset positions (Helfat, 1997) and moulded by its evolutionary and co-evolutionary paths.   The branches of the organisation cladogram (Figure 8-5) show the characteristics that differentiate one drug discovery strategy from another.   The main difference between the implemented drug discovery strategies of individual organisations is the core knowledge they have acquired, i.e. the therapeutic areas.   Consequently, the cladogram clearly demonstrates that there is difference in the characteristics of their drug discovery strategies and thus validates the first part of the hypothesis.

The second part of the hypothesis requires the strategy of each branch to demonstrate variation in their fitness.   Fitness was defined in chapter 5 as:

> *The condition where the configuration of an organisational strategy*
> *matches that of the environment and the frequency of its characteristics*
> *appearing in future strategies is high.*

The fitness of organisations may be demonstrated on a cladogram by observing the response of drug discovery strategies to a change in an element of the environment such as the world wars (which could be classified as a political situation).   The branch *externally enforced management pattern* includes the drug discovery strategies of organisations that were present during the world wars.   Therefore, these strategies have been successful in curing diseases to a degree that have managed to make the organisations successful and present up to the end of the 20th century.

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The organisation cladogram (Figure 8-5) provides evidence for the fitness of drug discovery strategies following a change in the environmental conditions. However, such evidence is not present for the fitness of these strategies in the market i.e. the degree to which these strategies help the organisations achieve their market objectives. Evidence for this requires detailed market analysis and comparison with the performance of the pharmaceutical organisation where each strategy is implemented. The use of the cladogram is limited to the classification of strategies within a population and does not provide any data about the market conditions. One suggestion however, may be made from the cladogram with regard to the market performance of organisations. The sustainability of organisations could imply that the implemented strategies have been successful. Although the success of a pharmaceutical organisation heavily relies on the discovery of new drugs, other issues like marketing, diversification, mergers and acquisitions play an important role. Therefore, difference in the financial performance of an organisation could imply difference in the implementation of strategies. The cladogram does not provide enough supporting evidence for this argument, but it is an interesting issue to examine in future work.

Therefore, the organisation cladogram provides appropriate evidence to support the 2nd hypothesis. It has demonstrated that within the classified populations of drug discovery strategies, there are strategies that differ to each other in terms of their characteristics such as the therapeutic areas and fitness such as the survival of the organisations following the world wars. However, the cladogram does not provide enough evidence for the fitness of drug discovery strategies in the market

8.9.3. 3rd hypothesis

Those characteristics of drug discovery strategies credited with successful drug discovery performance are likely to be present in future strategic configurations, while those characteristics that are not are likely to be absent.

This hypothesis is validated by the organisation cladogram (Figure 8-5), because the characteristics of the early strategies are also present in the later ones. For instance, characteristics 4, 6, and 7 (industrial revolution, chemical extraction, and microbial theory of disease) are also present in later strategies, while characteristics such as the therapeutic areas, which only depend on the specialisation of each organisation, are not. The mechanisms by which the characteristic transfer takes place could be explained by the three types of isomorphic change discussed in detail in chapter 5; coercive isomorphism; mimetic processes, and normative isomorphism.

An additional mechanism that enhances the transfer of characteristics is that of collaboration between two organisations. As it was also explained in chapter 5 this collaboration might take several forms e.g. mergers, acquisitions, and research agreements. When the result of the collaboration is the formation of a new organisation, as is usually the case with mergers and acquisitions, then the newly founded organisation acquires the majority of the characteristics of the previous organisations. Naturally, through the reorganisation and restructuring that usually follows such an action, the characteristics change. On the other hand when the collaboration is the result of a research agreement between two organisations then the diffusion of characteristics could be more selective and is usually focused on the core knowledge that is being acquired.

The occurrence of characteristics' transfer is also present on the population cladogram (Figure 7-7). Those characteristics that have proved to be successful have been transferred to later drug discovery strategies This is clearly illustrated by characteristics 16 and 28 (R&D focus and marketing). These characteristics were considered vital for the sustainability of a pharmaceutical organisation Consequently, these characteristics are present in both main branches of the organisation cladogram (alternative strategies and technology driven)

The second part of the hypothesis suggests that those characteristics that have not been credited with the success of strategy will be absent from future strategic configurations This part is demonstrated by the fact that early characteristics such as *herbals' use (1)* and *random discoveries with no scientific justification (2)* that were present on the population cladogram (Figure 7-7) have not been included in the organisation one (Figure 8-5). As it was discussed earlier strategies such as *unorthodox* are not pursued anymore and thus their characteristics have not been transferred in later strategic configurations.

Therefore, the organisation (Figure 8-5) and population (Figure 7-7) cladograms provide enough evidence to support the third hypothesis. They demonstrate that those characteristics of the drug discovery strategies, such as chemical extraction that have been credited for the success of a strategy in the past, are present in future strategic configurations, while those characteristics that are not, such as herbals' use, are absent.

8.9.4. 4th hypothesis

With a change in environmental conditions those drug discovery strategies that remain are the ones, whose strategic characteristics are favoured by the environment.

As it was discussed earlier, the organisation cladogram (Figure 8-5) does not provide clear information about the market conditions surrounding the drug discovery strategies. However, it provides information about significant events that have influenced the drug discovery strategies (shown in Table 8-5) with the most significant of those being the world wars. The world wars have provided significant changes in the environmental conditions of the drug discovery strategies. The way that strategic configurations were affected by the wars was discussed in section 8.8.1.1.

The organisation cladogram (Figure 8-5) has grouped the drug discovery strategies of organisations affected by the wars together (*externally enforced management pattern* in Figure 8-6). It could therefore be argued that these strategic configurations were the ones that had the capability to withstand the pressures exerted by the war. Those strategies that were present prior to the wars, but were not favoured by the changes are not included in this branch and may thus be assumed that they do not exist anymore. Such an assumption, however, is not directly supported by the cladogram since some of the strategic configurations of the remaining branches correspond to drug discovery strategies that were founded after the war e.g. biotechnology. However, the drug discovery strategies that belong to the *externally enforced management pattern* were sustained after the war was ended. The fact that they have been grouped together by the cladogram demonstrates the importance of knowledge as a core competency in pharmaceutical organisations. As explained in chapter 4 the ability of this industry to quickly recover technological and business momentum after the war's restrictions and destructions suggests that the core competencies of the organisations were not in their physical plant and technology. They were in the collective knowledge they possessed about organic chemistry and

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the associated techniques of their research laboratories' personnel, (Bogner and Thomas, 1996).

In summary, the cladogram provides support for the validation of the fourth hypothesis. It demonstrates that following a change in the environmental conditions the drug discovery strategies that were sustained are the ones whose strategic characteristics such as the collective knowledge are favoured by the environment.

8.10. Fittest strategies

The fourth research question seeks to identify the fittest drug discovery strategies. This section attempts to address this question by identifying the key characteristics that have been revealed on the organisation cladogram Figure 8-5.

Similar to the construction of the population in chapter 7, the construction of the organisation cladogram used three different algorithms (Wagner, Camin-Sokal and Paup). This resulted in the construction of a number of different cladograms. To select the optimal cladogram the statistics of each cladogram were used. One important observation of this process is that a number of characteristics are more decisive than others i.e. they have a stronger influence on the classification than others.

Regardless of the different arrangements of the cladograms, several characteristics have been consistently selected as the most decisive i.e. the ones that are responsible for the formation of the main branches. These characteristics are shown in Table 8-9.

Table 8-9 Decisive characteristics of conglomeration cladogram

Characteristic number	Characteristic name
2	Instrumentation development
6	Combinatorial chemistry
7	Rational drug design
8	High throughput screening
9	Proteomics
10	Genomics
13	Diversification
16	R&D focus
21	Limited discovery
22	Dependence on strangers' research (generics)
24	Merger
25	Acquisitions
28	Marketing
39	World Wars

Instrumentation development is a key characteristic in the history of drug discovery since its acquisition enabled organisations to increase their efficiency. Characteristics 6, 7, 8, 9, and 10 constitute the key enabling technologies, which have been discussed in chapter 4. *Diversification (13)* is an approach that has been used by many organisations as a result either of limited discovery or in an effort to increase market share. *R&D focus (16)* is a characteristic that has been identified in the literature as a source of competitive advantage. *Limited discovery (21)* has forced organisations to seek alternative strategies in the endeavour to survive and be successful. Characteristic 22, *dependence on strangers' research*, is a decisive characteristic as it defines the generics industry. Mergers and acquisitions have been changing the pharmaceutical industry especially over the last two decades and have therefore a significant effect on the drug discovery process. Finally, the *world wars (39)* have also been a significant parameter in the formation of the drug discovery strategies.

