A determination of the key factors and characteristics that SME-scale commercial biomedical ventures require to succeed in the South African environment

by

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I declare that **A determination of the key factors and characteristics that SME-scale commercial biomedical ventures require to succeed in the South African environment** is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

…….. 21st September, 2015

SIGNATURE DATE

(MR J R SAYER)

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ABSTRACT

The potential for private sector healthcare business in Africa has been forecasted to reach $35 billion by 2016, with South Africa being regarded as the most industrially advanced country on the continent. South Africa's entry to modern biotechnology is fairly recent, though, with companies in the private sector still in a developmental phase, and most having limited bioproduct ranges.

While considerable research has been conducted in the past to attempt to define the biotechnology environment of South Africa, as yet, a concise overview is lacking. In particular, a synopsis of the biomedical or commercial health technology environment has not been forthcoming for entrepreneurs to refer to as a 'roadmap'. The purpose of this study was to perform a comprehensive study on the attributes that should be met for a successful, sustainable health technology venture (HTV) to be started in South Africa; while identifying the opportunities and threats that have existed in the South African market; thereby, affecting their success and sustainability to date.

In this study, two phases of research were conducted. The first was a small-sampled mixed-methods (both qualitative and quantitative) study involving 21 medical devices, biogenerics, diagnostics, and contract services companies. The second was a quantitative study, involving 107 vaccines, biogenerics, therapeutics, nutraceuticals, reagents, diagnostics, medical devices, biotools, contract services and public services companies. Inferential statistical tests were conducted on the data, including Pearson's Chi-Square, ANOVA, bivariate correlation, linear regression, logistic regression and multinomial logistic regression.

From the study, the overall proportion of business sustainability for HTVs was found to be 66.7%, and at least 30% were unsustainable (or not yet at a level of sustainability). Variations were observed in the overall rate of sustainability for companies, based on their core functional classification, location, production type, size and start-up or R&D spending. By converting the observed frequencies of activity level, as an indication of sustainability, into a probability, it was possible to observe the company type that was most, and least likely to succeed in South Africa. Based on the statistical observations in this study, the HTV type most likely to succeed in South Africa, with a 63.7% probability of reaching sustainability, is a 'vaccines', 'biotools' or 'public services' company from Johannesburg with at least 20 employees; that has developed its goods or services internally, but manufactured externally and spent between R20 million–and–R30 million on its R&D or start-up. Conversely, least likely to succeed (3.2% probability) is a nutraceutical company from Cape Town with between six and 20 employees, that has developed and produced internally, and which has spent between R1 million–and–R10million on its start-up.

Key words: Medical biotechnology; biomedical science; health technology commercialisation; business success factors; RT-PCR; genetic profiling.

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LIST OF ACRONYMS AND ABBREVIATIONS

AFLP	Amplified Fragment Length Polymorphism
AHH	Aryl Hydrocarbon Hydroxylase
AhR	Aryl Hydrocarbon Receptor
AMTS	Advanced Manufacturing Technology Strategy
ANOVA	Analysis of Variance
ASO	Allele Specific Oligonucleotide
BEE	Black Economic Empowerment
BM	bone marrow
BRICs	Biotechnology Regional Innovation Centres
BRICS	Brazil, Russia, India, China and South Africa
CC	Cultural Capital
CF	Crowdfunding
CMO	Contract Manufacturing Organisations
CPGR	Centre for Proteomic and Genomic Research
CPI	Cost Price Index
CRO	Contract Research Organisations
CSIR	Council for Scientific and Industrial Research
CPUT	Cape Peninsula University of Technology
DBT	Department of Biotechnology (South Africa)
DoH	Department of Health (South Africa)
DoL	Department of Labour (South Africa)
DST	Department of Science and Technology (South Africa)
DTI	Department of Trade and Industry (South Africa).
DV	Dependent Variable
EGCG	(2)-epigallocatechin-3-gallate
EC	Economic Capital
ECSOD	Extracellular Superoxide Dismutase
FDA	Food and Drug Administration
FDI	Foreign Direct Investment
GABP	GA Binding Protein
G&S	Goods and/or Services
GDP	Gross Domestic Product
GMO	Genetically Modified Organism
GST	Glutathione S-Transferases
HBM	Human Biological Material
HOV	Homogeneity of Variances

HPCSA	Health Professions Council of South Africa
HQ	Headquarter
HRT	Hormone replacement therapies
HSC	Hematopoietic stem cells
HTA	Human Tissues Act
HTV	Health Technology Venture
IDC	Industrial Development Corporation (South Africa)
IDCs	Innovative Developing Countries
IES	Income and Expenditure Survey
IF	Innovation Fund (South Africa)
IFC	International Finance Corporation
IP	Intellectual Property
IPR	Intellectual Property Rights
IV	Independent Variable
NACI	National Advisory Council on Innovation (South Africa)
NBN	National Bioinformatics Network (South Africa)
NBS	National Biotechnology Strategy (South Africa)
NBTV	National Biotechnology Board (South Africa)
NHA	National Health Act
NRF	National Research Foundation (South Africa)
NTD	Neural Tube Defects
PAH	Polycyclic Aromatic Hydrocarbons
PAPS	3'-phosphoadenosine 5'-phosphosulfate
PCR	Polymerase Chain Reaction
PFMA	Public Finance Management Act
PMMC	Pearson's Product Moment Correlation Coefficient
RAPD	Random Amplified Polymorphic Detection
R&D	Research and Development
ROS	Reactive oxygen species
ROW	Rest of the world
SAMRC/MRC	Medical Research Council of South Africa
SANBI	South African National Bioinformatics Institute
SC	Social Capital
SEDA	Small Enterprises Development Agency
SME	Small to Medium Enterprise
SMME	Small, Medium and Micro Enterprise
SNP	Single Nucleotide Polymorphism
SPII	Support Programme for Industrial Innovation

SWOT	Strength, weakness, opportunity and threat analysis
SYMC	Symbolic Capital
TDIH	The Durban Innovation Hub
TE	Tissue engineering
TF	Transcription Factor
TIA	Technology Innovation Agency (South Africa)
THRIP	Technology and Human Resources for Industry Programme
TRIPS	Trade Related Aspects of Intellectual Property Rights
UCB	Umbilical cord blood
UCB-SCB	Umbilical cord blood Stem cell Bank
UCT	University of Cape Town
UNISA	University of South Africa
UTR	3′-untranslated region
UWC	University of the Western Cape
VC	Venture Capitalist
WMDA	World Marrow Donor Association
WTO	World Trade Organisation

CHAPTER 1
INTRODUCTION

1.1 SPECIFIC WORKING TITLE

A determination of the key factors and characteristics that SME-scale commercial biomedical ventures require to succeed in the South African environment.

1.2 INTRODUCTION

The potential opportunity for private sector healthcare business in Africa has been forecasted to reach $35 billion by 2016 (Al-Bader et al. 2009), with South Africa being regarded as the most industrially advanced country on the continent (Chakma et al. 2010). It is the strongest economy in the region, providing over 30% of Africa's gross domestic product, while its population of over 52 million accounts for only a small fraction of the total one billion people in Africa (United Nations Department of Economic and Social Affairs 2012). South Africa is considered as one of the world's most innovative developing countries (IDCs) with significant gains in research capacity and outcomes due to an increase in the number of scientific publications, health products and patents over recent years (Abuduxike and Aljunid 2012). Biotechnology in Africa is, however, predominantly targeted towards agricultural development (Sithole 2011).

South Africa's entry to modern biotechnology is fairly recent, with companies in the private sector still in a developmental phase, and most having limited bio product ranges (Cloete et al. 2006). The National Biotechnology Survey of 2003 found that there were 106 biotechnology companies in the country, with 47 being identified as 'core' biotechnology companies, such that the majority of their activities involved biotechnology (Mulder and Henschel 2003). Of these, 29% were derived from research groups, 34% from start-ups, and 37% were derived from another enterprise. The biotechnology industry sector comprised almost exclusively of private companies, with most falling into the Small, Medium and Micro Enterprise (SMME) category of ten or fewer researchers (Cloete et al. 2006). Furthermore, during the survey, 154 biotechnology products and/or services were identified to earn a combined profit of at least R368 million, with the majority falling into the category of human health (23%), followed by support services and plant biotechnology comprising 20% and 18% respectively. The biomedical goods and/or services (G&S) included primarily therapeutics, diagnostics, natural health products and phytopharmaceuticals (Mulder and Henschel 2003).

In 2006, a second follow up survey of the South African biotechnology environment was conducted by the Department of Science and Technology (DST) (Department of Science and Technology 2008). Greatly varying results were apparent, as compared to the first survey, however according to the DST report on the survey, the two reports were not directly comparable, with "any attempt to

do so causing potentially misleading assumptions" (Department of Science and Technology 2008). The DST suggested that the reason for this was because of a discrepancy in the definition of what constituted a biotechnology company, and differences in the response rates of the survey. This was clear, for example, because the 2006 survey discussed 78 biotechnology active companies; of which 38 were core-biotechnology companies that had declared revenues of R767million and R520million, respectively, from biotechnology, increasing from revenues of R624.4 million in 2004 (Department of Science and Technology 2008). This greatly differed from the afore-mentioned report of Mulder and Henschel (2003) which described revenues of R368million in 2003.

Therefore, while considerable research has been conducted in the past to attempt to define the biotechnology environment of South Africa, as yet, a concise overview is lacking. Furthermore, a detailed synopsis of the biomedical or commercial health technology environment has not been forthcoming for companies and entrepreneurs in the field to refer to as a 'roadmap' for company development. Such guides are highly desirable, as they offer insight for prospective business developers.

The aim of this study was to determine what characteristics a SME-scale commercial biomedical or health technology venture (HTV) should attempt to achieve in order to succeed and be sustainable in South Africa, and highlight how these differ and are therefore unique to other developing nations.

The purpose of this study was, therefore, to perform a comprehensive study on the requirements that should be met for a successful HTV to be started in South Africa. At the same time, the study attempted to identify the opportunities that have existed in the South African market, which have aided the HTVs to operate. Conversely, it attempted to highlight any of the threats that have existed in the country, thereby allowing a range of possible solutions to be generated for new and existing HTVs to overcome these barriers, and maximise their chances of reaching a level of sustainability and success.

1.3 BACKGROUND TO THE STUDY

According to Huggett and Lähteenmaki (2012), a biotechnology company is one whose processes involve biological organisms, processes, systems, or specialist services to facilitate the understanding thereof. While Huggett and Lähteenmaki exclude medical device firms, pharmaceutical companies and organisations that contract research services, biotechnology is often considered in five domains, covering agricultural, environmental remediation, aquaculture, healthcare and industrial biotechnologies (Black et al. 2011). According to Klerck (2005), biotechnology is a "cluster of techniques that use biological systems, living organisms or [their] derivatives to make or modify products or processes for [a] specific use." Klerck also notes that biotechnology is among the most promising of the "frontier technologies" of the future.

In the literature (Uctu and Essop 2013), biotechnology is noted to have potential in three areas: creating market dynamism, increasing economic growth and increasing global levels of innovation. Biotechnology is, thus, regarded as a significant tool for advancing economic development.

Klerck (2005) suggests that the primary founders of the biotechnology industry, globally, have been government laboratories and laboratories based at institutions of higher education; whereby, the success and expansion of each of the biotechnology sectors have been intrinsically based on their basic scientific components. For example, the cell infusion and DNA techniques that created monoclonal antibodies in health biotechnology primarily drew on discoveries in immunology and molecular biology, and many of the new biotechnology sectors have been intricately tied to the recent discoveries in biochemistry, genetics, general medicine and cell biology.

Biotechnology has a significant effect on most sectors of industry and provides a key element “in the transition from an agricultural-based to a knowledge-based economy” (Tonukari 2004). Klerck, therefore, argues that biotechnology is not an industry or discipline as such, but rather a collection of “interrelated technologies” that are relevant to a wide range of industries and disciplines. This author asserts that the evolution of biotechnology has occurred through three distinct generations, or phases, where the first phase occurred over many centuries, and included the proliferation of yields such as yoghurt, wine, vinegar and cheese, and the breeding of new plant and animal strains for human use. The second phase of biotechnology evolution comprised procedures such as the mutagenesis and selection of cultivars and strains to improve crop and metabolite yields, while the third involved the use of recombinant DNA techniques for biological enhancement (Klerck 2005).

The purpose and functions of biotechnology are very broad, and for the purpose of this study, only medically related biotechnology firms, or ‘health technology’ ventures (HTVs) have been considered in detail.

1.3.1 Categories of medical biotechnology, or health technology ventures

Biotechnology firms may be categorised based on their function or purpose (Asanuma 2012). These categorisations are pertinent to this study, as the companies that have been analysed here have also been categorised into classifications for ease of understanding and to aid in answering the research questions. The following main categorisations of health-related biotechnology exist; and for the purposes of this study the term health technology venture (HTV) is used to encompass all possible variants of the following:

Vaccines: These are a category of drugs that are used to stimulate the production of antibodies in the body, and provide immunity against one or a group of diseases. Such compounds are generally prepared either from the causative agent of a disease, its by-products, or a synthetic

substitute of the disease to perform as an antigen without actually inducing the disease (Boven et al. 2013).

Biogenerics: These are biotechnology-based drugs that have lost their patent protection (Niosi et al. 2012).

Therapeutics: This refers to products that are produced by biotechnology companies for healing purposes, or for the treatment of diseases or disabilities. This includes substances or drugs, and comprises among others, cellular therapeutic agents such as stem cells and cancer treatment agents (Torrey 2013).

Nutraceuticals: According to Kalra (2003), the term “nutraceutical" was coined in 1989 by Dr Stephen DeFelice from the terms nutrition and pharmaceutical, and constitutes products that are manufactured to act as dietary supplements or otherwise to boost human health through diet.

Reagents: This refers to compounds that are manufactured by biotechnology processes for use in chemical reactions or in laboratories as reagents, such as enzymes and laboratory support-related compounds (Rouse 2005).

Diagnostics: Diagnostics in biomedical biotechnology forms an important part of the foundation of healthcare, and describes diagnostic tests and systems that play an integral role in the early detection, evaluation, targeted screening and monitoring of diseases (Roche 2014). It also includes the field of molecular diagnostics, which Kiechle (2014) describes as the diagnostic tests for detecting specific sequences in DNA or RNA that analyse the alterations that relate to diseases, such as single nucleotide polymorphisms (SNPs), insertions, deletions, and so forth. Note that for the purposes of this study, a distinction has been made between companies that produce diagnostic tests, and companies that perform diagnostic tests as a type of contract or public service.

Medical devices: This constitutes the branch of health technology relating to the research, development and manufacturing of medical devices, instruments, implants, and other physical apparatuses that are used to prevent or treat disease or other ailments, without involving a drug-like chemical action (Asanuma 2012). Medical devices fulfil many roles, but are defined by Asanuma (2012) as those that satisfy the following:

- Diagnosis, monitoring, prevention, treatment or alleviation of diseases;
- Diagnosis, treatment, monitoring, alleviation or compensation for injuries;
- Investigation, modification, support or replacement of the anatomy or a physiological process; and
- Support or sustenance of life.

It should be noted that in the case of this study, companies that produce diagnostic medical devices are classified as ‘diagnostics’ companies, unless they themselves offer the diagnostic

service to the end user (using a medical device), in which case they are classified as ‘contract or public service’ companies.

Biotools: This includes all companies that deliver equipment within the supply chain of the health biotechnology industry, such as laboratory or factory machinery and equipment. This includes, for example, PCR machines, bio-incubators and laminar flows (Hirsch 2014).

Contract services: This includes all companies that provide services within the supply chain of the health biotechnology industry, such as laboratory or research-related services. It includes pre-clinical and clinical contract research organisations (CROs), bioinformatics research organisations, regulatory consultants, and contract manufacturing organisations (CMOs) (Hirsch 2014).

Public services: The final category considered in this research includes organisations that provide services and facilities for the general public; for example, bio banking, genetic testing, forensic services, and the afore mentioned organisations that offer diagnostic services to the end user.

1.4 THE PROBLEM STATEMENT

There is a complex dynamic in South Africa affecting the success and sustainability of HTVs in the country. These are described as follows.