All characteristics of Table 8-9, but 9 and 14 (World wars and limited discovery) are controlled by organisations and therefore can be included in strategic planning. Therefore, the fittest strategy as this has been identified by this study is one that includes the twelve characteristics included in Table 8-9. It is important to note that successful strategies heavily rely on good planning and good execution of this planning. The strategic configuration that is being selected in by the environment is the one that reduces the degree of randomness. Using the terminology from the fourth chapter it is the less emergent strategies that are being favoured. These are the strategies that highly utilise knowledge and technology to plan their strategy. This point comes as no surprise to those who employ the latest knowledge and technology to achieve their targets. It is however, of significant importance from a strategic management point of view. This point supports the argument that the less emergent and the more planned strategies equip organisations with the competitive advantage, in this case the discovery of new drugs.

Finally, a note has to me made about the lack of characteristics from the codified knowledge category. The selection of a therapeutic area depends on idiosyncratic parameters such as the research interests of the founder or the geographical area were an organisation was first established. Therefore, although the development of a specialisation in a therapeutic area is considered key for the success of the development of a pharmaceutical organisation, there is not one single therapeutic area that appears to be more significant.

8.11. Conclusions

The aim of this chapter was to construct a cladogram of drug discovery strategies of individual organisations. The chapter explained in detail the methodology followed to

construct the cladogram, and how the data was collected. Using this cladogram (Figure 8-5), the chapter also discussed the validity of the four hypotheses developed in chapter 5 and thus addressed the third research question of this thesis (*How can an evolutionary and classification approach be used to study drug discovery strategies?*).

Similar to the population cladogram (Figure 7-7), the unit of analysis of the organisation cladogram, shown in Figure 8-5, is drug discovery strategies as these were defined in section 4.8 and not organisations. If the unit of analysis was organisations then the resulting treelike structure shown in Figure 8-5 would be a *phenogram* i.e. a branching diagram (dendrogram) that represents phenetic relationships (i.e. *the arrangements by overall similarity based on the available characters without any weighting* (Cain and Harrison, 1960 in Sneath and Sokal, 1973)). This is because organisations selected and used in the organisation cladogram, were not done so according to phylogentic principles. The organizations were used for collecting data about the evolving entity and unit of analysis (i.e. drug discovery strategy). The organizations shown in Figure 8-5 do not have ancestors in the conventional use of the term and therefore, the classification would be based only on the organisations' phenetic relationships. Drug discovery strategies on the other hand, could have ancestors, which would be older patterns of behaviour adopted by the management of one or more pharmaceutical organisations.

The cladogram showed that there is evidence to support the first part of the first hypothesis. That is, the organisation cladogram showed that there are similar drug discovery strategies employed by different organisations to form populations. However, such is not the case for the second part of the hypothesis, which requires the population's size to follow a concave pattern of growth and decline. As explained in

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this chapter, patterns of change of the population size are not depicted on the organisation cladogram (Figure 8-5).

Similar to the first hypothesis, the organisation cladogram (Figure 8-5) provides evidence to support the first part of the hypothesis, but not the second. The cladogram shows that within a drug discovery population, there are strategies that differ to each other in terms of their characteristics, which is the first part of the hypothesis. The cladogram also provides support about the variation of the fitness of the drug discovery strategies following a change in the environmental conditions. However, the cladogram does not provide any evidence about the fitness of the drug discovery strategies in the market.

The third hypothesis required the characteristics of drug discovery strategies credited with successful drug discovery performance to be present in future strategic configurations, while those characteristics that are not to be absent. The population (Figure 7-7) and organisation (Figure 8-5) cladograms provide evidence to support this hypothesis. Characteristics such as *R&D focus (16)* and *marketing (28)* are present in later strategic configurations, while characteristics such as *herbals' use* and *random discoveries with no scientific justification* (characteristic 2 of the populastion cladogram) are absent.

Finally, the fourth hypothesis is also validated by the organisation cladogram. Following a change in the environmental conditions such as the world wars the drug discovery strategies that were sustained are the ones whose strategic characteristics such as the collective knowledge are favoured by the environment.

The chapter also addressed the fourth research question of this thesis, which requires the examination of the characteristics of the fittest strategies. The process followed

for the construction of the organisation cladogram used three different algorithms (Camin-Sokal, Wagner, and PAUP). This resulted in the construction of several cladograms. Although the cladograms were different in terms of both the statistic indices (see chapter 6) and the arrangement of the drug discovery strategies there were 14 characteristics (Table 8-9) that were decisive in all the arrangements. The chapter argued that these characteristics constitute elements of the fittest strategy.

9. CONCLUSIONS

9.1. Introduction

Throughout this thesis, each chapter has an aim and resulting conclusion that contributes to or advances this research towards addressing the research questions listed in chapter 1 and justified in chapter 3. This final chapter presents an overview of the research questions and how they were addressed, and summarises the contribution made to knowledge.

The process followed to address the research questions of this thesis is summarised in Figure 9-1. It begins with the definition of the research problem, and the formulation of the research questions. Following a literature review of drug discovery strategy, strategic management, and evolution, the research questions were reformulated to reflect the findings from the literature, and four hypotheses were developed as part of the third research question. To validate these hypotheses, a business historical study was conducted and two cladistic classifications (cladograms) were constructed, a population cladogram and an organisation cladogram. The black boxes of Figure 9-1 illustrate the process followed to construct the population cladogram while the grey boxes illustrate the process followed to construct the organisation cladogram. The former classified drug discovery types identified from historical and generic industry data collected (e.g. Liebanau, 1987, Jones, 2001, Weatherhall, 1990, Mann, 1999). The characteristics and types identified were used to design the data collection methods for the classification of drug discovery strategies of individual organisations (organisation cladogram). The data collected was found from i) histories of companies, and ii) annual reports. To demonstrate the groupings identified on the organisation cladogram and to bring the organisation cladogram to

the same level as the population cladogram, an aggregated organisation cladogram was also constructed and presented in chapter 8 together with a discussion on the validation of the four hypotheses. This chapter presents the overall research conclusions (answers to research questions), discusses the limitations of the research, and suggests directions for future work.

9.2.   Research Questions

1.   How does the discipline of strategic management relate to the process of drug discovery and what is the definition of a drug discovery strategy?

2.   What are the factors (internal and external) that influence and define different drug discovery strategies?

The first two research questions explore the nature of the concept of drug discovery strategy. Due to the strong link between the two questions, they are addressed together

Chapter 4 reviewed, developed, and integrated the literature of strategic management to i) identify and justify the factors that influence drug discovery strategies, and ii) provide a working definition of the term drug discovery.
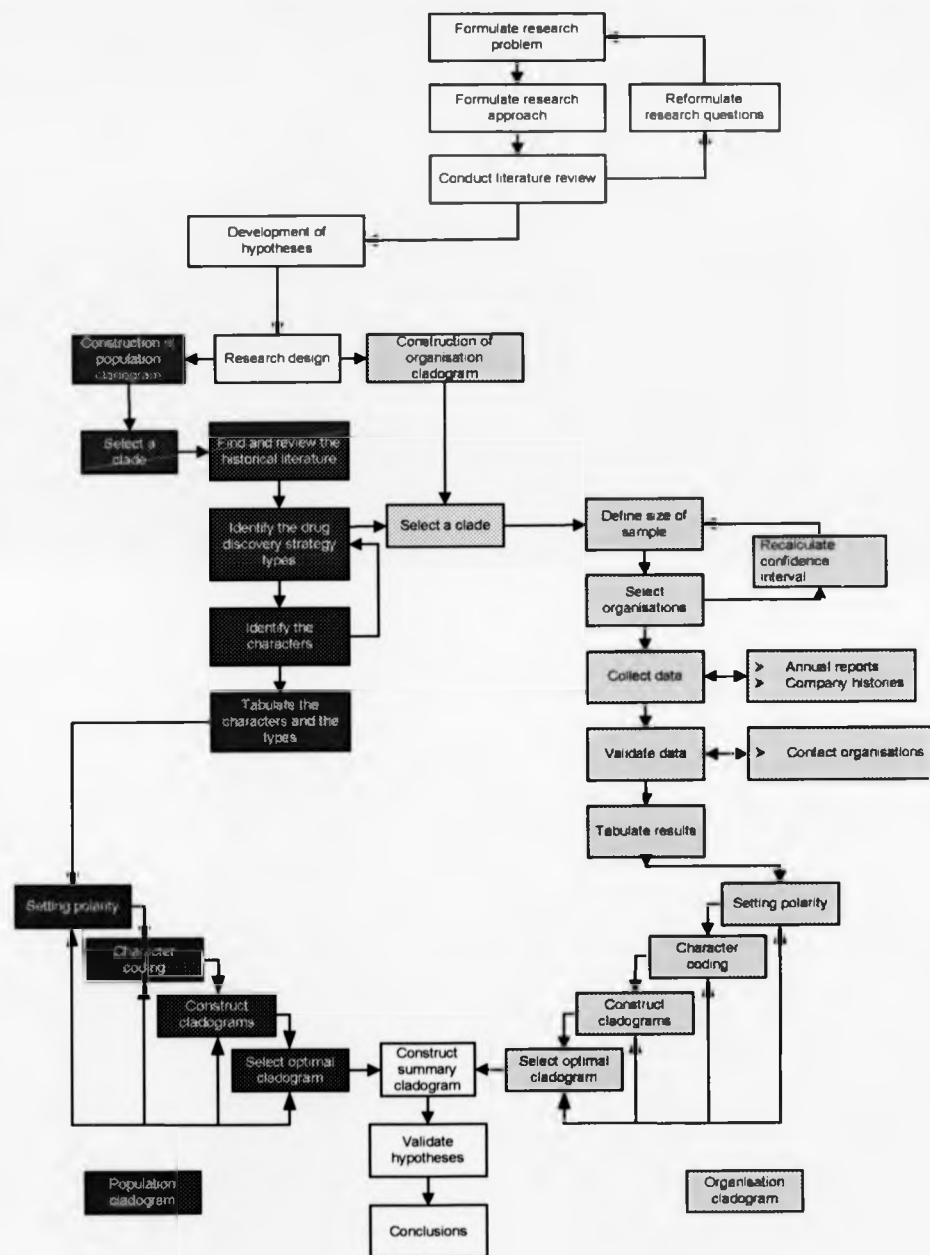
Figure 9-1 Research process

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The four factors identified are:

- **Knowledge** Scientific knowledge acquired by an organisation is a resource critical for discovering new drugs. Such knowledge is generated tacitly, but is then codified and combined with other existing knowledge. The resulting knowledge is then communicated both within an organisation and with other organisations and institutions. The absorptive capacity of an organisation is also critical in the formation of drug discovery strategies as it reflects the ability of an organisation to use the external knowledge and convert it into new drugs.

- **Technology** Advances in technology have altered the pattern by which new drugs are discovered. This alteration has influenced both the success rates of drug discovery and the structure of pharmaceutical organisations since new capabilities are now required. Consequently, technology is similar to scientific knowledge in that it constitutes an important asset of a pharmaceutical organisation, and is critical to any drug discovery strategy.

- **Organisation**. The advances in scientific knowledge and technology created the need for worker job specialisation in different sections of the drug discovery process. This in turn created the need for communication interfaces between these individuals and their teams. Management techniques evolved to address the challenge of exercising control without influencing creativity. Over the last century, these techniques together with the scientific knowledge and technology have played an important role in the formation of drug discovery strategies.

- **Environment**. The elements of the environment that affect the formation of drug discovery strategies are those that are directly associated with the competitive advantage of an organisation, i.e. the drug discovery process. The environment of the drug discovery process is described as consisting of the technology and knowledge of other organisations, the legislation and political situation that directly influence the drug discovery process, and the diseases that are targeted.

The key points that underpin the definition developed in chapter 4 are as follows:

- Drug discovery strategy is seen as a pattern of behaviour rather than a predetermined plan

- Drug discovery strategy is considered a business strategy, rather than a corporate or a functional strategy

- The formation of a drug discovery strategy is determined by using the four strategic factors: knowledge, technology, organisation, and environment.

Therefore, the working definition of drug discovery strategy created in chapter 4 is:

'The pattern of behaviour defined or adapted by the management of a pharmaceutical organisation, within a certain environment, to effectively materialise the corporation's goals and policies in order to achieve a competitive advantage through the application of knowledge and technology on the discovery of new drugs.'

The manner by which the four factors influence drug discovery strategies and each other is outlined in Figure 9-2.
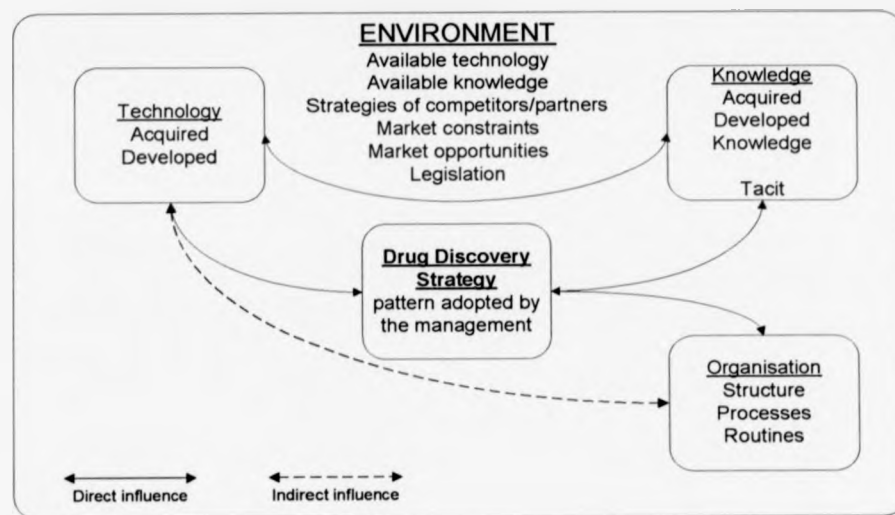
Figure 9-2 Factors influencing the drug discovery strategy

3. How can an evolutionary and classification approach be used to study drug discovery strategies?

To address this research question, chapter 5 identified four requirements that systems should meet for evolution to explain their change These requirements were developed into four hypotheses for the evolution of drug discovery strategies (Table 9-1).

Table 9-1 Hypotheses

Requirement	Hypothesis
1. Existence in populations	*There are similar drug discovery strategies employed by different pharmaceutical organisations to form populations whose (the population's) size follows a concave pattern of growth and decline.*
2. Variation	*Within a drug discovery population, there are strategies that differ to each other in terms of their characteristics and their fitness.*
3. Heredity	*Those characteristics of drug discovery strategies credited with successful drug discovery performance are likely to be present in future strategic configurations, while those characteristics that are not are likely to be absent.*
4. Selection	*With a change in the environmental conditions those drug discovery strategies that remain are the ones whose strategic characteristics are favoured by the environment.*

To validate these hypotheses, chapter 6 justified the use of classification and cladistics. Chapter 7 constructed a cladogram of populations of drug discovery strategy, and chapter 8 constructed a cladogram of drug discovery strategies of individual organisations. The unit of analysis of both cladograms are drug discovery strategies as defined in section 4.8. The differences between the two cladograms are the level of analysis and the sources of data.