1.4.1 The African condition

The African diaspora is such that there is a low relative technology culture across the continent, which is further compounded by a low level of education and literacy (Abuduxike and Aljunid, 2012). This has resulted in a generally low level of technology-related entrepreneurial culture, such that the majority of entrepreneurs are not highly technology-inclined; or those that are highly skilled in their respective fields are either not entrepreneurially motivated, or are “wearing many hats” (Smith et al. 2005). According to Smith et al., this implies that entrepreneurs are being so stretched between their various rolls and duties that they do not have the time to dedicate to the arduous task of starting ventures. Moreover, the scientific environment in South Africa is predominantly research based, whereby researchers are mostly engaged in a culture of publishing their research rather than transferring medical discoveries to the population (Katsnelson 2004).

1.4.2 Legislation and corporate Involvement

The relatively bureaucratic nature of medical legalities, which are either over complex in some cases, or non-existent in others, as well as the high costs and time barriers to patent rights and licenses has resulted in a retardation of entrepreneurial creativity (Andanda 2009). Therefore, overcoming these barriers in the majority of cases is only possible by multinational corporate enterprises which have the capital, man-power and global experience to be able to enter into the African markets (Chakma et al. 2010). Additionally, due to the predominantly corporate nature of

the South African business environment, small start-ups are considered inferior to the larger multinational corporations in terms of service capability and reliability, which means that they are often unable to gain market-share over their enormous counterparts. As a result, the majority of main stream medical breakthroughs are dominated by large pharmaceutical giants, major hospital chains and branded service providers (Chakma et al. 2010).

Andanda (2009) suggests that a lack of policies and guidelines towards biotechnology is a major challenge and a considerable limitation for biotechnology in African countries since appropriate policies are necessary for biotechnology to progress. In South Africa, the policies are predominantly focused on agricultural biotechnology or genetically modified organisms (GMOs), and the lack of policies in the pharmaceutical and industrial sectors have resulted in a major limitation in South African biotechnology (Andanda 2009). For example, the legal framework of the National Health Act (NHA), which was meant to regulate the use of stem cells, was still only in its draft form by 2011 (Sithole 2011); and according to Pepper (2010) this meant that South Africa was operating in a “regulatory vacuum” in terms of stem cell development, in which “the rules and guidelines were fragmented”. As a result, South Africa’s growth in the fields of regenerative medicine has been inhibited (Sithole 2011).

In May 2007, the South African Department of Health (DoH) published the ‘Regulations Relating to Human Stem Cells’ for public comment in terms of the National Health Act. While the regulations have dealt effectively with important matters of quality assurance and accreditation, according to Keetch et al. (2007), if passed in their current form, they would severely discourage investment into the stem cell biotechnology industry, and place South Africa among the most conservative countries in the world regarding stem cell research and developments. Another particular feature of these regulations would have been the effective ban of private umbilical cord blood (UCB) banks in South Africa (Jordaan et al. 2007).

Medical industry structures are dominated by multinationals and export businesses, and large corporations have pre-established distribution networks and relationships, which makes it difficult to find clinicians that are willing to be involved in the local development and testing of products (Chakma et al. 2010). Furthermore, according to Chakma and Sammut (2011), almost 90% of pharmaceutical and medical devices are imported into South Africa, which makes the scientific equipment for research and commercialisation of medical biotechnology less affordable.

1.4.3 Advanced research and clinical trials

The advanced nature of the field of biomedical science, in terms of new discoveries and advanced research, combined with the huge spectrum of unknowns between all the biological systems of plant, animal and human models has resulted in a general scepticism by the public towards advanced medicine (Al-Bader et al. 2009). Business opportunities that remain for the smaller start-

up ventures exist more typically in innovative goods and services that target existing, or long-standing conditions, as opposed to the latest break-through medical practices.

1.4.4 Funding and resource factors

The low-technology environment in Africa has resulted in most forms of HTVs being considered as high risk enterprises (Chakma et al. 2010). This means that there has been a relatively cautious approach from venture capital funds and funding bodies towards new start-up ventures in this field (Al-Bader et al. 2009).

According to the National Biotechnology Survey of 2007, the participating company groups identified that the major constraints they faced were related to the "long times for regulatory approvals" and "access to capital and human resources" (Al-Bader et al. 2009; Department of Science and Technology 2008). Additionally, the survey groups indicated that additional support services were needed in the fields of intellectual property management, marketing and fund raising. The companies also raised the issue of a lack of financial resources for attracting appropriate candidates as inhibitory to their businesses (Department of Science and Technology 2008). Meanwhile, Cloete et al. (2006) have referred to a lack of adequate expertise and skilled personnel in South Africa, which has caused a major handicap on biotechnological development in the country; and this has been further compounded by limited employment opportunities that have forced skilled individuals out of the country.

In an attempt to combat this, the Skills Development Act of 2003 was developed to inspire universities and financial assistance schemes from the National Research Foundation (NRF), Department of Labour (DoL) and Department of Science and Technology (DST) to promote student entry into scare-skills-based university science programmes (Cloete et al. 2006). Courses in biotechnology and the biomedical sciences are offered in over 20 institutions of higher learning in South Africa, varying from technikons to universities (Lekgari 2010), with the University of South Africa (UNISA), for example, extending the 12 available bachelor's in Life Sciences degrees with additional biomedical sciences and biotechnology majors (UNISA 2014).

This study has attempted to address these issues, and determine whether these efforts by the government to combat the shortcomings in South Africa's health technology sector have been successful, and how companies have been able to overcome the country's complex dynamic that may otherwise have affected their success and sustainability.

1.4.5 Problem hypothesis

A problem that the researcher would like to hypothesise is that in Africa, and South Africa specifically, there is a unique disease profile that is not being comprehensively covered by HTVs. While there is a considerable amount of research being conducted on the primary disease categories, such as HIV/AIDS, tuberculosis, cerebrovascular disease, ischemic heart diseases and

lower respiratory infections, there are relatively few new start-up biotechnology ventures targeting the entire spectrum of diseases, and especially the 'lower profile' diseases. Furthermore, there is a hypothesised lack of follow through from the research being done and the health technology facilities that are being provided to the public. The problem can be simply postulated that while there is advanced research being performed on diseases in South Africa, largely on the core diseases, and to a lesser degree on the none-core ones, there is still a predominantly inhibitory environment for new health technology ventures to transfer any new scientific knowledge to the public who need it. A complex scientific and legislative environment, combined with an adverse technological and entrepreneurial climate in Africa, high start-up costs and limited incomes by funders are all factors that are hindering the more prolific formation of HTVs. This is creating a general retardation for solving many African-specific disease problems, since the majority of enterprises that would be motivated to offer the therapies and solutions, are unable to even progress from their concept stage.

However, there are companies and organisations that have been able to succeed in the South African business climate, which suggests that while barriers exist, it is possible for them to be overcome.

1.5 AIMS AND OBJECTIVES

The aim of this study was to determine the features and characteristics that SME-scale commercial biomedical ventures, or HTVs of the size and business scale of standard SMEs, should achieve in order to succeed and be sustainable in South Africa.

1.5.1 Research objectives

Four objectives were stated for this study, in order to achieve the aim. These were the following:

i) To observe any correlations or patterns between the majority of HTVs and the types of core function techniques that they are using, while examining the detailed theoretical elements of some of the scientific techniques that are being used at one of these ventures;
ii) To examine the challenges that advanced HTVs face in South Africa, as compared to other developing and developed countries;
iii) To identify the types of costs involved with advanced HTVs in South Africa, and whether there are any correlations between the start-up spending, technology type, size, location, production method, and activity state (sustainability) of the companies; and
iv) To determine what constitutes success in the South African HTVs, the proportion of HTVs that are successful or sustainable, and the keys to their success or sustainability.

1.5.2 Research questions

The research questions that were posed in order to address the objectives were the following:

i) Are there any correlations or patterns between the majority of HTVs and the types of core function techniques that they are using; and what are the detailed theoretical elements of some of the scientific techniques that are being used at one of these ventures?

ii) What challenges do advanced HTVs face in South Africa, as compared to other developing and developed countries?

iii) What types of costs are involved with advanced HTVs in South Africa, and are there any correlations between the start up spending, technology type, size, location, production method, and activity state (sustainability) of the companies?

iv) What constitutes success in the South African HTVs, what proportion of the HTVs is successful or sustainable, and what are the keys to their success or sustainability?

1.6 CONTRIBUTION OF THE STUDY

This study considered aspects of potentially far reaching value and importance. In a country where there is a substantial need for improved medical services and advanced medical therapeutics, there is a sizeable benefit to be enjoyed from studies that attempt to present information that can help to strengthen and accelerate the proliferation of health technology ventures in the country. With a higher rate of HTV start-ups in South Africa, which in turn have a higher chance of success, the situations of both the South African society and economy stand to be greatly improved.

With the information gained in this project:

- Health technology ventures will be in a better position to identify key areas of success in the South African environment, and structure new and existing ventures to capitalise more effectively on their capabilities for success. Conversely, by identifying areas of general failure, health technology firms will be able to structure their company strategies to overcome the threats that could inhibit their success and sustainability;
- University programmes, such as the upcoming biomedical and biotechnology majors at UNISA Florida Campus may be able to incorporate the information from this study into their course material, making it more current and industry-related; thereby preparing students better for the South African health technology environment.
- Identifying the costs involved with ventures relative to their technology type, company size and location may give entrepreneurs insight to where the best location, technology type, and size requirements would be to suite their start-up budgets and resources.
- The study may also be useful to state bodies in South Africa, such as within the Department of Health, and the Department of Science and Technology, as it will augment the available knowledge base pertaining to the problems that exist in the country. This may assist in facilitating changes, for example, to health technology legislations that could more efficiently overcome the country’s barriers to health technology proliferation.

1.7 OUTLINE OF THE DISSERTATION

This first chapter of the dissertation has covered the introduction to the study, including the pertinent background information, a detailed problem statement, the objectives of the study, and the limitations, delimitations and contribution of the study. The subsequent chapters of the dissertation provide the supporting material of the study.

Chapter 2 follows, next, with an in-depth literature review detailing the global state of biotechnology, factors that have been observed in the literature to motivate biotechnology success, the existing knowledge on South Africa's biotechnology sector, and aspects that have already been published that aid in answering this study's objective of defining the features and characteristics that SME-scale commercial biomedical ventures should achieve in order to succeed and be sustainable around the world, and specifically in South Africa.

In line with the scientific nature of the dissertation, a detailed review is presented in Chapter 3 on the scientific basis behind one of South Africa's prototypical health technology ventures, DNAlysis, which has succeeded in attaining a status of success and sustainability in the challenging South African health technology sector.

Chapter 4 follows, thereafter, with a description of the methods that were followed for the study, along with a deliberation of any relevant information pertaining to the techniques that were employed.

The results of the study are outlined in Chapter 5. The chapter presents the outcomes of the methodologies that were employed in each phase of the study, and the basis upon which the discussion and conclusions of the dissertation are drawn.

The final chapter of the dissertation covers the discussion and conclusion of the study. It provides a deliberation on the findings of the study, along with answers to the research questions that were posed here. The chapter also ties the study together with the literature to present a complete conclusion to the features and characteristics that SME-scale commercial health technology ventures should achieve in order to succeed and be sustainable in South Africa.

The dissertation follows, next with a critical review of the appropriate literature for this study.

CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

This chapter of the dissertation covers the review of the pertinent literature that relates to the study. In line with the principles of a critical literature review (Saunders and Rojon 2011), papers and publications were perused on topics that have already been published on the questions and objectives of this study. The chapter is structured to present them in an ordered and logical manner.

The chapter begins, therefore, with an introduction to the literature on the global state of biotechnology, with a focused review of the global state of public and private biotechnology. Next, the factors limiting the success of health technology are deliberated, with a specific review of the aspects of funding and venture capitalism. The converse of this is discussed in the subsequent section, where the factors that are necessary for generating biotechnology success are reviewed; along with an in-depth reflection on the roles of entrepreneurial culture, handling negative publicity, patents and legal issues, company development, and biotechnology clusters.

The direction of the literature review alters, thereafter, concentrating on biotechnology in Brazil, Russia, India, China and South Africa (BRICS) and other IDC countries, with a specific overview of Brazil, India and China being presented. Refining the literature review further, the South African biotechnology sector is then deliberated according to each of the aspects of South Africa's early government involvement in biotechnology, and the evolution of the country's funding bodies. Case studies on two former Biotechnology Regional Innovation Centres (BRICs) – Acorn Technologies, and Bioventures are then presented. As a significant current player in South African biotechnology, the Technology Innovation Agency (TIA) is also then discussed in a dedicated section of the chapter.

In the final sections of the literature review, the interaction between the academic and higher-education institutions and the Health technology industry are contemplated, followed by a critical analysis of South Africa's biotechnology sector, and the shortcomings that have been observed in the industry. Finally, commercialisation of biomedical science in South Africa is discussed, as it focuses directly on the topic of this dissertation.

The chapter begins, next, with the introduction to the global state of biotechnology.

2.2 THE GLOBAL STATE OF BIOTECHNOLOGY

Global biotechnology may be considered in two general measures, in terms of the size of their product outputs or financial turnovers: smaller private biotechnology companies (Huggett 2012), or larger corporations of publically registered organisations (Huggett and Lahteenmaki 2012). Each of the two capacities of biotechnology is subject to their own trends and conditions, and these are described throughout this subsection of the chapter.

Public biotechnology companies include large organisations that are specialised in the various biotechnology sectors, and unlike private biotechnology companies, are involved in the process of publically trading shares (Huggett and Lahteenmaki 2012). When considering the distribution of the sizes of the public biotechnology companies, these authors differentiate the companies based on their total 'market cap', which is the total value of the issued shares of a publically traded company. The authors note the company sizes as:

- Large cap: Over $5 billion;
- Mid-cap: $1 billion to $5 billion;
- Small cap: $250 million to $1 billion; and
- Microcap: under $250 million.

A review of the global distribution of public biotechnology companies is informative as it presents an overview of the distribution of biotechnology power around the world. In studies by Huggett et al. (2009); Huggett et al. (2010); Huggett et al. (2011); Huggett and Lahteenmaki (2012) and Huggett (2013b), data are presented that offer a temporal overview of the global biotechnology trends. The United States retained the majority of public biotechnology companies, by number, with 214 companies in 2012, as shown in Figure 2.1. This was followed by Europe, Australia and Canada, with 128, 42 and 34 companies, respectively; while the rest of the world (ROW) was only represented by 7 publically traded biotechnology companies in 2012.

The majority of publically traded biotechnology companies fell under the microcap category, whereby in 2012, approximately 68% of companies traded shares less than $250 million, as shown in Figure 2.2 (Huggett et al. 2009; Huggett et al. 2010; Huggett et al. 2011; Huggett and Lahteenmaki 2012; Huggett 2013b). This showed an increase, so that 2012 had the highest number of large cap corporations in the 5 years reviewed, along with the lowest number of microcap companies. The number of mid-cap companies appears to have remained consistent, according to the literature reviewed, while the number of small-cap companies appeared to fluctuate between 64 and 90 over the 2008-2012 periods.

An interesting observation, according to the Huggett and Lahteenmaki (2012) study, is the distribution of employees in the global public biotechnology sector. The authors provided figures to suggest that the large cap corporations, which held the fewest number of organisations, employed

the vast majority of individuals by number, at over 100,000 people. Conversely, the microcap companies, which comprised nearly two thirds of the number of public biotechnology companies in 2012, only employed around 20,000 people, or 10% of the public biotechnology-employed work force. This is indicated in Figure 2.3.