The conclusions of the analysis of these classifications are as follows:

1. The two cladograms constructed in chapter 8 (organisation (Figure 8-5) and aggregated organisation (Figure 8-6) cladograms) classified the drug discovery strategies of individual organisations into five groups. Within these groups there are variations of drug discovery strategies implemented by different organisations. Therefore, the first part of the hypothesis is validated (There are similar drug discovery strategies employed by different pharmaceutical organisations to form populations).

The second part of the hypothesis has not been validated by either of the two cladograms because patterns of change of the population size cannot be depicted on a cladogram. However, as argued in chapter 8, the fact that the branches of the population cladogram (Figure 7-7) do not match all the branches of the organisation cladogram could provide some information with regard to the change of the populations' sizes. Early drug discovery strategy types, such as *unorthodox, and use of herbals*, are not pursued anymore due to their inefficiency and thus they could be extinct. The elimination of these strategy types shows that populations of drug discovery strategies may follow a concave pattern of growth and decline as suggested by the second part of the 1st hypothesis. Yet, there is not enough evidence on the cladogram to validate this argument.

2. The branches of the organisation cladogram (Figure 8-5) show the characteristics that differentiate one drug discovery strategy from another. The drug discovery strategies are differentiated by characteristics that belong to each of the four categories, technology, knowledge, organisation, and environment identified and justified in chapter 4. However, the main difference between the implemented drug discovery strategies of individual organisations is the core knowledge they have acquired, i.e. the therapeutic areas. Therefore, the cladogram clearly demonstrates that there is difference in the characteristics of their drug discovery strategies and, thus, validates the first part of the hypothesis (Within a drug discovery population, there are strategies that differ to each other in terms of their characteristics).

The second part of the second hypothesis requires the strategy of each branch to demonstrate variation in their fitness. In chapter 8 it was argued that the

organisation cladogram provides evidence for the fitness of drug discovery strategies following a change in the environmental conditions. The branch *externally enforced management pattern* includes the drug discovery strategies of organisations that were present during the world wars. As argued in chapter 8, these strategies have been successful in curing diseases to a degree that they have managed to make the organisations successful and present up to the end of the 20th century. However, the cladogram does not provide any evidence about the fitness of the drug discovery strategies in the market.

3. The organisation (Figure 8-5) and population (Figure 7-7) cladograms demonstrated that characteristics of early strategies are also present in later ones. As argued in chapters 4 and 8, the mechanisms by which the characteristic transfer takes place could be explained by the three types of isomorphic change, namely, coercive isomorphism; mimetic processes, and normative isomorphism.

   Also, the organisation and population cladograms provide evidence to support the second part of the hypothesis (...those characteristics that are not are likely to be absent). Characteristics of earlier drug discovery strategy present on the population cladogram are not included in the organisation one.

4. Finally, the organisation cladogram (Figure 8-5) has grouped the drug discovery strategies of the organisations affected by the world wars together (*enforced management pattern* branch). As explained in chapter 8, the world wars have provided significant changes in the environmental conditions of drug discovery strategies. The fact that they have been grouped together demonstrates the importance of knowledge as a core competency in

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pharmaceutical organisations. Therefore, the drug discovery strategies that remaine are the ones that had acquired before the war the knowledge characteristics favoured by the environment. Thus, the fourth hypothesis is also validated.

4. What are the characteristics of the fittest drug discovery strategies?

To address this research question, chapter 8 identified 12 key characteristics in the formation of the fittest strategies. These are listed in Table 9-2.

Table 9-2 Decisive characteristics of conglomeration cladogram

Characteristic number	Characteristic name
2	Instrumentation development
6	Combinatorial chemistry
7	Rational drug design
8	High throughput screening
9	Proteomics
10	Genomics
13	Diversification
16	R&D focus
22	Dependence on strangers' research (generics)
24	Merger
25	Acquisitions
28	Marketing

Chapter 8 categorised the characteristics according to the factors that influence drug discovery strategies (Table 8-5). According to this categorisation, characteristics 2, 6, 7, 8, 9, and 10 belong to the *technology* category, characteristics 13, 22, 24, 25, and 28 belong to the *tacit knowledge* category, and characteristic 16 belongs to the *organisation* category. The characteristics that belong to the category environment are omitted because they are outside the control of a pharmaceutical organisation and thus cannot be included in strategic planning. Finally, as explained in chapter 8,

(section 8.10) none of the characteristics that fall under the *codified knowledge* category are included in Table 9-2.

9.3. Contribution to knowledge

The contribution to the body of knowledge of this thesis is summarised in the following points:

- The creation of a definition of drug discovery strategy.

- The identification of the factors that influence the change of drug discovery strategies

- The creation of an evolutionary classification that identifies and arranges different types of drug discovery strategy, and reveals the characteristics of the fittest

- The validation of evolution as a process for understanding change as a process for understanding change in drug discovery strategies.

9.4. Limitations of this research

As with all research projects, the limiting aspects of the work are often associated with the tools and methods used. Regardless of the method or tool, they all provide a partial representation of reality. The following discussion considers the limitations of the resulting cladograms and the data collection method.

9.4.1. Low indices

As discussed in chapter 6, the theoretically perfect cladogram would be the one where the consistency and retention indices are equal to one. Lower values suggest low performance of the data set, i.e. there are characters that appear on the cladogram

more than once. Some indices of cladograms found in the literature are shown in Table 9-3.

Table 9-3 Indices found in the literature

Source	Reference	Consistency index	Retention index
The automotive cladogram	Leseure, 1999	0.89	(not calculated)
The hand tool industry cladogram	Leseure, 1999	1.0	(not calculated)
Electronics industry cladogram	Fernandez, 2002	0.1	0.48
The population cladogram		**0.79**	**0.92**
The organisation cladogram		**0.26**	**0.50**

Although the consistency and retention indices calculated for the population cladogram are high, the ones calculated for the organisation cladogram (Figure 8-5) are relatively low. This implies that the data set does not fit well to the proposed cladogram. The following discussion provides reasons for the low indices and compares them with the other indices shown in Table 9-3.

One possible reason is the large number of taxa. Kitching et al (1998) argue that as the number of taxa increases, values of CI tend to decrease. In fact, they argue that when the number taxa increases, the consistency index will decrease irrespective of any change in the information content. The number of taxa of the automotive cladogram (Leseure, 1999) is 16 while its consistency index is high (0.89). In the case of this research, the number of taxa is 36. Such a number is considerably high and therefore a low consistency index is expected and should not undermine the structure of the cladogram.

Organisations could implement more than one strategy at any given time. Therefore, an organisation could belong in more than one branch at any given moment. As the structure of the cladogram does not allow the strategic configuration of an organisation to appear more than once on the cladogram, the characteristics of a strategy may appear a number of times on the cladogram. Although this is the main reason why the consistency and retention indices are low, it does not reduce the value of the analysis. This is because the analyst is aware of the multiple appearances of the characteristics on the organisation cladogram and they are taken under consideration.

Although the branches are different, the organisation cladogram has classified the drug discovery strategies according to most dominant characteristics (the selection of the dominant characters depend on the algorithm used). The fact that most of the cladograms are similar means that the selection of the characteristics for the development has been consistent. However, a researcher using cladistics must be careful when conclusions are drawn as a characteristic, which has been considered important for one branch, may not be so for another. Although this could be true within the scope of the cladogram, it may not be so in reality. Therefore, a researcher has to check that the characteristics have been selected realistically.

Comparing the values of the indices shown in Table 9-3, it may be concluded that the indices of the population cladogram are closer to those of the automotive cladogram (Leseure, 1999) while those of the organisation are closer to the electronics industry cladogram (Fernandez, 2002). As explained in chapter 6, the level of analysis of the population cladogram (Figure 7-7) is that of drug discovery strategy types (classes of strategies that share a common profile along conceptually distinct characteristics) while that of the organisation cladogram is drug discovery strategies of individual organisations (see Figure 9-3). The automotive cladogram classified

automotive manufacturing systems, i.e. those technologies and processes used for assembling cars (Leseure, 1999). These systems may have been adopted by classes of organisations. Therefore, the level of analysis of the automotive cladogram is consistent with that of the population cladogram constructed in this thesis, hence, the similar values. The fact that the values of the automotive cladogram are higher is due to the condition of its data set. Compared to the pharmaceutical, the automotive industry is widely documented and it is far easier to collect and process relevant data.

On the other hand, the electronics industry cladogram classified manufacturing systems of individual organisations. Therefore, the level of analysis of the electronics industry is consistent to that of the organisation cladogram. Again, the values of the indices of the two cladograms (organisation and electronics industry) are close. Similar to the previous cases, the fact that the values of the indices of the organisation cladogram are higher is due to the condition of the data set. The electronics industry cladogram collected data from a very large set of individual organisations. This resulted in a large number of taxa and characteristics, which, as argued before, affects negatively the indices.

To conclude this line of argument, the levels of analysis for the organisation and population cladograms lie between the levels of analysis for the automotive and electronics industry cladograms.
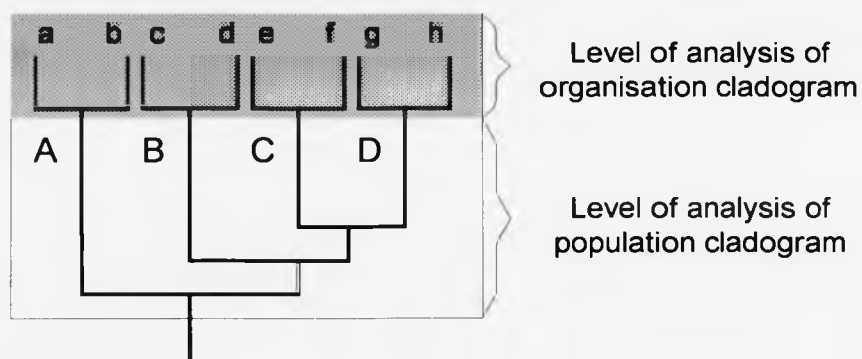
Level of analysis of
organisation cladogram

Level of analysis of
population cladogram

Key:
Uppercase letters: Drug discovery
strategy types
Lowercase letters: Drug discovery
strategies of individual
organisations

Figure 9-3 Levels of analysis of cladograms

9.4.2. Relative subjectivity in the selection of the best cladogram

As argued in chapter 6, one of the strengths of cladistics is that the resulting
classifications are objective. They should represent real, unambiguous and natural
properties of the entities (evolutionary relationships) and, thus, different rational
people, working independently should be able to agree on these classifications.
However, two stages in the construction of the cladogram required judgement from
the researcher. The first involved the selection of the characteristics The history of
drug discovery is long and the characteristics that have influenced its development are
numerous. Therefore, the selection of all the characteristics is an unrealistic option
and a selection procedure is conducted. Although several rules (identified and
described in sections 6.2.7.2, 7.3, and 8.3) have been employed to ensure the
consistency and objectivity of this selection process, a degree of subjectivity is
unavoidable.

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The second area of subjectivity is that of the selection of the optimal cladogram. Step 5 in the construction of the population and organisation cladograms provides the user with a big number of possible cladograms. The first filtering of the cladograms is done through the use of the treelength, retention and consistency indices. Although the selection of the cladograms up to this stage is objective, it provides the researcher with more than one possible cladograms with equal statistics. Therefore, the researcher is left to decide which cladogram is best for his study. Unfortunately, the method of selection at this stage is subjective as it depends on the researcher's judgement.

However, as argued in chapter 8, all cladograms produced were very similar, and changes between them were insignificant. Therefore, this limitation should not considerably affect the conclusions drawn from the cladogram.

9.4.3. Limitations in the collection of data

The main limitations associated with the collection of the data are its exhaustiveness and reliability in the construction of the organisation cladogram. The quality of the research results depends on the exhaustiveness of the collection of data. This is because the pattern of change of the organisational strategies may have been affected by innumerable factors. However, the collection of all the possible data is not feasible because there is limited access to data. The required information is not limited to one department of one organisation or indeed to one organisation. Exhaustive collection of data would require the careful examination of all the pharmaceutical organisations garound the world. As explained in chapter 8 the margin of error for the sample was 16%.

9.5. Further Work

There are many stimuli for further work originating from this thesis. In chapter 8 it was argued that the constructed cladograms do not present sufficient evidence to fully support the first and second hypotheses. Therefore, the first area for future investigation is associated with collecting further evidence to validate or refute the hypotheses.

With regard to the validation of the first hypothesis, future research efforts should be directed towards an examination of the sizes (number of drug discovery strategies) of populations over time. For example, if the size of one or more of the populations, depicted on the aggregated organisation cladogram of Figure 8-6, were measured at various moments in time over the last century, then its pattern of change would be revealed. If the pattern were cyclical, i.e. if the size of the population follows a concave pattern of growth and decline, the first hypothesis would be fully validated.

With regard to the validation of the second hypothesis, future research should be directed towards the examination of the financial performance of the organisations included in the population. If a correlation between the financial performance of the organisations within the population and the size of the population were found, then it could be argued that there is variation in terms of the fitness of the drug discovery strategies.

A second area of future investigation is associated with the development of management tools and techniques that will use the knowledge developed in this thesis. The creation of the working definition of drug discovery strategy along with its defining factors could provide a new perspective for understanding and planning strategy within a pharmaceutical organisation. In addition, the population and

organisation cladograms could provide the basis for constructing *road maps* for strategic change. The two cladograms provide a list of characteristics that could be adopted to move from one strategic configuration to another.

Finally, the research conducted here cannot claim that it has covered all the aspects of drug discovery strategy. However, as argued in chapter 3, there is no existing introductory account, definition and classification to drug discovery strategy. This research has made a contribution towards providing a rigorous and systematic approach in this area. Also, from a methodological standpoint, this study has advanced the development and application of evolutionary classifications to an area of strategic management. Yet, more research is required to fully understand both the area of drug discovery strategy and the mechanisms by which it changes over time.

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APPENDICES

Appendix A: Matrix of population cladogram

Drug Discovery Types

Characteristic Number and Name	1. Herbals' Use	2. Random Discoveries/ No Scientific Justification	3. Symptom Focused	4. Industrial Revolution	5. Homeopathy	6. Chemical Extraction	7. Microbial Theory of Disease	8. Vaccines/ Antitoxins
Unorthodox	1	1	0	0	0	0	0	0
Individual efforts	1	1	1	0	0	0	0	0
Technology dominated (high serendipity random discoveries)	1	1	1	1	1	1	1	1
Multidisciplinary research	1	1	1	1	1	1	1	1
Disease focused	1	1	1	1	1	1	1	1
Knowledge and instrumentation focused	1	1	1	1	1	1	1	1
Science driven	1	1	1	1	1	1	1	1
Biotechnology	1	1	1	1	1	1	1	1
Computer driven I	1	1	1	1	1	1	1	1
Computer driven II	1	1	1	1	1	1	1	1
Partnerships/ Acquisitions	1	1	1	1	1	1	1	1
Outsourcing	1	1	1	1	1	1	1	1
Me-too	1	1	1	1	1	1	1	1
R&D concentration for innovation and competition	1	1	1	1	1	1	1	1
R&D concentration for niche markets	1	1	1	1	1	1	1	1

9. Synthetic Dyes	10. Government Legislation	11. Organic Chemistry/Biochemistry	12. Insulin	13. Development of antibacteria	14. Interdisciplinary Thinking	15. Federal Regulation	16. Instrumentation development	17. Antibiotics	18. World Wars
0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0
1	1	1	0	0	0	0	0	0	0
1	1	1	1	1	1	1	1	0	0
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1

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19. Fight against malaria anemia	20. Vitamins	21. Introduction of Computer Aided Drug Discovery	22. Governmental Support	23. Instrumentation Wave	24. Computing Technology	25. DNA Understanding	26. Joined Analytical Chemistry and Biology	27. Biomedical Instrumentation Enhanced
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
1	1	1	0	0	0	0	0	0
1	1	1	1	1	1	1	0	0
1	1	1	1	1	1	1	1	1
1	1	1	1	1	0	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1