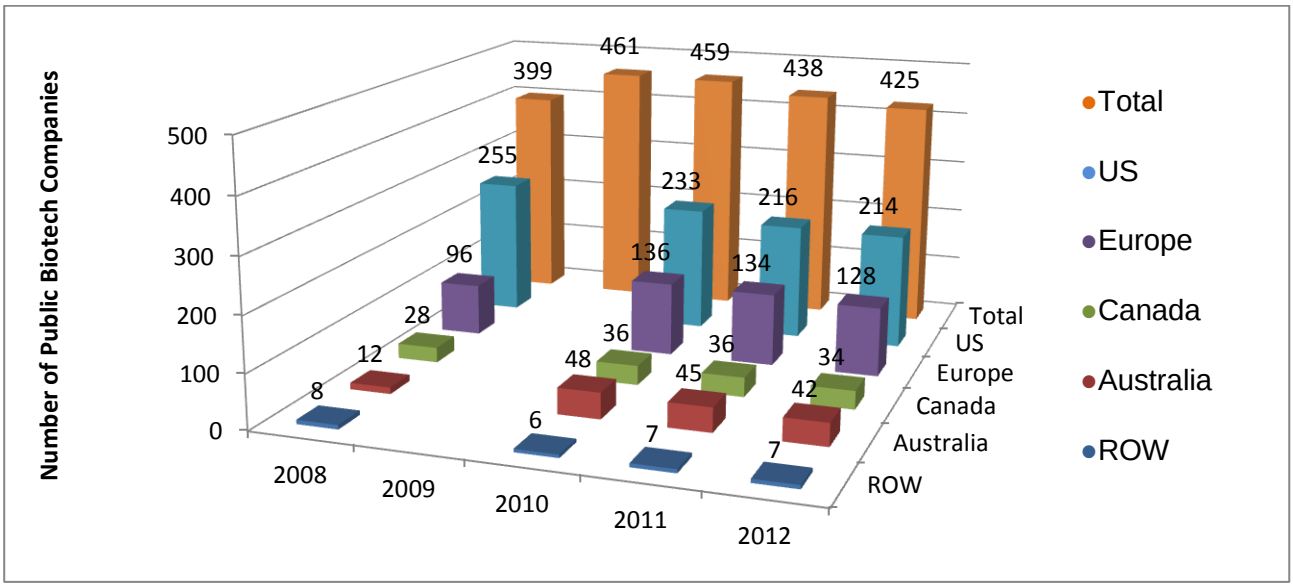


Figure 2.1 Global number of public biotechnology companies, 2008-2012

Sources: Huggett et al. 2009; Huggett et al. 2010; Huggett et al. 2011; Huggett and Lahteenmaki 2012; Huggett 2013b

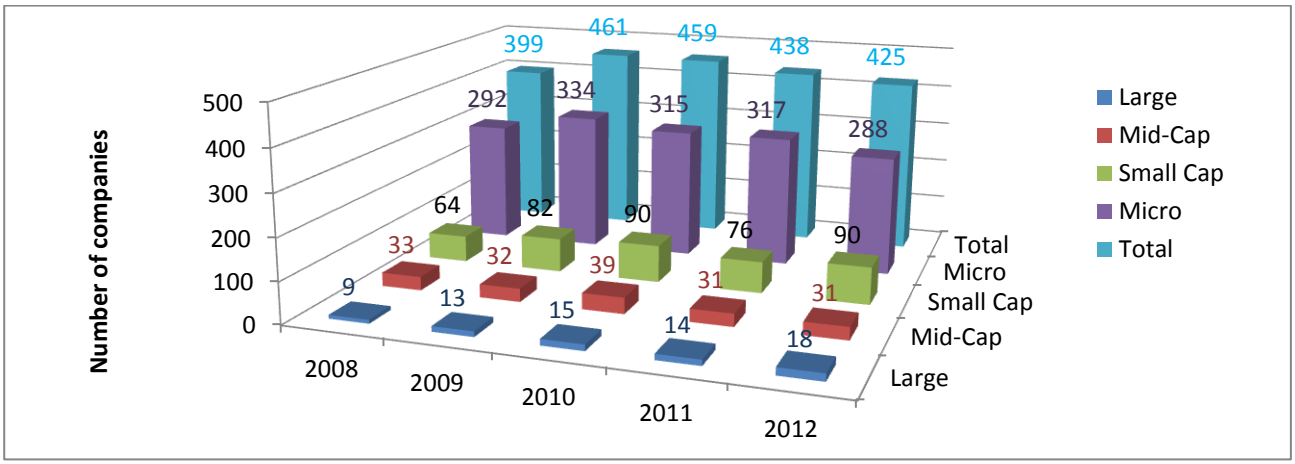


Figure 2.2 Global distribution of public biotechnology companies based on market cap, 2008-2012

Sources: Huggett et al. 2009; Huggett et al. 2010; Huggett et al. 2011; Huggett and Lahteenmaki 2012; Huggett 2013b

In terms of private biotechnology, according to Huggett (2012), there has been a slow decrease in the number of private biotechnology ventures in the world's "biotechnology strongholds" in recent years. This is evident in locations such as Europe and the US, where the number of private

biotechnology companies has seen a reduction from around 3 360 private biotechnology companies in 2007 to 3 290 by the end of 2011 (Huggett 2012).

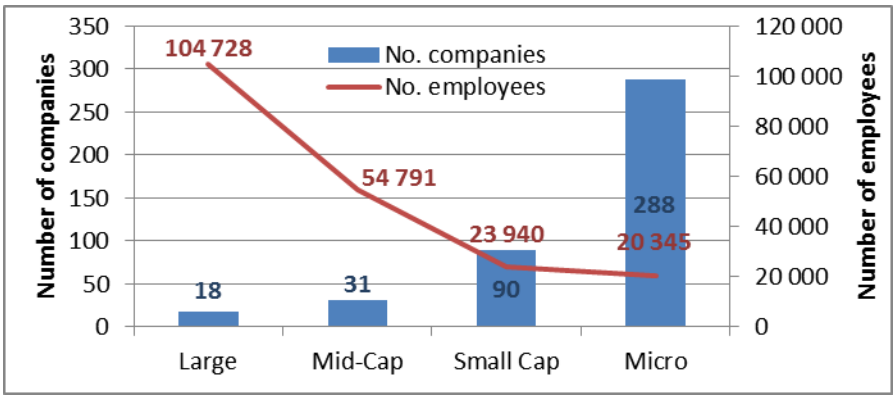


Figure 2.3 Global distribution of public biotechnology companies and employees, 2012

Source: Huggett 2013b

Various factors have been observed to cause this decline, which are discussed in the next section.

2.3 FACTORS LIMITING HEALTH TECHNOLOGY SUCCESS: FUNDING AND VENTURE CAPITALISM

One form of funding for new enterprises is through Venture Capitalists (VC). Masum and Singer (2010) define VCs as "organisations that invest funds into new enterprises in order to provide financing and support that helps to scale up promising technologies and business ideas", and either directly or through a share-holding, generate a profit for the VC. The authors note that for decades, VCs have helped to shift health technologies from the idea phase to implementation in developed countries. Huggett (2012), however, argues that biotechnology start-ups that have been based on academic science have, in recent years, found it more difficult to attract venture capitalist investment; as in many cases, the financiers are attempting to lower their risks, while they improve their profits and returns on investments. Figure 2.4 depicts the reduced funding provided by VCs between 2008 and 2012, where both the amount invested, and the numbers of rounds of investment have both seen a general decline.

This has led many researchers to suggest that the future of innovative life-science for commercialisation may be under threat. Furthermore, the number of VCs that financed biotechnology firms reduced from 313 in 2007 to 194 in 2011, most of which were headquartered in the US (Huggett 2012). Canada and Israel, however, have seen relatively consistent VC funding, as shown in Figure 2.5, while China's VC capital has been increasing considerably. Values shown in Figure 2.5 are at log scale, however, and funding in the US is at a magnitude higher than the rest of the world, followed only by the EU, as shown in Figure 2.6 (Huggett 2013a). Aspects relating to the South African biotechnology environment are discussed in Section 2.6.

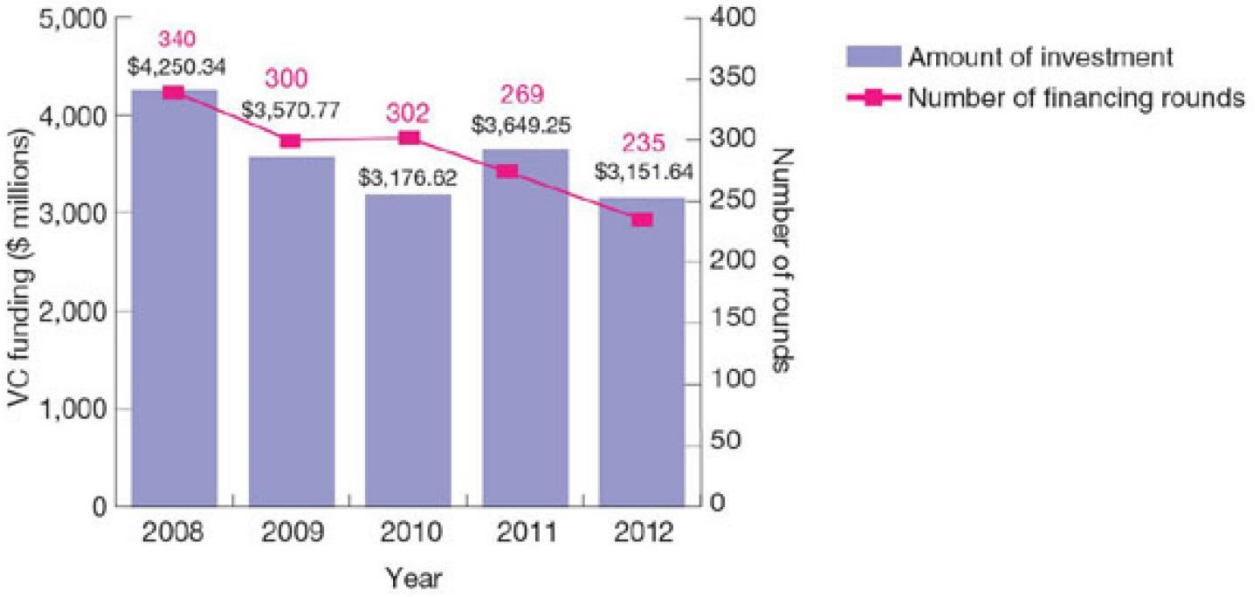


Figure 2.4 Venture capital investment for biotechnology therapeutic companies, 2008–2012

Source: Huggett 2013a

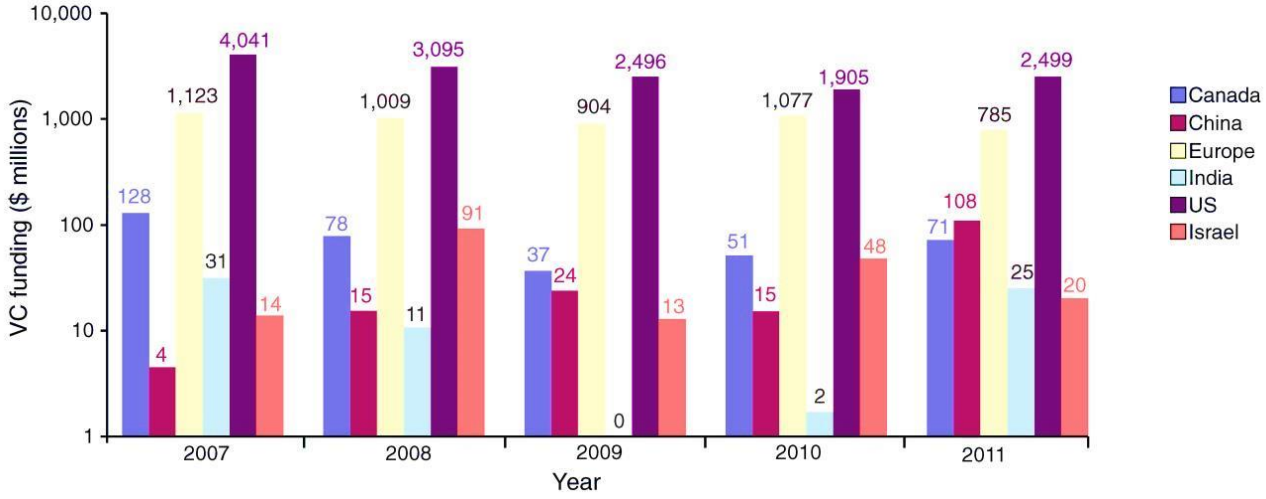


Figure 2.5 Venture capital investment for biotechnology therapeutic companies by region, at log scale, between 2007 and 2011

Source: Huggett 2012

Huggett (2012) asserts that one reason for this reduced funding could be “disappointing” returns from the sector, although life-sciences have been seen to perform better than the healthcare and IT sectors. Jon Soderstrom of Yale University (cited in Huggett 2012), therefore, suggests that “the VC model is dead.” Herskowitz (2012, cited in Huggett 2012) states the following reasons that pharmaceutical companies and investors have reduced funding to the private biotechnology sector:

- Companies want risk to be minimised, further than ever before;
- VCs want to hold the patents longer;

- VCs are requiring further work by new start-ups on proof of concept, before providing any funding.

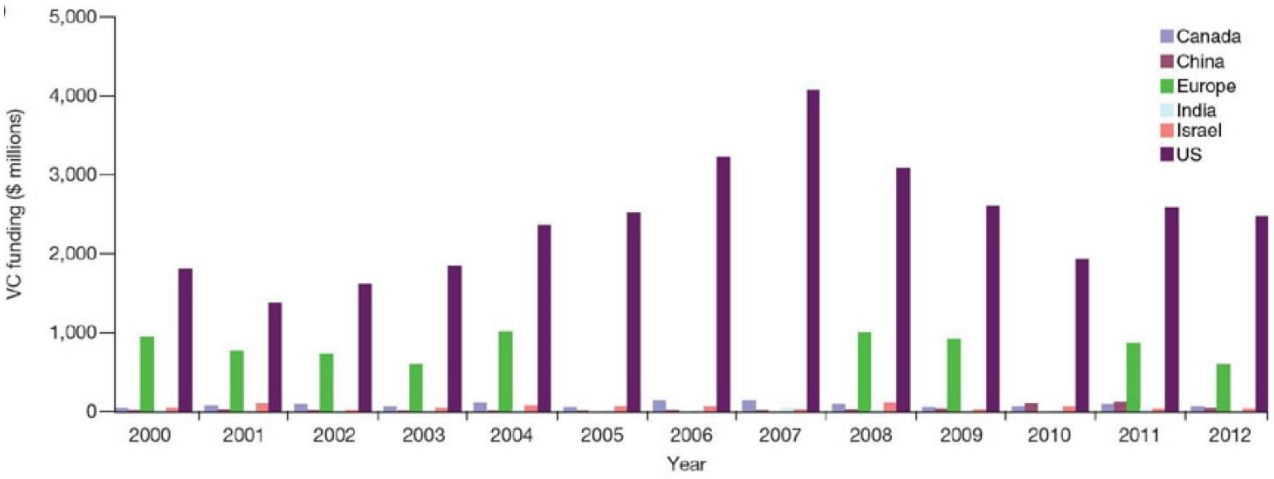


Figure 2.6 Direct comparison of venture capital investment for biotechnology therapeutic companies by region, between 2000 and 2012

Source: Huggett 2013a

A perhaps encouraging observation by Huggett (2012), is that while VCs are being "choosier" about which biotechnology companies they invest in, once they have invested in a company, their amount committed within each round of payment is increasing, thereby providing start-ups with larger buffers to reach their next evaluation points. As a form of protection to the VCs, though, a system of 'tranche' investing is being applied, where the investor supplies only a portion of the total amount up front, while the remainder is secured under performance targets and milestones, as an additional element of safety for their funds. Milestones include, for example, reaching progress points towards the clinical validation of a drug, or preclinical trials and so forth.

According to Huggett (2012), contrary to the public sector, the total amount that has been invested in the private sector over the past decade has remained relatively consistent. This is due to an increase in the number of "academic spin-outs", which has offset the reduction in the number of VCs that wish to invest in early stage biotechnology start-ups. As shown in Figure 2.7, between $3.2 billion and $6.2 billion has been invested in the sector, each year, between 2000 and 2011, producing an average investment of $4.5 billion per annum.

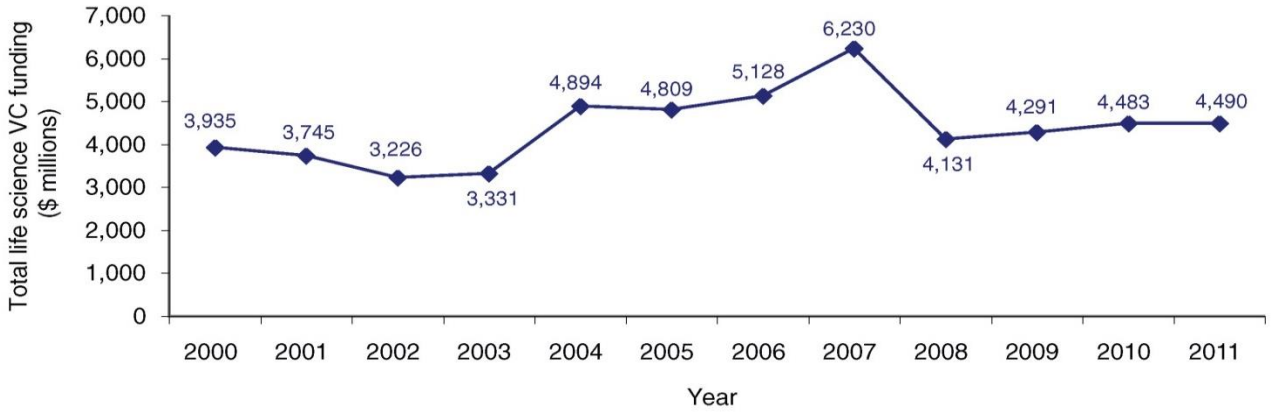


Figure 2.7 Global venture funding of private biotechnology companies, 2001–2011

Source: Huggett 2012

The majority, or approximately 78% of funding from VCs is awarded to private biotechnology companies that are at the product development stage, such as companies that have experimental compounds, products in development or products under clinical trials (Huggett 2012).

According to an analysis of the Dow Jones, relating to medical therapeutic indications that received the most VC funding in recent years, companies involved with oncology have consistently received the most funding, although the global investment figures have dropped significantly since 2007, wherein the field received approximately $6.1 billion globally (throughout the biotechnology and pharmaceutical sectors), to approximately $2.4 billion in 2011 (Huggett 2013a). The fields of infectious diseases have considerably reduced in support from the VCs, globally, since 2007, while ventures aimed at renal and pulmonary diseases have both increased. These sentiments are reflected in Table 2.1 below.

Table 2.2 shows the investments that were made into innovative therapeutic companies, globally, over the periods 2008 to 2012. The number of investments in biomaterials reduced from 22 rounds of investment in 2008, worth approximately $108 million, to only seven in 2012, worth a value of approximately $29 million. Vaccines and immunotherapies also had a significant drop from 70 rounds, totalling $1.06 billion in 2008, to 33 rounds in 2012, totalling $367 million. While gene therapy, cell therapy and small molecule therapeutics all had reductions in investment, gene therapy managed to sustain investment over 2011 and 2012. The top recipients of funding by VCs still remained companies that were developing protein therapeutics or other small molecules (Huggett 2013a).

Table 2.1 Venture capital funding by medical indication, in 2007 and 2011

Therapeutic area	Number of deals in 2011	Amount raised in 2011 ($ millions)	Number of deals in 2007	Amount raised in 2007 ($ millions)
Autoimmune	59	1,538	81	2,139
Cancer	143	2,390	199	6,083
Cardiovascular	30	814	49	902
Endocrine/metabolic	71	2,350	89	2,489
Gastrointestinal	16	897	0	0
Genitourinary	7	92	10	249
Hematology	70	371	23	855
Infectious	81	1,600	154	3,659
Inflammation	73	1,867	102	2,495
Musculoskeletal	18	271	22	434
Neurology	65	996	78	2,449
Opthalmic	39	581	19	657
Pulmonary	24	425	7	164
Renal	21	712	16	560
Transplant	1	1	19	309

Source: Huggett 2012

Table 2.2 Venture capital funding of innovative therapeutics in the US, from 2008 to 2012

	2008		2009		2010		2011		2012	
Modality	No. of deals	Amount invested ($ millions)	Deals	Amount	Deals	Amount	Deals	Amount	Deals	Amount
Biomaterials	22	108	13	78	15	75	15	91	7	29
Cell therapy	44	472	35	372	41	259	28	352	29	356
Gene therapy	16	235	15	180	10	70	24	241	13	162
Immunotherapy	70	1,056	44	630	57	626	42	627	33	367
Protein therapeutics	48	566	47	637	41	530	33	430	33	798
Small molecule	50	788	45	598	48	585	46	610	42	622
Specialty pharma	16	294	17	283	18	220	15	457	15	143
Other	74	730	84	794	72	812	66	812	63	674

Source: Huggett 2013a

2.4 FACTORS GENERATING BIOTECHNOLOGY SUCCESS

Many studies have been done to determine the critical success factors for the biotechnology sector (Gertler and Vinodrai 2009; Uctu and Pillay 2012; Pillay and Uctu 2013). While Thorsteinsdóttir et al. (2004) argue that there is no “one-size-fits-all solution”, and that there are many different ways to succeed in health biotechnology, much of the research has concluded complementary results, suggesting that a skilled workforce, governmental policy support, the availability of financing and services, and a supportive infrastructure all promote a successful biotechnology industry. Though these factors are features of many industries, biotechnology is especially affected by these influencers.

Since biotechnology is a science-based field, ventures often develop in close vicinity to the primary knowledge centres, such as public research institutes, universities, hospitals and other R&D

centres that conduct high-level research (Pillay and Uctu 2013). Public research organisations, universities, research hospitals and R&D institutions are noted as “key players” for the advancement of knowledge and expertise, as they provide a concentrated source of workers for local firms.

Sainsbury (1999) presented an overview of the factors that encourage the promotion of biotechnology, which, as shown in Table 2.3, can be separated into three groups.

Table 2.3 Critical factors for promoting biotechnology

Group I: Exploitation of the research base	
Strong science base	Leading research organisations: university departments, hospitals/ medical schools and charities; Critical mass of researchers; World leading scientist(s)
Entrepreneurial culture	Commercial awareness and entrepreneurship in universities and research institutes; Role models and recognition of entrepreneurs; Second generation entrepreneurs
Group II: Company development	
Growing company base	Thriving spin-out and start up companies; More mature “role model” companies
Ability to attract key staff	Critical mass of employment opportunities; Image/Reputation as biotechnology cluster; Attractive place to live
Premises and infrastructure	Incubators available close to research organisations; Premises with wet labs and flexible leasing arrangements; Space to expand; Good transport links: Motorways, Rail, International airport
Availability of finance	Venture capitalists; Business angels
Business support services and large companies	Specialist business, legal, patent, recruitment, property advisors; Large companies in related sectors (healthcare, chemical, agrifood)
Skilled workforce	Skilled workforce; Training courses at all levels
Group III: Government support	
Effective networking	Shared aspiration to be a cluster; Regional trade associations; Shared equipment and infrastructure; Frequent collaborations
Supportive policy environment (national, regional and local)	National and sectoral innovation support policies; Proportionate fiscal and regulatory framework; Support from RDAs and other economic development agencies; Sympathetic planning authorities

Source: Sainsbury 1999

The first group of factors include the exploitation of the research base, and requires a strong entrepreneurial culture and a strong scientific basis. The second includes company development, through the ability to attract skilled staff and finance, and through access to business support services and other supportive infrastructures. The third group of factors comprise the support of government, through effective networks and other government related facilities (Sainsbury 1999).

2.4.1 Entrepreneurial culture

Pillay and Uctu (2013) argue that SMEs are the driving force in the development of local biotechnology industries, through start-up ventures that bring biotechnology processes and products to the market. Collet and Wyatt (2005) state that success by these companies requires "champions" who have a sound knowledge of the respective scientific principles, as well as an understanding of business principles that relate to market development, product innovation and venture capital. However, they argue that, above all, the factor to develop the biotechnology industry is "entrepreneurial culture", and that scientists should not only view the scientific side of research, but also the "commercial exploitation of their results."

Klerck (2005) asserts that scientists must remain at the forefront of technological development and knowledge-seeking to remain on top of the field. This author suggests that developing countries are at a significant disadvantage, as they are often presented with a range of obstacles that prevent them from gaining a footing in the biotechnological sectors. This includes their limitations in expanding their research infrastructure and scientific base beyond a limited selection of academic institutions and suitably qualified scientists.

2.4.2 Handling negative publicity

Fambrough (2012), suggests that, while a concept in the biotechnology field may be exploited when the public's idea of that concept is "hot", the real value of biotechnology is not based on public perception, and that a value of a technology should never be confused with being out of the public's favour, since one can never win over all of one's critics. The author suggests that staying true to the science and its commercial potential results in better investments by venture capitalists in the long-term, than if a company were to simply follow prevailing trends and wisdom.

In order to change perceptions, emphasis should be placed on three aspects. These are the data, the scientific model, and outside validation (Fambrough 2012). The data and scientific model provide potential investors with the technical background to placate their fears, and clearly communicate the model and the data of the concept. The critical thinkers of a financial decision, for example, require understanding of a concept before they begin to trust it. Finally, the outside validation, which is the endorsement by third party observers, provides the basis for people to "pay attention"; and Fambrough (2012) recommends three steps to countering adversity in the field:

- Firstly, solve the greatest challenges that confront the company;
- Secondly, refrain from attacking or criticising the competitors, as good news for one company implies good news for the whole field; and
- Thirdly, keep the investors and partners well-informed, as they will be more supportive when they are receiving a consistent flow of fact-based news about the company's progress.

2.4.3 Patents and the legal issues of biotechnology

Internationally, intellectual property (IP) protection is a sombre issue for biotechnology success, since if national patent laws did not protect intellectual properties or technological discoveries, few companies would be interested in investing in research, development or manufacturing of such products (Niosi et al. 2012). In a bid to protect the IP of companies on a global scale, the Trade Related Aspects of Intellectual Property Rights (TRIPS) international regulatory accord was signed in 1994, and enforced since 2005. According to Thorsteinsdóttir et al. (2010), several developing countries are now signatories of TRIPS, and Niosi et al. (2012) suggest that most developing countries have gradually increased their IP protection of drugs and other types of biotechnology-related products. Within the clause of the Doha agreement, though, some of the least developed countries have postponed the signing of large portions of the TRIPS agreement until 2016 (Mercurio 2004). Shortcomings in the IP global protection system have also been observed, especially in some large developing countries, such as Brazil, China, Argentina, and India, where cases of counterfeit products have been detected (Niosi et al. 2012). These authors attribute this to deficiencies in the TRIPs accord, which has a “lengthy, cumbersome and unpredictable” enforcement process.

South Africa has a firm process of patent protection in line with international norms, and in 1997, as a member of the World Trade Organisation (WTO), was brought in line with the TRIPS accord for IP regulation in the country (Zainol et al. 2011; Al-Bader et al. 2009). In South Africa, patents are governed by the Patents act of 1978, with an amendment in 2005 intended to protect people or communities with traditional knowledge from being “exploited by bio prospectors” (Cloete et al. 2006). With this amendment, the patent registrar may refuse new patent applications unless strict guidelines and conditions are met, while the Department of Environmental Affairs and Tourism may enforce compensations, co-ownership and benefit sharing of patent ideas, as well as contest the application of the patent worldwide if it is based on a South African resource. This has resulted in a major deterrent for bio prospectors (Cloete et al. 2006).

The majority of scientific focus in South Africa is on publication output, rather than commercialisation of discoveries, which has caused South Africa to considerably lag behind when compared to the number and percentage ownership of patents from other developed or developing countries (Katsnelson 2004). Additionally, another potential cause for the low rate of biotechnology patents is the considerable expenses involved with registering of foreign patents, which for international filing of a biotechnology patent can amount to R500 000 or more (Pouris 2003).

In a bid to improve the entrepreneurial attitude of universities and research institutes, legislation revisions were being drafted in the nature of the United States Bayh-Doyl Act, which would afford ownership of any inventions that were developed with government funding to the respective institution (Katsnelson 2004). Additionally, South African biotechnology companies could also

expect greater access to rights on patent licensing when they had invested in university research, thereby improving the reciprocal flow of research and commercialisation (Katsnelson 2004).

According to Sathar and Dhai (2012), the national ethics regulations and legal aspects pertaining to the use of Human Biological Materials (HBMs) in South Africa are governed by Chapter 8 of the National Health Act (NHA), Act No. 61 of 2003. However, there is considerable speculation regarding the efficacy of this act; since, according to Sithole (2011) and Pepper (2010), it was still not in operation, even though it had been in existence for nine years. As a result, the provisions of the predominantly outdated Human Tissues Act (HTA) were being relied on as a regulatory framework instead.

Research ethics guidelines for the use of HBMs have been issued by the Department of Health (DoH), The Health Professions Council of South Africa (HPCSA), and the Medical Research Council of South Africa (SAMRC), while intellectual property rights, patents and benefits that may be applicable to HBMs have been regulated by the South African Intellectual Property Rights from the Publicly Financed Research and Development Act (IPR Act No. 23) (Sathar and Dhai 2012).

2.4.4 Company development

Sainsbury (1999) asserts that successful biotechnology start-ups require a sound base of established biotechnology companies that act as “role models” for new ventures. The author suggests that while different regions have different requirements, there is a critical mass of larger companies that is typically needed to provide the foundation upon which new companies may begin.

Attracting key skilled staff is important for driving the growth of start-ups to maturity, and this is often achieved by drawing top scientific researchers and management from abroad. Employment opportunities for career growth, a high quality of life within friendly environments, and areas of natural beauty within vibrant international cities are often prerequisites for such individuals to be attracted to growing biotechnology ventures (Sainsbury 1999).

As in most technology-related businesses, financial availability is a fundamental requirement for business growth, and in the biotechnology sector, financial support is often required for long periods of time. It has also been found that companies and investors place value on being geographically and in principal, closely related (Sainsbury 1999).

Support from the government can also greatly encourage development of the biotechnology sector. Aside from policy formation for streamlining company formation, co-ordination between government departments, public research facilities and regional economic development agencies, support can also take many other forms. Private services can be substituted, for example, for public services that are lacking, and incentives may be provided to prevent ‘brain drain’ (Uctu and

Pillay 2012). The government in China, for example, has made concerted efforts since the late 1990s to counter the problems of ‘brain drain’, by encouraging expatriated professionals to return through incentives for funding research laboratories, and schemes to allow returning scientists to establish ventures (Thorsteinsdóttir et al. 2004).

2.4.5 Biotechnology clusters

Uctu and Pillay (2012) claim that one of the critical factors for the success of biotechnology in many countries has been the development of ‘clusters’, and a characteristic of highly developed biotechnology industries has been a high concentration of firms, geographically. While, according to Pillay and Uctu (2013), there is no standard definition of a cluster, it is most frequently described as “a geographically proximate group of interconnected companies and associated institutions in a particular field, including product producers, service providers, suppliers, universities, and trade associations”. Within the biotechnology sector, for example, the industry tends to develop in geographically concentrated locations.

These ‘clusters’ act to provide “knowledge-based hubs” through the creation of a platform for networking and efficient communication, infrastructure, resources and expertise among research institutions, governments, industries and universities. Many studies have been done on the critical success factors for biotechnology clusters, and the conclusions of these studies have revealed the following influences (Pillay and Uctu 2013):

- A strong science-base;
- An entrepreneurial culture;
- A growing company base;
- The ability to attract vital staff;
- Access to the necessary infrastructure and premises;
- The availability and access to finances;
- Access to business support services and large companies;
- A skilled workforce;
- Effective networking; and
- A supportive legal policy framework.

Clusters are often considered as drivers of business and economic development, and structures for enhancing productivity and creating competitive advantage. Authors such as Rosson (2003) have explored the benefits and advantages of clusters, and these authors state that clusters:

- Encourage collaboration between institutions;
- Raise productivity and innovation;
- Facilitate the transfer of both formal and informal knowledge;

- Create sharing of knowledge about protocols and best practices;
- Reduce costs by combining the sourcing of suppliers, services and infrastructures; and
- Develop the capacity of the skilled workforce.

These advantages and benefits of clusters have stimulated many government agencies to introduce clusters as a tool for promoting technology and economic development (Pillay and Uctu 2013).

2.4.5.1 Bio-clusters in the developed world

In the US and UK, most firms are concentrated in clusters within a few metropolitan areas or states (Pillay and Uctu 2013). The strong driving force behind this clustering is their access to public and government research organisations, large markets in major cities and venture capital. Audretsch (2001) also argues that entrepreneurial culture, specialised knowledge, strong networks and high labour mobility have also contributed to the successful clustering in these countries.

The clustering model varies from one country to another (Uctu and Pillay 2012), and clusters in the US are focused on investment attraction and commercial outcomes, as well as placing main strategic multinational companies in the middle of their regional clusters. Conversely, in Europe, the R&D institutes and universities constituting the public sector provide the primary drive for clusters.