28. Powerful Computers Employed	29. Breakthroughs in Disease Etiology	30. Genetic Engineering	31. Entrepreneurial Trend	32. DNA Sequencing	33. Move for Development Of Various Chemotherapies for Various Cancers	34. Reverse Trancriptise	35. Performance Revolution of Computers	36. AIDS
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
1	1	0	0	0	0	0	0	0
1	1	1	1	1	0	0	0	0
1	1	1	1	1	1	1	1	0
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1

	37. Immunology	38. Birth of Drug Design	39. Genetic Algorithms	40. Fuzzy Logic	41. Limited Discovery of Biotechnology Research	42. Computational Power	43. High Specialisation in Certain Field		45. Genomics	46. Rational Drug Design
	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	1	1
	1	0	0	0	0	0	0	0	1	0
	1	0	0	0	0	0	0	0	0	0
	1	1	1	1	1	1	1	0	0	0
	1	1	1	1	1	1	1	0	0	0
	1	1	1	1	1	1	1	0	1	0
	1	1	1	1	1	1	1	0	0	0
	1	1	1	1	1	1	1	0	1	0
	1	1	1	1	1	1	1	0	1	0

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47. Combinatorial Chemistry	48. High Throughput Screening	49. Robotics/ Automation	50. Proteomics	51. Bioinformatics	52. Generics	53. Trend for Formation of Multinational Organisations	54. Medium Organisational Size	55. Be the First With Generics
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	1	0
0	0	0	0	0	0	0	1	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
1	1	1	1	1	0	0	1	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
1	1	1	0	0	0	1	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	1	0	0	0
1	1	0	0	0	0	1	0	0
0	0	0	0	0	0	0	1	1

56. Division of Labour	57. Internet
0	0
0	0
0	0
1	0
0	0
0	0
1	0
1	0
0	0
0	0
1	0
0	0
0	0
1	0
0	1

Appendix B: Description of characteristics

Tacit knowledge

13. Diversification

This characteristic means that an organisation pursued a diversification approach for bringing new products to the market. This approach could be either product or market diversification. It is considered as characteristic because it influences the approach of an organisation to drug discovery. Diversification usually happens through mergers, acquisitions or building of new capabilities.

0. The company has not pursued a diversification strategy

1. The company has pursued a diversification strategy

14. Reduction of diversification

Throughout the history of the pharmaceuticals there are examples of organisations that realised that extreme diversification caused losses either in terms of profits or in terms of expertise. This characteristic means that organisations after realising that this strategy was not beneficial for the company they abandoned it and focused on the discovery and development of a smaller number of drugs. This realisation usually follows a change in an organisation's status such as change of management or acquisition. The methods followed to reduce diversification include direct termination of the non-profitable projects and selling of the non-efficient divisions.

0. An organisation has not gone through a reduction of diversification exercise

1. An organisation has not reduced its diversification

15. Focus on pharmaceuticals

This characteristic means that the management of organisations has decided to focus on the manufacturing and development of pharmaceutical products. Many pharmaceutical organisations develop products such as diagnostic equipment, nutritional tablets etc. The acquisition of this characteristic means that an organisation has focused only on the development of pharmaceutical products. The difference between this characteristic and the reduction of diversification is that this one is more focused i.e. reduction of diversification does not necessarily mean focus on a certain type of product.

0. An organisation does not focus only of pharmaceuticals

1. An organisation focuses only on pharmaceuticals

16. R&D focus

Research and development focus is a characteristic that means that an organisation that has acquired it focuses on the development of new drugs. This means that they see R&D as a major function for the acquisition of a competitive advantage. In addition organisations that have acquired this characteristic are usually the ones that bring new drugs to market and are consequently the market leaders.

0. An organisation does not focus on R&D

1. An organisation focuses on R&D

17. Increase in R&D expenditure

The acquisition of this characteristic means that an organisation has gone a step further in focusing on R&D by devoting more resources to it. It has been considered as an important characteristic because its acquisition implies that an organisation has changed its approach towards R&D and has consequently affected its drug discovery strategy.

0. An organisation has not decided at any point in time to increase its R&D spending

1. An organisation has at least once decided to significantly increase its R&D spending

18. Cost cutting R&D

This characteristic has the opposite effect to the previous one. Its acquisition means that the capital spending on R&D has been reduced. This is usually the direct result of the financial state of the company and it is usually a condition enforced to the company.

0. An organisation has never been forced to cut its R&D expenditure

1. An organisation has been forced to cut its R&D expenditure

19. R&D performance

The acquisition of this characteristic means that an organisation has combined the research and development goals with performance objectives.

0. An organisation has not explicitly combined the R&D goals with performance objectives

1. An organisation has explicitly combined the R&D goals with performance objectives

20. R&D concentration

The acquisition of this characteristic means that an organisation limits its R&D efforts to the most promising efforts. Usually this happens when organisations weigh their portfolio of projects and conclude that some of their projects do not have a market potential.

0. An organisation has not concentrated its research efforts

1. An organisation has concentrated its research efforts

21. Limited discovery

The acquisition of this characteristic means that an organisation has not managed to achieve any breakthroughs for a considerable amount of time. The importance of this characteristic is that limited discovery for a considerable amount of time may result in organisational changes and restructuring of an organisation.

0. An organisation makes discoveries at frequent intervals

1. At least once in the lifetime of an organisation there has a been a significantly long period when no discoveries were made

22. Dependence on strangers' research (generics)

This characteristic means that an organisation focuses on developing drugs that have been discovered by other institutions (usually competitors). Pharmaceutical companies

have exclusive rights to their discovery for seventeen years after which other companies may also produce the same drug Several companies are pursuing this tactic to survive and be profitable.

   0.   An organisation focuses on its own research

   1.   An organisation produces generic drugs

23. Reformation of others' rejected/unfinished research

Due to reasons like reduction of diversification, review of portfolio and concentration of research and development the management of an organisation may reject a project. This research however, may be potentially beneficial for other organisations competing in different environment and aiming on different goals. The acquisition of this characteristic means that an organisation is pursuing this type of strategy.

   0.   An organisation focuses on its own research

   1.   An organisation seeks the development of others' reearch

24. Merger

This characteristic means that two organisations have combined their efforts for the discovery of new drugs. The merger of two organisations may result in the acquisition of several other characteristics like *diversification* and *increase in R&D expenditure*

   0.   An organisation has not merged

   1.   An organisation has merged

25. Acquisitions

This characteristic means that an organisation has acquired one or more smaller organisations to expand its research capabilities. The acquisition of other organisations results in product and market diversification. In addition, acquisitions may result in access to knowledge and technology that was previously impossible.

0. An organisation has not pursued an acquisition strategy

1. An organisation has pursued an acquisition strategy

26. Collaboration with academia

The research capabilities of a single organisation are in many occasions not enough to achieve the goals. Therefore, organisations have sought collaborations with academic institutions. The advantage of collaborating with such institutions is that knowledge that has been acquired by them may be available to the companies. The acquisition of this characteristic implies that such collaboration has taken place.

0. An organisation has not collaborated with academic institutions

1. An organisation has established collaborations with academic organisations

27. Collaboration/joint ventures

Due to similar reasons to the ones that led organisations to seek collaborations with the academia, organisations have collaborated with each other. This has taken the form of exchange of information or joint ventures where jointly funded research develops

products beneficial to both companies. The acquisition of this characteristic means that an organisation has experienced such collaborations.

0. An organisation has not collaborated with academic institutions

1. An organisation has established collaborations with academic organisations

28. Marketing

Marketing has always been a decisive factor in the pharmaceutical industry. The acquisition of this characteristic within the scope of this thesis means that an organisation's marketing has affected the way drugs are being discovered for example by understanding the market needs better.

0. Marketing has affected the discovery of new drugs

1. Marketing has mot affected the discovery of new drugs

29. Focus on effective analysis and treatment

This characteristic means that an organisation is undertaking research to satisfy the need for cost effective analysis and treatment in health care. For instance, the development of comprehensive nutritional therapy programmes to speed the recovery of health patients and thereby reduce medical costs.