Clusters in the UK are generally closer to industrial groups and are among concentrations of university graduates. The largest clusters include Greater London, followed by Oxford and Cambridge: the latter two of which are supported by leading research-intensive universities, research institutes and research hospitals, have large pools of individuals to provide a skilled workforce and access to large local VCs or business angel networks. These clusters provide patent, property, recruitment and legal advisers, science parks, and incubators, and as a result, each of these regions has witnessed a rapid growth in biotechnology companies.

The biotechnology cluster in Montreal, Canada, benefits largely from government programs within each of the provinces, as well as from national research laboratories. Out of the 351 companies situated in the cluster, 130 are concentrated on human health, and 171 provide services for company support. The remaining 50 companies are involved in human nutrition, agriculture and the environment (Philips and Ryan 2007). Within Uppsala, Sweden, as in many clusters, there is historically a close relationship between academia and the industry, which is noted by Waxell and Malmberg (2007) as a significant contributing factor to its success. The cluster, which is home to some 80 biotechnology firms, employs approximately 5000 people, and provides job infrastructures in and around Uppsala for around 8000 people.

2.5 BIOTECHNOLOGY IN THE BRICS AND OTHER IDC COUNTRIES

As described by Mahoney et al. (2005), Innovative Developing Countries (IDCs) are countries that are actively involved in health biotechnology, and which have reached a certain capacity or capability in health innovation relative to a global “four stage framework”. Within this framework, six determinants are measured including the capacity for companies to conduct R&D, the regulatory mechanisms available for drug and vaccine safety, the manufacturing capability for new health related technologies, the provision of national distribution systems in the private and public sectors, the presence of international distribution systems, and the implementation of effective systems for the protection of IP (Mahoney et al. 2005).

South Africa is considered as one of the IDCs, since it is involved in, and has reached a certain stage of health innovation, along with other developing countries such as India, China, Brazil and Cuba. Furthermore, in 2010 South Africa was included in the BRICS group of countries, which, apart from Russia, are newly industrialised developing countries with large, fast growing economies, and which together accounted for 53% of the entire global GDP growth for the period 2007-2010 (Patel 2012; Gomes 2013). They are therefore a significant influencer of regional and global affairs; however, in spite of the growing economic infrastructure in these countries, they have still not created a modern, broad healthcare system as presented in the G7 industrialized countries, and extensive differences in health expenditure exist between these regions (Gomes 2013).

Bioclusters have also been pivotal in establishing the biotechnology industries in developing countries, such as Cuba, Brazil, India and China. Clusters in these regions have provided technical, financial and other resources for company start-ups. For example, there are approximately 181 private companies which specialise in the life sciences in Brazil, of which 19% are in the Southeast region, with major undertakings in the agricultural sector, followed by health-biotechnology, natural resources and the environment (Pillay and Uctu 2013).

Abuduxike and Aljunid (2012) suggest that the capacity for science and technology in developing countries is dependent on several main factors, including expertise and human capital in the healthcare technology-related disciplines, the accessibility and availability of investments and funding for health development and research, the effectiveness and focus of universities and research institutions, and the link between the public and private sectors along with their scale of collaboration towards health-related innovation. They also suggest that governmental policies towards health-related technologies are critical for science and technology to succeed.

2.5.1 Brazil

The government of Brazil provides various incentives to boost the sector, including improvements to its policies on capital investment, providing fiscal benefits to facilitate the importation of

equipment, and improving the regulations for goods and services (Resende 2003). There are three clusters in Brazil: Minas Gerais, Sao Paulo and Rio de Janeiro. The success of the Minas Gerais cluster has been attributed to its interaction with the public institutions in the region, including the University of Minas Gerais, which is home to some 160 biotechnology specialists. The institutions allow companies in the industry, for example, to use their facilities (Zylberberg et al. 2012). Furthermore, in the Minas Gerais biocluster, the government is heavily involved with the provision of investments, while private VCs are also noticeably supportive.

2.5.2 India

The Bengaluru biocluster in India was among the first in the developing world, which began in 1978 (Pillay and Uctu 2013), when *Biocon*, the country's first biotechnology company was founded for the production of industrial enzymes, and later Biotherapeutics (Gandhi et al. 2011). Through the formation of the National Biotechnology Board in 1982, which later became the Department of Biotechnology (DBT), the government created a major boost to the industry by providing a body for identifying priority areas and producing long-term plans for biotechnology development in the country. This facilitated the creation of a broad scientific workforce; a strong support for R&D in the life sciences, such as tax holidays on spending for R&D; a large infrastructure network; subsidies for capital limits; and fiscal incentives, such as relaxed price controls for drugs (Natesh and Bhan 2009).

Within the leading biotechnology states in India, clusters have been developed as publically-funded R&D institutions, with strong academic ties. There are over 380 biotechnology companies in India employing more than 20,000 scientists (Gandhi et al. 2011), with the main focus on bio-pharmaceuticals, such as therapeutic drugs, vaccines and animal biologicals, followed by bio-services, such as clinical trials, data management and bioavailability studies; and bio-agriculture, such as BT-cotton (Pillay and Uctu 2013). Revenues in the Indian biotechnology sector have skyrocketed, with 2007-2008 revenues of $2.2 billion being generated, increasing exponentially to $2.6 billion in 2009, $3.1 billion in 2010, and $4.0 billion in 2011 (Gandhi et al. 2011).

2.5.3 China

Following the introduction of the national long-term plan in China in 2005, which aimed to expand China to the status of one of the leading science and technology powerhouses of the world, biotechnology received considerable government investment. More than 20 biotechnology parks are operating around the country, which are primarily focused on human therapeutics and agriculture (Pillay and Uctu 2013). According to Miller et al. (2010), the principal factor contributing to the competitive edge of China's growing biotechnology sector, especially in Shanghai and Beijing, is the low cost of expertise for production and development. As a result, more than 75% of the 158 companies, 22 higher education institutions and 31 R&D centres in Shanghai are involved

in manufacturing (Pillay and Uctu 2013). Nearly 70% of Shanghai's R&D expenditure is also targeted on the development of products and processes, with only 26% and 6% on applied and basic research, respectively. Problems remain in Shanghai's biotechnology sector, however, which have included the inadequate protection of IP, poor VC investment and a slowing supply of skilled individuals for its workforce (Miller et al. 2010).

2.5.4 International collaborations

In recent years, the developing countries have attempted to reduce their reliance on trade with the politically and economically-dominant developed countries, or "Northern [Hemisphere]" countries, and have opted rather to create synergistic partnerships in a "South-South" topology to bolster the strengths of these regions and, therefore, their competitiveness (Thorsteinsdóttir et al. 2010). In a study by these authors on health biotechnology collaborations, they determined that there is now a substantial South-South collaboration between the developing countries, present on both the governmental and commercial agendas of these countries for technical and scientific interaction.

Collaboration has included attempts to boost innovation and development of new products and processes; and end-stage commercialisation activities, such as marketing and distribution, or access to markets, as opposed to R&D. Thorsteinsdóttir et al. (2010) found that approximately 25% of firms in their study had an active collaboration with firms in other developing countries, although the South-North collaboration was still far more prevalent, being present in closer to 50% of companies. Countries with larger populations were also seen to collaborate more in South-North collaborations than those with smaller populations (Thorsteinsdóttir et al. 2010).

2.6 OVERVIEW OF SOUTH AFRICA'S BIOTECHNOLOGY SECTOR

South Africa has had a noteworthy involvement in the 'first-phase' types of biotechnology, globally, as defined in Section 1.3, producing various high quality beers, wines and cheeses; with the South African Breweries being one of the largest in the world. South Africa has also had a considerable presence in the second-generation of biotechnologies, where companies, such as AECI, began producing lysine in 1987. Participation in the third-generation of biotechnology, however, has been limited (Klerck 2005).

The majority of biotechnology projects in South Africa are based at "historically advantaged institutions" (Klerck 2005). Due to the internationally recognised researchers, and their sophisticated facilities and infrastructures at these institutions, they have therefore attracted the vast public sector investments. The author notes that support for innovation and R&D by the state in South Africa has been limited, historically.

According to Powell (2002, cited in Klerck 2005), the successful biotechnology firms in South Africa have positioned themselves as "hubs of overlapping networks" among various academics and

researchers in the field, and have encouraged broad research collaborations at multiple stages of product-development, in order to progress in the field. Innovation in the biotechnology sector has, therefore, been found predominantly in knowledge-intensive networks, as opposed to in individual firms.

Klerck (2005) asserts that, although South Africa has a relatively under-developed biotechnology sector, the available technologies span a range of industrial sectors, including mining, manufacturing, fishing and agriculture. The author attributes the state of the industry to a shortage of the necessary skills, funding and organisational resources, which would require immense additional investment by the government to develop a globally-competitive industry. This is because of the science-dependent link to innovation in the field, the knowledge-intensive style of collaborations, and the imperatives of the industrial policies and drives that act to significantly shape the content and form of research in a country.

In terms of cell-based therapy, which includes stem cells, there have been ventures in operation for many years in South Africa, according to Keetch et al. (2007), in the form of bone marrow transplantation, and stem cell therapy companies. As described by Samadikuchaksarae (2007), in a study of international opportunities for tissue engineering (TE), it was found that South Africa exhibited all 4 favourable criteria for TE promotion, such as the presence of a national policy or plan for the promotion of TE, along with the government's investment in the sector; the presence of marketable TE goods and services; the existence of active private companies in the field, and the presence of academic institutions and/or publications focusing on TE.

Biotechnological development in South Africa is also greatly driven by public research institutes, laboratories and universities. There are four main research institutions that are governmentally supported, however only the SAMRC is exclusively focused on the promotion of human health research. The other three consist of the Agricultural Research Council, MINTEK, and the Council for Scientific and Industrial Research (CSIR), which is the principal scientific and technological R&D and implementation organisation on the continent (Cloete et al. 2006).

Figure 2.8 presents an overview of the biotechnology industry in South African, including an indication of the distributions of core biotechnology companies and biotechnology products (Cloete et al. 2006). In 2006, at the time of Cloete et al.'s research, 106 companies were identified within the biotechnology sector, 47 of which were classified as core biotechnology companies. A core biotechnology company is considered as one whose primary economic activity is within the field of biotechnology, and which uses at least one biotechnology-related technique.

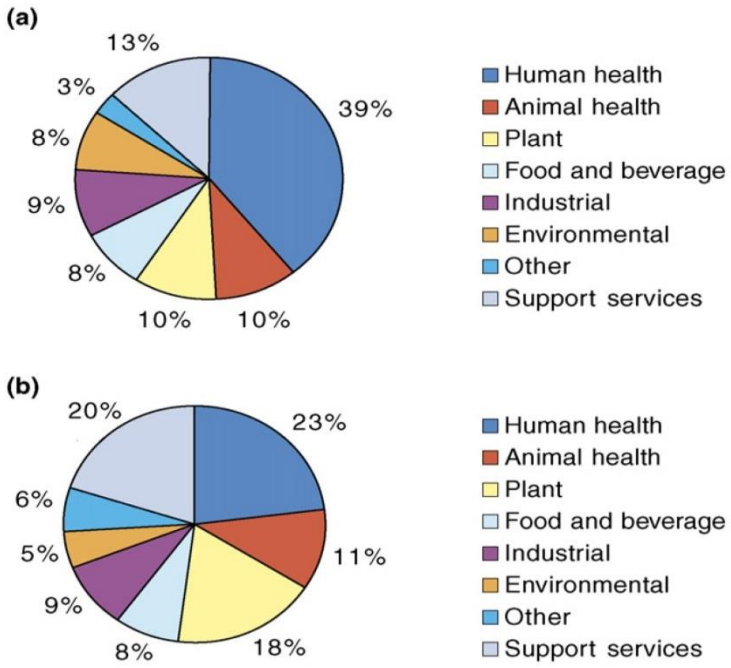


Figure 2.8 Overview of the South African biotechnology industry with (a) core biotechnology companies, and (b) biotechnology products

Source: Cloete et al. 2006

Conversely, a biotechnology 'active' company is one that either manufactures and sells biotechnology products, or conducts R&D in the field (Uctu and Essop 2013). These companies consisted predominantly of new start-ups, or 'spin-offs' from other companies. At least 154 goods and services were produced by these companies, and the majority of these were targeted at human health, followed by food and beverage, and plant products.

According to the National Biotechnology Audit (Department of Science and Technology 2008), the biotechnology industry of South Africa is still relatively small and underdeveloped, when compared to developed countries. As shown in Table 2.4, at the time of the audit in 2008, there were 78 'active' biotechnology companies in South Africa, with 38 'core' biotechnology companies — somewhat different to the Cloete et al. (2006) report. The DST (2008) report noted that over 72,800 people were employed at active biotechnology firms, while the number at 'core' biotechnology firms was approximately 760. Active firms generated revenues in 2006 of around R767 million, which was up from the 2004 revenues of R624 million. Core firms, however, turned a comparable amount to this in 2006, with a turnover of around R520 million (Uctu and Essop 2013).

Table 2.4 The core and active biotechnology companies in South Africa

Characteristics	Core biotechnology companies	Active biotechnology companies
Number of companies	38	78
Location	Gauteng 43%, Western Cape 30%, KwaZulu-Natal 19%, rest of SA 8%	Gauteng 43% Western Cape 26%, KwaZulu-Natal 12%, rest of SA 19%
Spin-offs	Companies: 16 (from universities: 44%, from government: 31%)	Companies: 25 (from universities: 28%, from government: 36%)
Foreign owned	Companies: 5	Companies: 12
Number of employees (2006)	765	72,844
Products	559	1542
Profits (2006)	R520 million	R767 million
R & D expenditure	R76 million	–
Fund raised (2003–2006)	R216 million	–
Major funding sources	BRICs: 36%; innovation fund: 19%	–

Source: Department of Science and Technology 2008

2.6.1 Early South African government involvement in biotechnology development

The industrialisation that took place in South Africa to substitute the importation embargoes of the Apartheid era ran out of steam during the 1970s, according to Klerck (2005), leaving behind a poorly developed local capital goods sector (stocks related to the manufacture or distribution of goods), high costs for imported technologies and poor investment in local R&D.

During the apartheid era, local technological and scientific capabilities were only developed and encouraged in “politically strategic” industries, such as mining, textile, armaments and medicine. While such sectors received considerable attention from the government, science-based sectors, such as nanotechnology and biotechnology, received far less support (Uctu and Essop 2013). During the late 1980s, the apartheid government began to show an interest in biotechnology, but it was only after 1994 that the post-apartheid government truly invested in the sector. Thorsteinsdóttir et al. (2004) argue, however, that some of the success of the health technology sector in South Africa is owed to the decisions that were made during the apartheid era, where the country’s isolation over a prolonged period provided the drive for self-sufficiency, and the need to develop its own research capabilities.

2.6.2 Evolution of the funding bodies

The national system of research, development and innovation was, by 2005, generally quite underfunded, whereby the total expenditure on R&D in 2005 amounted to approximately 0.7% of the Gross Domestic Product (GDP). In contrast, the average expenditure within the countries of the Organisation for Economic Cooperation and Development (OECD) was approximately 2.15% of GDP at the same time. Klerck (2005) states that human resources in science and technology have been inadequately developed, and there has been a significant recent decline in R&D in these areas by the private sector, blamed in part on the rigid institutional arrangements and funding structures in this domain. For example, various government departments were tasked with managing a variety of technology-based programmes and institutions, with little strategy coordination or sharing of learning.

Within the post-apartheid South Africa, the policy of the government has been to promote R&D, and to structure investment and labour policies towards attaining high-value-added and high-technology exports. Training and education to produce a skilled workforce is also being emphasised, along with a restructuring of the manufacturing sector. South Africa's national R&D strategy has, therefore, been to adopt an approach to "Capitalise on the established natural resource base while actively pursuing stronger manufacturing, information technology and biotechnology" (DACST 2002, cited in Klerck 2005).

In 2001, the National Biotechnology Strategy was initiated by the South African government. The National Biotechnology Strategy (NBS) recognised that South Africa had failed to "extract value" from the recent developments in biotechnology, unlike other developing countries, such as Brazil, Cuba and China (DACST, 2002; Uctu and Essop 2013). In an approach to realise South Africa's biotechnology potential, the NBS aided the formation of the country's Biotechnology Regional Innovation Centres (BRICs) with the goal of stimulating the development of internal life science ventures along with international partnerships (Cloete et al. 2006). The Biotechnology Regional Innovation Centres were designed to offer the following services:

- To offer entrepreneurial services;
- To offer services for intellectual property management;
- To offer platforms for providing advanced technologies;
- To act as business incubators; and
- To promote R&D.

Three key Biotechnology Regional Innovation Centres were developed in order to leverage opportunities for biotechnology in the country. Each BRIC comprised of a conglomerate of private and academic institutions, and research councils that specialised in the respective biotechnology disciplines. They were distributed according to specialisation, and included Biopad in Gauteng for

environmentally-related technologies, animal health and agriculture; EcoBio in KwaZulu-Natal for bioprocessing, plant biotechnology, and human health; and Cape Biotech in the Western Cape for bioprocessing and human health (Klerck, 2005; Uctu and Essop 2013).

The Biotechnology Regional Innovation Centres were established as “nuclei for the development of biotechnology”; and as a result, several bioclusters were spawned (Al-Bader et al. 2009). These centres were situated nationwide, and included centres in the Western Cape and Kwa-Zulu Natal (KZN), such as the Cape Biotechnology Initiative (Cape Biotech), and the East Coast Biotechnology Consortium (EcoBio – operating as LIFElab), respectively (Cloete et al. 2006). These two centres were focused on biotechnology ventures that targeted R&D of human health, and an initial R450 million was committed by the government for their creation (Gastrow 2008).

The BRICs acted as independent, but interconnected nodes that were linked through the National Bioinformatics Network (NBN). The NBN was created independently of the BRICs for the development of bioinformatics in South Africa to offer advanced computational capabilities for networking links between the Regional Innovation Centres, and for advanced genomic science. The NBN also operated independently of, but in association with the South African National Bioinformatics Institute (SANBI) (Klerck 2005). Various financial bodies were also established to fund R&D, build technical capacity and facilitate technology transfer in South Africa (Cloete et al. 2006).

The Biotechnology Advisory Committee, which reported to the Department of Science and Technology (DST) and the National Advisory Council on Innovation (NACI), was responsible for overseeing the growth of biotechnology in the country. The National Biotechnology Strategy was also under the control of the DST, however the innovation and commercialisation of biotechnology was up to the Department of Trade and Industry (DTI) (Mulder and Henschel 2003). As such, the DTI was responsible for the establishment of Bioventures, the first dedicated biotechnology VC fund in the country, which provided seed funding for start-up medical biotechnology businesses (Simiyu et al. 2010). Since its initial investments in 8 “home-grown” ventures between 2002 and 2004, Bioventures had invested 80 million rand into health technology ventures until 2009 (Masum et al. 2010).

Figure 2.9 depicts the layout of biotechnology venture resources, in relation to their instigating bodies in 2006.

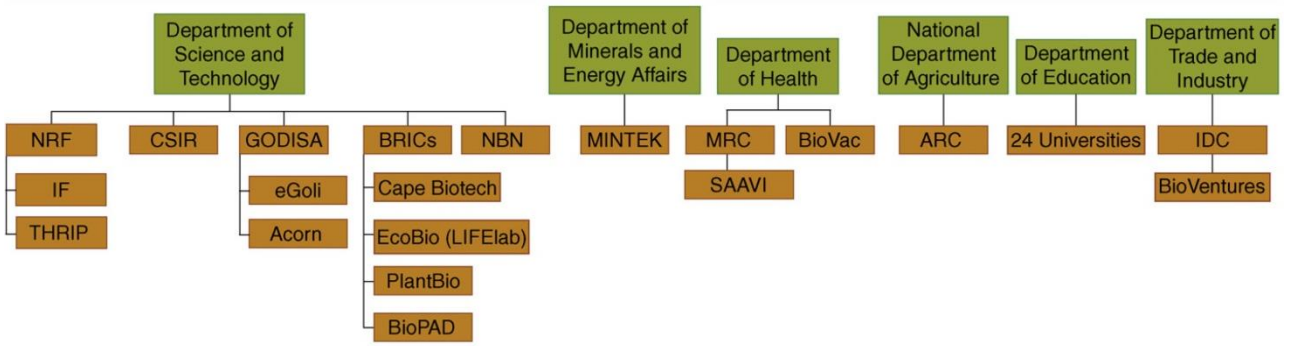


Figure 2.9 A graphical representation of the biotechnology development resources in South Africa in 2006

Source: Cloete et al. 2006

While the National Research Foundation (NRF) is the major funding body in academic institutions, the Innovation Fund (IF) was established to encourage technological innovation, increased cross-sectional collaboration and networking, and start-up capital for the R&D of products or prototypes, proof-of-concepts and initial marketing of novel ideas (Masum et al. 2010). The Technology and Human Resources for Industry Programme (THRIP) was established to provide funding to innovative research programmes that were involving an industry partner, thereby promoting interaction between skilled individuals and industry (Department of Science and Technology 2008).

The Small Enterprises Development Agency (SEDA), formerly GODISA, was developed as a South African initiative, jointly funded by the DST and the European Union to assist with the creation of incubators and pilot centres; two of which included eGoliBio Life Sciences and Acorn Technologies (Chakma et al. 2010; Cloete et al. 2006), the latter of which is considered in more detail in the following section. According to research in the US and Germany, close association with incubators has been important for the successful development of biotechnology companies (Audretsch and Stephan 1996; Muller 2002).

2.6.2.1 Acorn Technologies

Acorn Technologies was established in 2002 in Cape Town by a consortium of the Universities of Stellenbosch and Cape Town, the venture capitalist group Catalyst Innovations, and medical device merchant Disa Vascular, while under the auspices of the DTI, DST and the EU (Chakma et al. 2010). Acorn operated as a non-profit virtual incubator using a limited budget and staff complements to mentor early stage start-ups to create sustainable business strategies for their technologies, with both financial and local health impacts. It also assisted with registering patents, establishing networks and sourcing funding from the government and other investor sources, such as the SAMRC and Cape Biotechnology Trust, respectively. It achieved this by outsourcing all of its standard business services, such as auditing, business plan writing and market analyses (Chakma et al. 2010).

Remuneration to Acorn was in the form of royalties of between 3.5 and 5% of the companies' revenues for a fixed period of up to 18 months; or otherwise, equity stake in the ventures. Any funds generated were re-invested into new start-ups. From over 300 proposals, 12 were financed, with seven comprising biomedical device or consultancy companies, as listed below (Chakma et al. 2010):

- Gknowmix - genetic testing and counselling;
- Biovac - non-profit vaccine company;
- Pointcare Technologies - diagnostics "Lab in a Briefcase" for AIDS therapy/cardiac arrest;
- Real World Diagnostics - rapid diagnostic strip tests;
- One Eighty Metallurgic - consulting services for biomedical devices;
- Elective Lifestyle - cosmetic surgery;
- SunBio (from CBT) - third generation yeast strains for winemaking;
- Sinapi Biomedical - medical devices for thoracic surgery;
- Femipap - medical devices for female healthcare/cervix self-sampling;
- Smart Surgicals - robotic system for minimally-invasive surgery;
- Pin Sealer - negative pressure wound therapy devices; and
- Surgical Consent - online consent form management.

In 2003, the DST withdrew from the programme, and the local municipal government was unable to support Acorn, since their portfolio did not meet the criteria for supporting "projects for biofuels or plant biotechnology with a clear economic and development impact for local communities." By 2008, the funding provided by the DTI proved insufficient, forcing Acorn to merge with Cape Biotechnology Trust, wherein a new DST department was created as a dedicated biomedical device centre (Chakma et al. 2010). Soon thereafter, Cape Biotechnology Trust also merged into a national initiative along with the other regional Biotechnology Regional Innovation Centres to form the Technology Innovation Agency (TIA) (Campbell 2008).

2.6.2.2 Bioventures

Bioventures was established in 2001, as South Africa's first VC fund for life sciences, following a collaboration between the International Finance Corporation (IFC) and South Africa's Industrial Development Corporation (IDC). It was headed by CEO Heather Sherwin with an investment fund of R80 million (Masum et al. 2010). In order to select its eight primary investments, Bioventures reviewed over 300 proposals from universities, entrepreneurs and local scientists. Investments started in 2002, and by 2004, all of its investments had been made. As shown in Figure 2.10, of the eight investments, two were "outright failures", two were only able to break-even and return their initial investments, three provided returns of between two and three times their initial investment, and one returned up to seven times its initial investment (Masum and Singer 2010).

Investee	Summary	Return
Shimoda Biotech	One drug licensed and on market; 10 in various stages of development and trials; mostly enhanced generics. Company sold to Abraxis Biotech in 2008.	2.5x
Amandla Water Systems	Waste water bioremediation technology worked, but business model failed from long infrastructure tendering cycles and reliance on large water companies.	0x
Disa Vascular	Develops and produces stents for cardiac and other arteries, to keep previously blocked arteries open.	3x, not yet exited.
Synexa Life Sciences	Proprietary bioprocessing technology for production of natural compounds and recombinant proteins.	2.5x, not yet exited.
Electric Genetics	Bioinformatics spin-out from University of the Western Cape. Sector as a whole did poorly.	0x
Mbuyu Biotech	Joint venture with Council for Scientific and Industrial Research, to commercialize the Council's bio-processing technologies.	1x
PlatCo Technologies	Jointly owned with Shimoda Biotech, set up to explore the potential for novel platinum based anti-cancer compounds. Sold to Abraxis in 2008.	7x
Natural Carotenoids SA	Focuses on production and extraction of carotenoids from algae, for food, cosmetics, pharma industries.	1.5x, not yet exited.

Figure 2.10 Investment summary of Bioventures

Source: Masum and Singer 2010

According to Masum and Singer (2010), this was a proof of concept that life science investment is possible in South Africa, and that money can be generated by commercial life science ventures. When choosing investees, many of the proposals were disqualified for either being poor quality proposals or being too early in their seed stages. Also, since Bioventures saw challenges with competing against China and India's manufacturing sectors, R&D businesses were prioritised, as opposed to plain manufacturers (Masum and Singer 2010). The people who were chosen in the investee companies were also qualified PhDs, who had left university to pursue careers in business.

In order to generate a profit-return mechanism from potential investees, Bioventures agreed with the companies on amounts of investment that were required, and the expected future sales. To mitigate the risk, the investment was either provided in phases, based on milestone achievements, or if the sales figures were not reached, Bioventures would acquire a higher proportion of the companies' shares in recuperation (Masum and Singer 2010). Bioventures aimed, however, to receive much of its return on investment during 'exits', where the shares of the companies would be sold off for a profit to purchasers. For example, once the IP value of a company had been raised to a sufficient level for foreign companies to purchase, the plan was to sell the company and generate revenue.

2.6.3 The Technology Innovation Agency (TIA)

As indicated by Gastrow (2008), the TIA was generated as an initiative of the DST through the Technology Innovation Agency Act No. 26 of 2008 to enable and support "technology innovation across all sectors of the economy" (TIA report 2012), and to support the development and commercialisation of research activities from academic institutions, private research centres, science councils and public entities, with the goal of bringing them to the market. The Biotechnology Regional Innovation Centres were, thus, effectively replaced through the creation of

the TIA (Uctu and Essop 2013). The agency has since provided private sector companies with financial and non-financial resources to collaborate with science councils on early stage, high-risk research, while developing their technology infrastructures (TIA Report, 2012).

In the creation of the TIA, seven DST bodies were merged: the IF, Tshumisano Trust, Cape Biotechnology Trust (including the former Acorn Technologies), LIFElab, the Advanced Manufacturing Technology Strategy (AMTS), PlantBio Trust, and BioPAD Trust (Uctu and Essop 2013; Al-Bader et al. 2009), as shown in Figure 2.11.

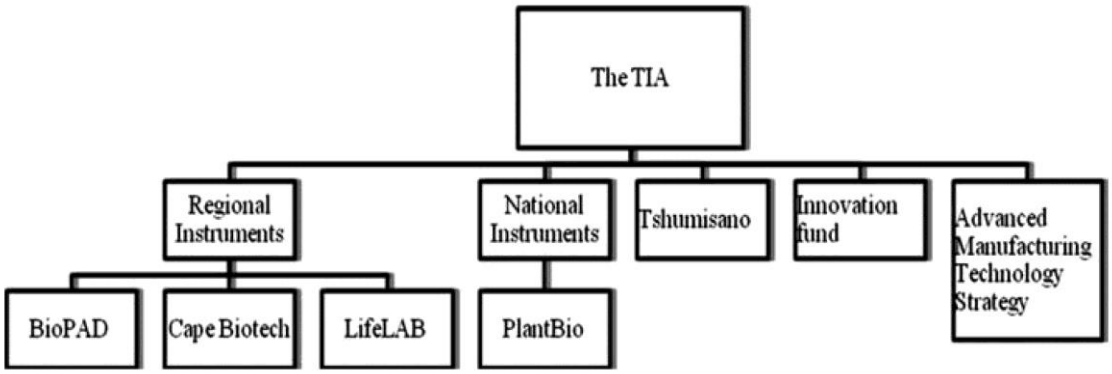


Figure 2.11 The seven integrated institutions of the TIA

Source: Uctu and Essop 2013

According to the TIA report of 2012, 13 technology stations, 3 tooling stations and 15 technology platforms have been made available that operate mostly from the country's academic institutions to provide technical skills and high-end equipment to SME inventors. By offering facilities in specialised fields, obstacles are reduced for entrepreneurs who would be unable to afford them, or who otherwise lack the necessary skills or training to operate them. This includes a R9.1 million investment from the TIA in the Centre for Proteomic and Genomic Research (CPGR) at the University of Cape Town (UCT), which provides access to high-end genomics and proteomics equipment and expertise to enable world-class research for private organisations (TIA Report 2012).

As shown in Table 2.5, during the 2011/12 period, 1718 entrepreneur groups received services from TIA technology stations to develop products, prototypes and pilot-stage manufacturing plants.

Table 2.5 List of TIA technology stations

Technology Stations	Number of clients Supported by TS & IATs		
	New	Repeat	Totals
ATS - CPUT	144	104	248
LATS - UL	86	16	102
DCTS - NMMU	32	34	66
TSC - TUT	30	10	40
TSC - MUT	38	49	87
TSCT , CPUT	78	407	485
TSE - TUT	33	26	59
ACTS - NMMU	36	165	201
TSMPT - VUT	41	85	126
RMPTS - DUT	13	71	84
PDTS - CUT	65	6	71
MCTS - UJ	27	23	50
IAT, Soshanguve	12	49	61
IAT, Stellenbosch	8	15	23
IAT, East London	8	7	15
	651	1067	1718

Source: TIA Report, 2012

According to this report, at least 249 new or improved products were developed, 174 ventures began exporting products internationally and 326 applied research, design and development projects were conducted, with some due for commercialisation within the following (2013) financial year. The Technology Station Programme assisted 329 entrepreneur groups to access new markets, 237 to secure additional employment and 207 to produce technology innovations with the potential to be licensed as new intellectual property (TIA Report 2012).

Chakma et al. (2010) indicate that the TIA had a forecasted annual budget of R1 billion by 2013, but the investment portfolio in the 2011/2012 TIA report indicates that R274 million was spent on investments, and a further R424 million was leveraged from other partners. This was divided between biotechnology and industrial sectors in both quantity and value at a ratio of 2:1 (Chakma et al. 2010; TIA Report 2012). Wild (2013) notes, therefore, that the TIA received R482million in the 2012-2013 financial year.

As indicated by the TIA Report (2012), other examples of biomedical or health-related ventures that received TIA support have included:

- Geoaxon's Kuduwave Audiometer: This was a hearing test that did not require soundproof booths and could be used predominantly in rural areas;
- Tenofovir Gel Microbicide: This received R1 million from the TIA and R9 million from the IDC and Cipla Medpro for a 12-month feasibility study on the prevention of HIV infection in women;
- Custommed Orthopaedics: This was an implant guidance system for use in shoulder and hip replacement surgeries, and was due for release in Southern Africa and Australia;
- Southern Access Technologies: This received a R5million co-investment to develop a heart valve deployment device to insert synthetic heart valves into patients via a catheter; and
- Endogrowth: This received support for the development of a prototype laparoscopic device to be used to grab and remove tissue during laparoscopic surgery.