0. An organisation is not undertaking such research

1. An organisation is undertaking research.

30. Centralised management

The acquisition of this characteristic means that an organisation has adopted a top-down approach to management. Pharmaceutical organisations being traditional and old organisations have been in most cases formed by an individual. Usually, organisations that are formed in such way, adopt a centralised approach to management, which may be sustained for a few generations. This may affect the strategies for drug discovery and this is when this characteristic is included in the *cladogram*.

0. Centralised management has not directly affected drug discovery

1. Centralised had an influence in drug discovery

33. Reorganisation (restructuring)

The acquisition of this characteristic means that an organisation has gone through an organisational restructuring which has affected the way research and development is carried out. This may include an organisation of the research based on therapeutic areas. Whenever organisations go through mergers organisations go through such restructuring. This characteristic is present only when the reorganisation has not been the result of a merger and has a direct impact on drug discovery.

0. An organisation has not restructured itself

1. An organisation has restructured itself

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35. Management innovations

This characteristic denotes the attempt of the management to encourage research by trying new management methods. For instance, a management innovation would be the achievement of working welfare and the division of labour.

0. No management innovations have been recorded

1. An organisation has attempted the application of management innovations

36. DNA marketing

This acquisition of this characteristic means that an organisation is in the biotechnology business and markets research. The biotechnology industry has made it possible to market research rather than final products.

0. An organisation is not in the biotechnology industry

1. An organisation markets is in the biotechnology industry

37. Niche Market establishment

The acquisition of this characteristic means an organisation has managed, through its research activities, to produce a niche market usually through the introduction of a novel drug or *blockbuster*.

0. An organisation has not established a niche market

1. An organisation has established a niche market

38. Individual efforts

This is a characteristic usually acquired by organisations during their founding. The research efforts of an individual have eventually led him or her to the development of a product, which has resulted in the foundation of a company.

0.   An organisation was not founded by an individual

1.   An organisation was founded by an individual whose legacy is carried by an organisation

Environment

39. World Wars

Both world wars have had an impact on the companies' future. However, to be considered as a characteristic for the construction of the cladogram the impact has to be specifically on the drug discovery strategy of the company. For instance, the need for the production of penicillin made organisations develop new techniques for its development in large quantities. Further implications of the war to drug discovery strategies are explained in chapter 8.

0.   The wars have not affected the drug discovery process

1.   The war has played an important role in the development of both the company and its drug discovery process

40. Cyclamates

In the 1960's the popularity of the cyclamates (the chemical that has a sweet taste and used as an artificial sweetener) was increased. This was due to the fact that people became more health and diet conscious and cyclamates were used as a sugar substitute in a wide variety of foods. In 1970 the American food and drug administration banned the use of cyclamates when they discovered that they were carcinogenic. The acquisition of this characteristic means that the drug discovery process of an organisation has been affected by this ban.

0. An organisation was not affected by the ban

1. Both an organisation and its drug discovery process have been affected by the ban

41. Enforced price reductions

Enforced price reductions have forced many organisations to reconsider their approach to drug discovery. This characteristic reflects this situation. The government or large insurance companies (the latter is more common in the USA) usually enforce these price reductions.

0. Price reductions have affected the drug discovery process

1. Price reductions have not affected the drug discovery process directly (although) they may have affected an organisation.

42. Intense competition

Intense competition on research activities may force organisations to consider alternative strategies in the development of new drugs.

0. Competition has not affected the drug discovery process

1. Competition has affected the drug discovery process

43. Community aid

This characteristic means that an organisation has undertaken community aid motivate and satisfy its employees. This is turn had a reported impact on the process of discovery i.e. through the improvement of productivity.

0. Community had an impact on drug discovery

Community aid had not been carried out or had no reported impact on the drug discovery

44. Price reductions through competition

Competition especially after the end of a patent may result in the price reduction especially in situations where two drugs may offer similar treatment and results. This characteristic is included in this study when these price reductions have affected the drug discovery strategy.

0. Competition has not forced an organisation to make any price reductions

1. Competition has forced an organisation to reduce the prices of the drug and this has a direct effect on the drug discovery process, for instance, by reducing the number of products

45. Government support

The support of government especially through the form of funding of associated academic institutions also may affect the way new drugs are being developed

0. Government support did not have direct impact on drug discovery

1. Government support had an impact on the drug discovery process

46. Government legislation

This characteristic denotes the effect that legislation may have on the development of new drugs. Before drugs are introduced to the market they have to go through the process of approval. Therefore, the formation of the drug discovery strategy also has to account for that.

0. The drug discovery process has not significantly affected by government legislation

1. Government legislation has forced an organisation to make changes on the drug discovery strategy

47. Patent protection laws

Patent protection laws have been in use since early in the century in most of the western countries. In countries like Japan these laws where not implemented until much later. Consequently the approach of these companies on drug discovery was much different.

Since they could not protect their research findings they were more focused on the development of generic drugs. This characteristic intends to show the difference that these laws had in drug discovery especially in Japanese companies.

0. Patent laws have been in place for significantly long time to be considered as given e.g. in western countries

1. Patent laws have made significant contribution to the R&D of an organisation e.g. Japanese organisations

48. Privatisation/Nationalisation

This characteristic represents a situation where the government has either assumed control of a company or sold it to private investors. Nationalisation may have an immediate effect on drug discovery as funding methods usually differs. The allocation of resources is also different in national companies

0. An organisation has not at any moment in history been nationalised

0. An organisation has been nationalised at least once

Technology

The characteristics that fall under this category include key technologies that have influenced the drug discovery process. These technologies are explained in chapter 4

State 0 of each characteristic indicates that the technology denoted by the characteristic has not been acquired by an organisation. State 1 means that the technology has been acquired.

2. Instrumentation development

The focus of an organisation is in the development of medical instruments including surgical equipment.

0. an organisation is developing such instruments

1. an organisation is not developing such instruments

Codified knowledge

The characteristics that fall under this category include the therapeutic areas where organisations are undertaking research. It is not within the scope of this thesis to provide information on the medical aspects of each therapeutic area.

State 0 of each characteristic indicates that an organisation does not undertake research in that area. State 1 means that an organisation undertakes research in that area.

Appendix C: Matrix of organisation cladogram

Characteristic Number and Name	1. Computational Power	2. Instrumentation Development	3. Disposable Devices Development	4. Biotechnology	5. Fermentation Technology	6. Combinatorial Chemistry
Abbot Laboratories	1	1	0	0	0	1
Wyeth	1	0	0	1	0	1
Genetics Institute	1	0	0	1	0	0
AstraZeneca	0	0	0	0	0	1
Baxter International	1	1	1	1	0	1
Novartis	0	0	0	0	0	1
Ciba Geigy	0	1	0	1	0	0
Sandoz	0	0	0	0	0	0
Fujisawa	0	0	0	0	0	1
Roche	0	1	0	1	0	1
Syntex corporation	0	0	0	1	0	0
Genentech	1	0	0	1	0	0
Eli Lilly	0	1	0	1	0	1
Aventis	0	0	0	0	0	1
Marion	0	1	0	0	0	0
Rorer Group	0	1	0	0	0	0
Roussel Uclaf	0	0	0	0	0	0
Merck	0	0	0	0	0	1
Mylan Laboratories	0	0	0	0	0	0
Pfizer	1	0	0	1	1	1
Pharmacia	1	1	0	1	0	1
Upjohn	0	0	0	0	0	0
Searle	0	0	0	0	0	0
Schering-Plough	0	0	0	1	0	1
Sanofi-Synthelabo	0	0	0	0	0	1
Sterling Drug Inc.	0	0	0	0	0	0
Sankyo	0	0	0	1	0	1
GlaxoSmithkline	0	1	0	1	1	1
Glaxo	0	0	0	0	0	0
Smithkline Beckman	0	0	0	0	0	0
Wellcome	0	0	0	0	0	0
Bristol Myers Squibb	0	0	0	0	0	1
Takeda	0	1	0	0	0	1
R.P. Scherer	0	1	0	0	0	1
Novo	0	0	0	1	1	1
Miles Laboratories	0	1	0	1	0	1