2.6.3.1 Loan structure of the TIA

Loans offered by the TIA have been offered on either of the following terms (TIA Report 2012):

- Loans have no fixed repayment terms and do not accrue interest;
- Loans have no fixed repayment terms and accrue interest at prime less 2.162%;
- Loans are to be repaid in monthly instalments from the second anniversary of the loan date, and accrue interest at prime;
- Loans are to be repaid in bi-annual instalments commencing from 18 months after granting the loan, and accrue interest at prime; or
- The TIA management does not expect loans to begin being realised within the first 12 months.

2.6.3.2 TIA operating issues

Wild (2013) argues that the TIA has been "dogged with problems" since its inception. According to this author, three main problems exist at the TIA: firstly, there appears to be confusion on both the part of the TIA and the Department of Science and Technology about the agency's mandate. Secondly, following the merger of the seven Biotechnology Regional Innovation Centres' entities, their "historic financial mismanagement and power-battles" have been transferred over to the TIA; while thirdly, the relationship between the TIA and the DST has deteriorated to a "toxic" status.

In November 2012, a panel was appointed by the then-Minister of Science and Technology, Mr Derek Hanekom to conduct an external institutional review of the TIA. The summary of the report indicated the following (Department of Science and Technology 2013):

- Establishing the TIA as a single entity with a clear mandate from the pre-existing entities presented challenges where each entity had had its own mandate and structural, legal and organisational infrastructures;

- The TIA was established with the budget allocations of the entities that were integrated into it, which had been predominantly committed to pre-existing projects, therefore leaving “limited uncommitted funds for the operations of the new agency”;
- “Serious tensions” appeared to exist among the senior managers from the former seven merged entities, as they “allegedly jockeyed for positions of influence in the new agency”;
- Although including the chairs of the boards of trustees of all the four merged Biotechnology Regional Innovation Centres into the TIA's inaugural board was intended to facilitate a healthy transition where all interests were considered, the ultimate effect was the delay of the TIA’s board with a unified agency vision;
- It became apparent that before their closure, the Biotechnology Regional Innovation Centres trusts had been operating with wider financial flexibility than they were authorised to do, effectively rendering them in contravention of the Public Finance Management Act (PFMA). This resulted in the TIA receiving a poor audit opinion by KPMG in the first external audit of their 2010/2011 financial statements; and
- The change in personnel from the DST that were responsible for establishing the TIA negatively affected the quality of guidance received from the DST.

According to Wild (2013), TIA Chief Executive Simphiwe Duma had stated that the mandate of the TIA was to be financially sustainable, and make a return on investment, while Derek Hanekom had argued that “making money was not the agency's ‘core mandate’”, but if they brought in “some [money], that's not a bad thing because it adds to the budget." Ultimately, Wild (2013) argues that there is also the question of who the TIA should fund, whereby the regional heads of technology stations, which are university-based, feel “marginalised”; while the private stakeholders and public feel a "distinct lack of confidence" in the agency.

2.6.4 Critical analysis of South Africa’s biotechnology sector

Pillay and Uctu (2013) summarise the South African biotechnology landscape as follows:

- The sector is still small in comparison to those of Cuba, Brazil, India and China;
- Entrepreneurial skills are needed to improve the country’s biotechnology sector;
- The Western Cape and Gauteng both have reputable higher-institutions in the scientific fields;
- Currently, no biotechnology parks exist in South Africa; and
- Access to finances is still the primary challenge for biotechnology organisations.

2.6.4.1 South African entrepreneurship

Within South Africa, Pillay and Uctu (2013) assert that there should be more entrepreneurial scientists who have skills and understanding in both the scientific, ethical and regulatory issues, as

well as in business management, who would be able to bridge between the science of biotechnology, and its commercialisation. They refer to only a few institutions and private organisations that have developed 'bio-entrepreneurship' programmes in recent years:

- Biotechnology in the Workplace-FABI: University of Pretoria;
- The Certificate in Bio-entrepreneurship: University of Pretoria, since 2008;
- The Cape Biotech Bio-entrepreneurship programme, since 2008;
- XCell Bioconsulting: a private company associated with the University of Cape Town, since 2010;
- The Certificate in Bio-entrepreneurship: presented by the TIA, since 2011.
- An undergraduate technology-commercialisation course: a collaboration between UWC, UCT and CPUT, since 2012; and
- The Gauteng Accelerator Programme in bioscience: in collaboration with Emory University in Atlanta, Georgia in the US.

Pillay and Uctu (2013) argue that in South Africa, university researchers are almost universally uninterested in creating companies, and lack entrepreneurial skills. The authors note that most researchers license their research at an early stage, and as a result, very few biotechnology spin-offs have resulted.

2.6.4.2 City dynamics

According to Pillay and Uctu (2013), Cape Town is a friendly, attractive and internationally renowned city. However, it is not at the "business level" of the cities in Gauteng province. Conversely, while Pretoria and Johannesburg are "vibrant cities", problems with crime are deterring the immigration and introduction of great business and scientific minds to assist with biotechnology development.

2.6.4.3 Financial availability

Compared to the other BRICS nations, South Africa is said to be lapsing in terms of financing, as shown in Figure 2.12, with the primary finance in the country being government-based, through the TIA. This includes, for example the Innovation Fund (IF), the Support Programme for Industrial Innovation (SPII), and the Industrial Development Corporation (IDC), which fund research across many different sectors.

Venture capital funding in South Africa is very limited for biotechnology, with South Africa's only private biotechnology investor, Bioventures, recently becoming dormant (Pillay and Uctu 2013). A core problem for biotechnology in South Africa is therefore the shortage of funds for seed and start-up companies.

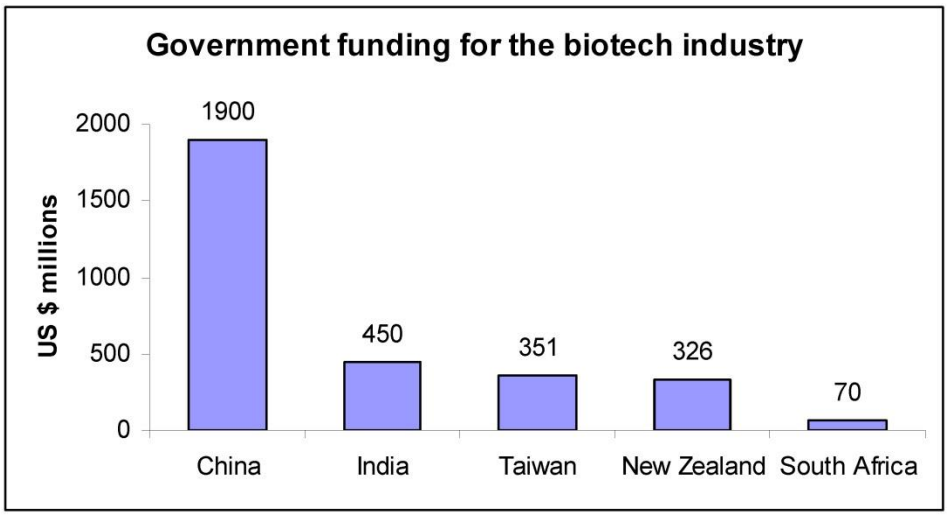


Figure 2.12 Government funding of the biotechnology sector, excluding research in academic institutions, over a three year period.

Source: Sherwin 2007

Sherwin (2007), who compares South African, US and European funding for start-ups, states that the amount of funding that is typically received by South African biotechnology companies is a fraction of what would be received in the US or in European countries, as shown in Table 2.6. Furthermore, the author argues that the limited funding for South African biotechnology companies is more a feature of the venture capital and private equity market, as opposed to the availability of investment.

Table 2.6 Comparison of the typical start-up funding for biotechnology ventures in South Africa, Europe and the US

Financing round	USA	Europe	South Africa
Seed stage*	$ 2 million	$1 million	$300 000
Series A**	$ 10 million	$5 million	$1.4 million
Series B	$ 20 million	$15 million	$ 2.5 million
Series C	$ 26 million	$22 million	***

Source: Sherwin 2007

While the seed stage in Table 2.6 refers to companies that are just starting out and developing a business plan, the cells in series A to C refer to companies that receive further rounds of investment from VCs. According to Sherwin (2007), at the time of publication, no company had managed to raise a Series C round of finance in South Africa.

South Africa, for example has a well-established total private equity industry that compares positively with the developed countries, relative to GDP; where at 2% of GDP, it is only slightly higher than Europe, which invests approximately 1.9% of its GDP. It is also on marginally less than the UK, and US, which spend 2.8% and 3.7% of their GDPs, respectively, on private equity

investment. Rather, as shown in Figure 2.13, the problem is the low level of investment for seed and start-up ventures, with the majority of the available capital directing into replacement capital, such as for BEE transactions and management buy-outs (Sherwin 2007). There is also little or no pure grant financing available in South Africa.

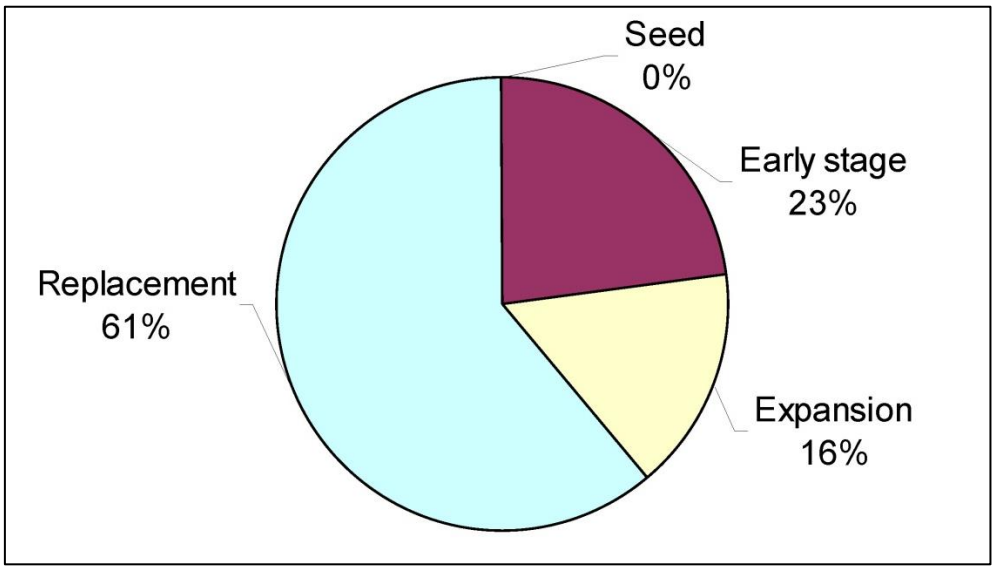


Figure 2.13 The investment of private equity investment, by stage in South Africa, in 2004.

Source: Sherwin 2007

Reasons that have been cited for the funding gap in biotechnology in South Africa include the lack of a dedicated biotechnology VC, a scarcity of investors who understand the sector, and the inclination of investors to risk less on biotechnology ventures than on the securer competing industries, which offer bigger returns on investment, such as information technology (IT) (Pillay and Uctu 2013).

Sherwin (2007) argues, however, that despite the challenges in South African funding for biotechnology, where companies are exceptionally under-resourced compared to other countries, the opportunity still exists for South African life science commercialisation to develop. The author maintains that the "groundwork has been laid", and the government has committed itself in terms of substantial funding and resources to develop the sector. Pillay and Uctu (2013) also argue that a main advantage of the Southern African region is that it has the potential to perform as an innovation hub for the entire African region.

2.6.5 Biomedical science commercialisation in South Africa

There is a considerable medical need in South Africa, which could be targeted by commercial ventures that specialise in the biomedical sciences. According to Meissner-Roloff and Pepper (2013), for example, there is a large unmet demand for bone marrow (BM) in the country. The chances of a person finding a match from the country's current BM stores are, for instance, around

one in 100,000 (Health24 2014). Umbilical cord blood (UCB) is a rich source of hematopoietic stem cells (HSC), which can be supplemented for BM transplantation or for use as mobilised peripheral blood stem cells. The authors maintain, therefore, that the establishment of a non-profit public umbilical cord blood stem cell bank (UCB-SCB) would assist in alleviating part of this BM demand. In so doing, it would help to improve the quality of health care in the country.

For more than 50 years, conditions such as immune deficiencies, certain genetic disorders, and malignant and non-malignant haematology disorders have been successfully treated with Bone marrow (BM) transplantation. For those who need transplants, however, need can far outweigh the supply. According to the World Marrow Donor Association (WMDA), for example, as many as 70% of patients with blood-related disorders, such as severe aplastic anaemia, leukaemia and other congenital disorders, do not have a suitably-matched donor (Meissner-Roloff and Pepper 2013). While siblings and parents offer a potential source, siblings only match in 25% of cases, and parents in less than 12.5% of cases. This leaves patients with a 1:4 chance of having a suitable supplier from a sibling, and 1:8 chance from either of their parents. With a well-supplied store of UCB, however, this rate of finding a suitable match would rise to over 40%. Currently, the demand for BM is supplied through a donor registry; however, according to Pepper (cited in Wild 2013), 70% of the donors that are listed on the bone marrow registry are Caucasian. Furthermore, purchasing cord blood internationally is prohibitive, with costs ranging around $25,000 for a donation, while bone marrow donation is dissuaded since it can be very painful to tap (Wild 2013).

Although public UCB-SCBs are operated as non-profit organisations through financial support from governments and professional organisations, the current debate on UCB-SCBs centres on commercial private SCBs that bank UCB for commercial purposes, resulting in various ethical issues, such as selling a service with no immediate therapeutic function (Meissner-Roloff and Pepper 2013). Furthermore, Pepper (cited in Wild 2013) argues that of the several thousand units that have been stored in private SCBs in the country, none had been “successfully used in surgery”, which could be attributed to damage to the cells during the freezing process.

Supporters of the private system, however, claim that people should still have the freedom to choose to store UCB without inhibition. Private UCB-SCBs that operate in South Africa, for example, can charge more than R12,000 to store an infant’s UCB, or more than R17,000 to store tissue.

Although a public UCB-SCB would offer access to stem cells to anyone who is genetically compatible, with only 30 people requiring treatment per 100,000 people, it would only benefit approximately 1,000 people per year. Thus, a UCB-SCB, which would cost “a few million rand to set up”, would be far less seriously considered in a population that is 25% affected by HIV/AIDS and TB (Wild 2013).

In the study by Meissner-Roloff and Pepper (2013), though, it was determined that the South African public was in favour of implementing “new avenues for access to health care” and increasing developments in the fields of molecular, cellular and regenerative medicine. It should be noted, however, that the general knowledge of the public on UCB, and SCBs was extremely limited, with as much as 70 % of the public indicating a poor or reduced knowledge of UCB-SCBs.

2.7 CONCLUSION

This concludes the literature review of the dissertation. In terms of private biotechnology, there has been a slow decrease in the number of private biotechnology ventures in the worlds “biotechnology strongholds” in recent years, evident by a reduction in the number of private biotechnology companies in locations such as Europe and the US. One reason for this reduction is because biotechnology start-ups, especially those that are based on academic science, have in recent years found it more difficult to attract VC investment, since VCs are attempting, progressively, to lower their risks.

One system that has been presented in the literature for promoting biotechnology growth is bioclusters, which are often considered as drivers of business and economic development, and structures for enhancing productivity and creating competitive advantage. Bioclusters have also been pivotal in establishing the biotechnology industries in developing countries, such as Cuba, Brazil, India and China.

South Africa’s biotechnology industry is still relatively small and underdeveloped, when compared to the developed countries, blamed in part on the selective industrialisation of the apartheid era. The policy of the post-apartheid government has been to promote R&D, and to structure investment and labour policies towards attaining high-value-added and high-technology exports. One such result of these policies is the TIA, which was established as an initiative of the DST to support and enable technology innovation, and to support the development and commercialisation of research activities from academic institutions, private research centres, science councils, and public entities. In spite of this, criticisms remain on the biotechnology sector in South Africa, including financial availability, city dynamics, entrepreneurship, and the commercialisation of biomedical science.

The dissertation next looks at the theoretical scientific principles that exist at one of the HTVs in South Africa that have been innovatively applied to generate a commercial output, and thereby overcome these drawbacks in the country’s biotechnology sector.