Organisations

7. Rational Drug Design	8. High Throughput Screening	9. Proteomics	10. Genomics	11. Procaine Development	12. Blood Collection	13. Diversification	14. Reduction of Diversification	15. Focus on Pharmaceuticals
1	1	1	1	1	0	1	0	0
1	1	1	1	0	0	1	0	1
0	0	0	0	0	0	0	0	1
1	1	1	1	0	1	0	0	0
1	1	1	1	0	0	0	0	0
1	0	0	0	0	0	0	0	0
0	0	0	0	0	0	1	0	0
0	1	1	1	0	0	1	1	0
1	1	1	1	0	0	1	0	0
1	0	0	0	0	0	1	0	0
0	0	0	0	0	0	0	1	0
0	1	1	1	0	0	1	0	0
1	1	0	0	0	0	0	0	0
1	0	0	0	0	0	1	0	0
0	0	0	0	0	0	1	0	0
0	1	1	1	0	0	0	0	0
1	1	1	1	0	0	1	0	0
0	0	0	0	0	0	1	1	0
0	0	0	0	0	0	0	0	0
1	1	1	1	0	0	0	0	0
0	0	0	0	0	0	1	0	0
1	1	1	1	0	0	1	0	0
1	1	1	1	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	1	1	1	0	0	1	0	1
1	1	1	1	0	0	1	0	1
0	0	0	0	0	0	0	0	1
1	0	0	0	0	0	1	0	0
1	0	0	0	0	0	1	0	0
0	1	1	1	0	0	0	0	0
1	1	1	1	0	0	1	0	0
1	1	1	1	0	0	1	0	0
1	1	1	1	0	0	1	0	0

16. R&D Focus	17. Increase in R&D Expenditure	18. Cost Cutting R&D	19. R&D Performance	20. R&D Concentration	21. Limited Discovery	22. Dependence on Strangers' Research (generics)	23. Reformation of Others' Rejected/Unfinished Research	24. Merger
1	1	0	0	0	1	0	0	1
1	0	0	0	0	1	0	0	1
1	0	0	0	0	0	0	0	1
1	0	1	0	0	0	0	0	1
1	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	1	0	1
0	0	0	0	0	1	1	0	0
1	0	0	0	0	0	0	0	0
1	0	0	0	1	0	0	0	1
1	1	1	0	1	0	0	0	1
0	0	0	0	0	0	0	1	0
1	0	0	0	0	1	0	0	1
1	1	0	0	0	0	0	0	1
1	0	0	0	0	0	1	1	1
0	0	0	0	0	1	1	0	1
1	1	0	0	0	0	0	0	0
1	1	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0
1	1	0	1	0	0	0	0	0
1	1	0	0	1	0	0	1	0
1	0	0	0	0	1	0	0	1
1	0	0	0	0	1	1	0	0
1	1	0	0	0	0	1	0	0
1	0	0	0	0	0	0	0	1
1	0	0	0	0	0	0	0	1
1	0	0	0	0	0	0	0	0
0	1	0	0	0	0	0	0	1
1	1	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	1
1	1	0	0	0	0	0	0	1
0	0	0	0	0	0	0	0	0

25. Acquisitions	26. Collaboration With Academia	27. Collaboration /Joint Ventures	28. Marketing	29. Focus on Effective Analysis and Treatment	30. Centralised Management	31. Research Units	32. Globally Organised Research
1	0	1	1	1	1	0	0
1	1	1	1	0	1	0	0
0	1	1	1	0	0	0	0
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1	0	0	0	0	1	0	0
1	0	0	1	0	0	0	1
0	0	0	1	0	0	0	0
1	0	1	0	0	0	0	0
1	0	1	1	0	0	0	1
1	0	1	0	0	0	0	0
0	0	0	1	0	0	0	1
1	1	1	1	0	0	0	0
1	1	1	0	0	0	0	0
1	0	0	1	0	0	0	0
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1	0	1	1	0	0	0	0
1	1	1	0	0	1	0	1
1	1	1	1	0	0	0	0
1	0	1	1	0	0	0	0
1	0	0	0	0	0	0	0
1	0	0	1	0	0	1	0
1	0	1	0	0	0	0	0
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1	0	1	1	0	0	0	0
0	0	0	0	0	0	0	0
1	1	1	0	0	0	0	0
0	0	1	1	0	1	0	0

33. Reorganisation (restructuring)	34. Division of Labour	35. Management Innovations	36. DNA Marketing	37. Niche Market Establishment	38. Individual Efforts	39. World Wars	40. Cyclamates	41. Enforced Price Reductions	42. Intense Competition
0	0	0	0	0	0	1	1	0	0
0	0	0	1	1	0	0	0	0	1
0	0	0	1	1	0	0	0	0	1
0	1	0	0	0	0	1	0	0	0
0	0	0	0	0	0	0	0	1	0
1	0	0	0	0	0	1	0	0	0
1	0	0	0	0	0	0	0	1	0
1	0	0	0	0	0	1	0	1	0
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1	0	0	0	1	0	0	0	0	0
0	0	0	1	0	0	0	0	0	1
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0	0	1	0	0	0	0	0	0	0
0	0	1	0	0	0	1	0	0	0
0	0	0	0	0	1	1	0	1	0
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0	0	0	0	0	1	1	0	0	0
0	0	1	0	0	0	0	0	0	0
0	0	0	0	0	0	1	0	0	0
0	0	0	0	0	0	0	0	0	0

43. Community Aid	44. Price Reductions Through Competition	45. Government Support	46. Government Legislation	47. Patent Protection Laws	48. Nationalisation	49. Synthetic Dyes	50. Alkaloids	51. Antibiotics
0	0	0	0	0	0	0	1	1
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	1	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	1	0	0
0	0	0	1	1	0	0	0	1
0	0	0	0	0	1	1	0	1
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0	0	0	0	0	0	0	0	0
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0	1	0	0	0	0	0	0	1
0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0

43. Community Aid	44. Price Reductions Through Competition	45. Government Support	46. Government Legislation	47. Patent Protection Laws	48. Nationalisation	49. Synthetic Dyes	50. Alkaloids	51. Antibiotics
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0	1	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	1
0	0	0	0	0	0	0	0	0

	52. Nutritional Therapy	53. Vitamins	54. Insulin	55. Apothecaries	56. Chemicals Enzymes	57. Neurology	58. Infectious Diseases/Vaccines	59. Haematology
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	0	0	0	0	0	1	1	1
	0	0	0	0	0	0	1	0
	0	0	0	0	0	1	1	1
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	0	0	0	0	0	1	1	1
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	0	0	0	0	0	1	1	0
	0	0	0	0	0	1	0	0
	0	1	0	0	0	0	1	0
	0	0	0	0	0	1	1	0
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	0	1	0	0	0	1	1	0
	0	0	0	0	0	1	1	0
	0	0	0	0	0	0	0	0
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	0	0	0	0	1	0	0	0
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60. Musculoskeletal	61. Oncology	62. Immunology	63. Transplant	64. Gynaecology	65. Metabolic Diseases	66. Cardiovascular	67. Gastroenterology
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1	0	1	0	0	0	1	0
0	0	1	0	0	0	1	0
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0	1	0	0	1	0	1	1
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0	1	0	0	0	0	1	0
0	0	1	0	0	0	1	0
0	0	1	0	0	0	0	0

68. Genitourinary	69. Opthamology	70. Endocrinology	71. Psychiatry	72. Respiratory	73. Paediatrics	74. Anaesthesia	75. Surgery	76. Orthopaedics
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0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0
0	0	0	0	1	0	1	0	1
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0	0	1	0	0	0	0	0	0
0	0	0	0	1	0	0	0	0
1	0	0	1	0	0	1	0	0
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0	0	1	0	1	0	0	0	0
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0	0	0	1	0	0	0	0	0
0	0	1	0	0	0	0	0	0
0	0	0	0	1	0	0	0	0
0	0	0	1	0	0	0	0	0

0 0 0 0 0 0 0 1 0 0 0 0 1 0 0 1 0 1 0 0 0 0 0 0 1 0 0 0 0 0 0 0 1 0 0 1