CHAPTER 3
CASE STUDY: LINKING SCIENCE AND BUSINESS

3.1 INTRODUCTION

As noted in the literature review chapter, the biotechnology environment of South Africa is complex. However, numerous HTVs are successfully thriving in the South African market, demonstrating that success is possible, once the need and commercial demand are identified; and provided this demand is met with good — scientifically sound — products or services. It is therefore useful to consider how technical scientific principles have been applied to satisfy a commercial need in South Africa, thereby linking the science to the commercial need. This chapter provides a scientific review of some of the principles and contexts involved in the commercialisation of a biomedical technology in South Africa, specifically reviewing the *DNA Oestrogen* test from DNAlysis (DNAlysis 2014f). It begins with a brief introduction to the company, followed by a discussion of the scientific basis of the *DNA Oestrogen* test, its application in identifying hereditary risks for diseases, and the scientific basis of oestrogen metabolism in the body.

The chapter then discusses in detail, each of the genes that is screened in the *DNA Oestrogen* test, as well as their discovered functions, allelic variations, and disease syndromes that are related to each polymorphism. It also briefly discusses material from the DNAlysis (2014f) white paper, and how the DNAlysis organisation responds to data from the tests.

3.2 BRIEF OVERVIEW OF THE COMPANY

DNAlysis Biotechnology is a Johannesburg-based company that develops and provides molecular-biology technologies to the South African health and wellness markets (Bloomberg 2014), by leveraging recent scientific advances that have been made in Human Genomics research, such as the complete mapping of the human genome in 2003 (Shout Africa 2013; DNAlysis 2014a). The company offers DNA-based dietary recommendations, with an emphasis on the relationships between genes, nutrition and lifestyle in determining health and wellness (DNAlysis 2014a). Through analysis of key selected genes, the company delivers personalised recommendations on modifications that individuals should make to their lifestyles and eating plans, in order to achieve optimal health, weight loss and fitness (Shout Africa 2013).

3.2.1 Product overview

Five products are currently available at DNAlysis, each offering personalised programmes to people based on the combination of the genes that they have analysed (DNAlysis 2014a). The products are:

DNA Diet: This product tests for 13 genes that are known to impact metabolism and exercise (DNAlysis 2014c).

DNA Health: This product tests for 20 genes that have been shown to be involved in seven key biological processes in the body (DNAlysis 2014d).

DNA Fit: This product provides elite performance athletes and recreational athletes, looking to maximise their training yields, with individualised profiles of their potential for "trainability and sporting performance", as well as optimum exercise strategies, recovery strategies and risks of certain injuries (DNAlysis 2014e). This test includes an analysis of 13 genes that are categorised into three areas relating to power and endurance, tendon pathology and recovery.

DNAlysis Pink or Blue: This product offers prospective parents the opportunity to discover the gender of their unborn children, from as early as the eighth week of pregnancy (DNAlysis 2014b).

DNA Oestrogen: DNAlysis biotechnology has developed South Africa's first locally produced oestrogen metabolism gene test (Health24 2012). It was developed in South Africa following six months of collaboration with integrative, anti-ageing and functional medical specialists to assist medical practitioners in making clinical decisions to lower the risk of breast cancer in women, and especially those taking hormones or contemplating hormone replacement therapies (HRTs) and oral contraceptives (Health24 2012). The DNAlysis Oestrogen Metabolism and Detoxification test includes nine genes involved in oestrogen biosynthesis, oestrogen metabolism, and phase I and phase II detoxification, with the purpose of identifying 11 gene variations or alleles that occur across the nine genes (DNAlysis 2014f). This product is only available through authorised healthcare practitioners who have completed the necessary training to interpret the test's findings, and provide an informed diagnosis to individuals (Health24 2012).

3.3 SCIENTIFIC BASIS OF THE DNALYSIS *DNA OESTROGEN* TEST

As noted by Health24 (2012), oestrogen metabolism and detoxification in women is a significant contributor to breast cancer. Joffe (2012, cited in Health24 2012) states that breast cancer is the most frequently diagnosed cancer in women, globally, constituting 16% of all cancers in females; and in South Africa, one in 29 women is affected with the condition. Joffe states that for 5% of women, a single inherited gene is responsible for the cancer, while in the remaining 95% of patients, the disease typically develops between the ages of 55 and 70 (Health24 2012). Although genetics, lifestyle and diet are all contributing factors in the majority of cases, one significant contributing factor is a woman's ability to metabolise oestrogen (Yager and Davidson 2006). Sex steroids, such as oestrogens, have a variable metabolism that is heavily influenced by environmental factors and genomics. Thus, genetic testing can provide an invaluable tool for managing peri- and post-menopausal treatments, fertility and profiling breast cancer risk (Bhana 2012, cited in Health24 2012). Indeed, many studies have found an association between the risk of breast cancer and persistently elevated blood levels of oestrogen (Yager and Davidson 2006).

Oestrogen carcinogenicity is largely attributed to several crucial metabolising processes, such as glucuronidation, O-methylation and sulfonation. However, substantial variability in cancer risk has been observed between individuals with variable steroid hormone metabolisms, carcinogen metabolism, and phase I and II detoxification rates (DNAlysis 2014f). The mechanisms of carcinogenesis in the breast that are caused by oestrogen are due to the metabolism of oestrogen into genotoxic, mutagenic metabolites, as well as the stimulation of tissue growth (Yager and Davidson 2006). Together, these processes help to initiate, promote and stimulate the progression of carcinogenesis. Heritable factors are typically found in approximately 25% of breast cancer cases, but germline mutations in *high-penetrance* cancer susceptibility genes, such as BRCA1 and BRCA2 have only been shown to account for around 5% of all breast cancer cases (Mitrunen and Hirvonen 2003). Therefore, since high-cancer susceptibility genes, such as BRCA1 and BRCA2, only account for a marginal 5% of all breast cancer cases, the incidence of breast cancer may be attributed to the interaction of more common, low penetrance genes with endogenous factors such as lifestyle risks (Cerne et al. 2011).

3.3.1 Identifying HRT risks

Hormone replacement therapies (HRTs) with hormones such as oestrogen are commonly practiced to offset the symptoms of menopause, such as mood fluctuations, hot flashes and vaginal dryness, and also to decrease the probabilities of diseases that are common in postmenopausal women, including heart disease and osteoporosis (Health24 2012). High levels of oestrogen, however, have been shown to increase women's risks of breast cancer, and women who use HRTs for five years or more increase their risk of this condition by up to 35% (Yager and Davidson 2006; Health24 2012). This is especially pronounced in women who ineffectively metabolise oestrogen (Joffe 2012, cited in Health24 2012). The purpose of the *DNA Oestrogen* test, by DNAlysis, is to observe a selection of genes involved in oestrogen biosynthesis and metabolism, and phase I and phase II detoxification, to determine a person's increased risk of getting breast cancer, while in conjunction, offering dietary and lifestyle recommendations to customers, based on the results of the test, to reduce their risks (DNAlysis 2014f). This is because, by understanding an individual's genetic variability, targeted lifestyle, diet and hormone interventions can be recommended by medical practitioners (DNAlysis 2014f).

3.3.2 Science behind the *DNA Oestrogen* test

Oestrogens play many important roles in the body, such as during reproduction and the menstrual cycle, appetite and eating behaviour, fat metabolism, auditory and visual processing, the prevention of heart disease, autoimmunity, and neuroprotection during cerebral ischaemia (Hirschberg 2012). They are also noted for their roles in many breast cancers, and in the development of osteoarthritis, multiple sclerosis and schizophrenia (Thomas and Potter 2013). Oestrogens apply their effects in various ways; however, in the "classic genome response", they

bind to specific intracellular receptors (ERα and ERβ) that, after binding to oestrogen, dimerise and translocate to the nucleus to modulate the transcription of target genes with oestrogen-responsive elements in their promoters (Thomas and Potter 2013). The three most common oestrogens are estrone (E1); estradiol (E2), which is the most potent; and estriol (E3), as shown in Figure 3.1; while a fourth, less common oestrogen is estetrol (E4) (Thomas and Potter 2013).

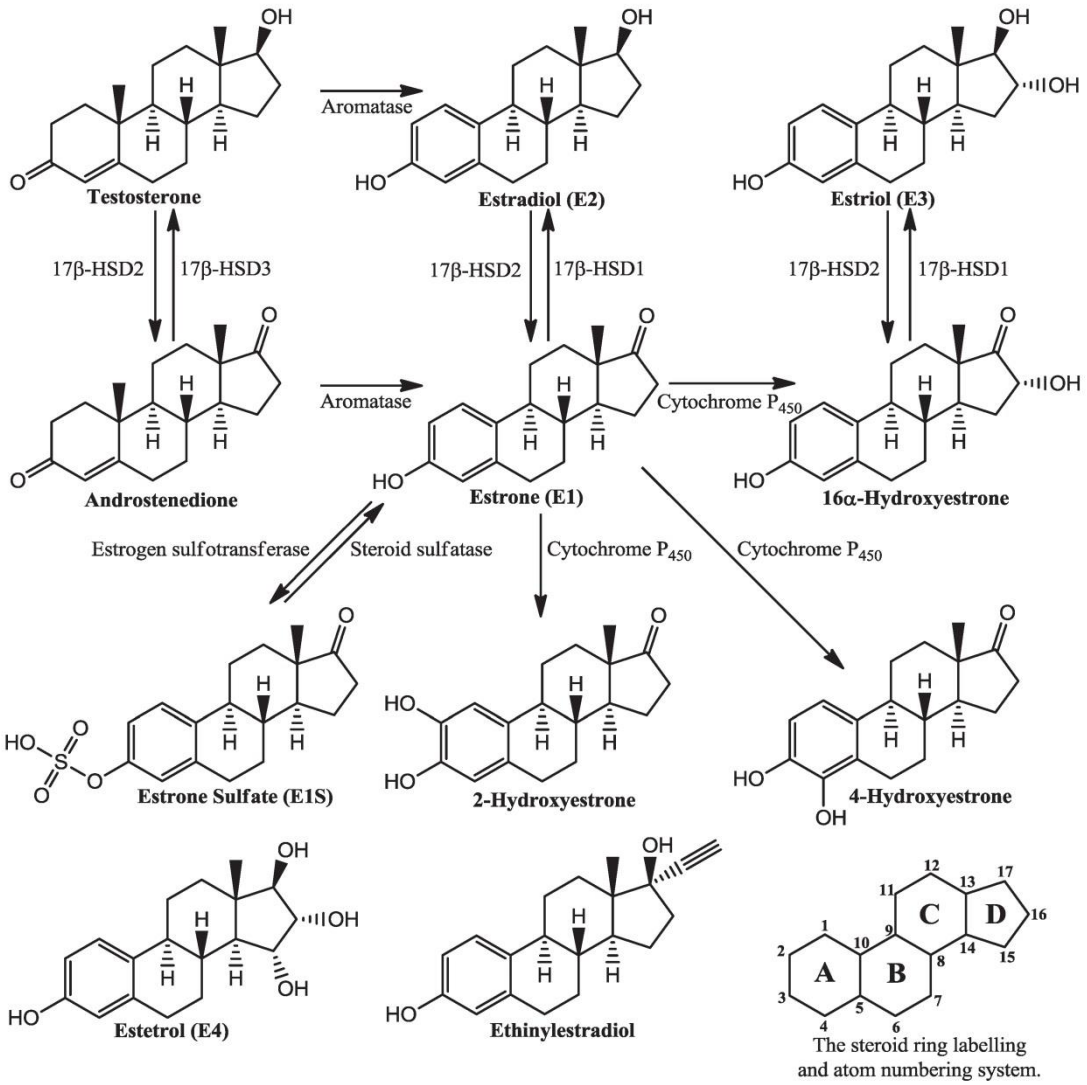


Figure 3.1 Diagram presenting the chemical structures of the oestrogens, and some of the main pathways involved with oestrogen metabolism.

Source: Thomas and Potter 2013

Estrone and estradiol are synthesised via the aromatisation of androstenedione and testosterone, respectively, as shown in Figure 3.1; or they may be interconverted by 17β-hydroxysteroid dehydrogenases (17β-HSDs), while estriol is synthesised from estrone by a 16α-hydroxyestrone intermediate (Thomas and Potter 2013). While it can be made on demand in some tissues, it is typically stored in the form of estrone sulphate, which is synthesised from estrone through the action of oestrogen sulfotransferase. Estrogens are removed from the body primarily as their

glucuronidated and sulfated derivatives (Thomas and Potter 2013). According to these authors, there is little published work on estetrol, and while it is known to be synthesised in the foetal liver, its function is otherwise presently unknown.

Various studies have strongly suggested the central role that oestrogens play in the growth of multiple cancers, such as breast cancer (Thomas and Potter 2013), where prolonged exposure to exogenous and endogenous oestrogens have been associated with considerably higher risks of such Cancers (Yager and Davidson 2006). Polycyclic aromatic hydrocarbons (PAHs), or organic compounds containing only hydrogen carbon and with multiple aromatic rings (such as oestrogen) have been shown to be mutagenic to breast cell lines, and because they are lipophilic compounds, they are stored in adipose tissues, including the tissue of the breast (Mitrunen and Hirvonen 2003).

Therapies that involve the inhibition of the esterone synthesis enzyme aromatase (see Figure 3.1), for example, with anstrozole, exemastane and letrossole, have been indicated as suitable treatments for a number of cancers, including breast cancer, ovarian cancer and possibly lung cancer (Thomas and Potter 2013).

Figure 3.2 shows a schematic presentation of some of the enzymes, with known polymorphisms, that are involved in oestrogen biosynthesis and metabolism (Mitrunen and Hirvonen 2003).

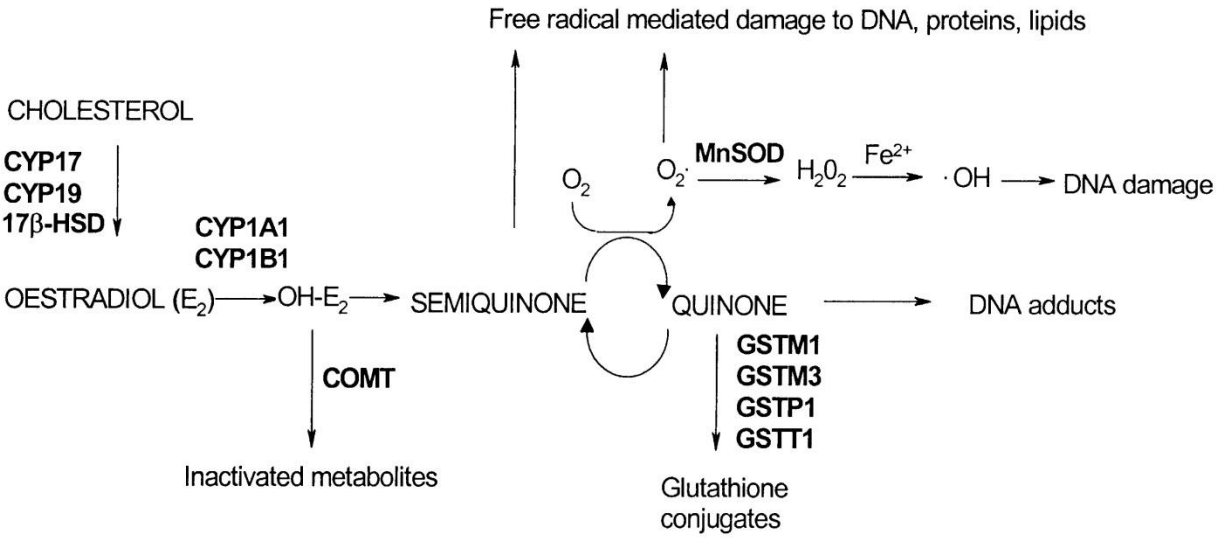


Figure 3.2 Schematic representation of enzymes with known polymorphisms that are involved in oestrogen biosynthesis and metabolism.

Source: Mitrunen and Hirvonen 2003

3.4 THE GENES OBSERVED IN THE *DNA OESTROGEN* TEST

Of the more-than 40 potential gene variations that are known to be related to oestrogen metabolism and breast cancer (Cerne et al. 2011; Yager and Davidson 2006; Thomas and potter 2013), a concise selection of variations was chosen for the *DNA Oestrogen* test that would offer the clearest insight into an individual's genetic profile, with the purpose of analysing their ability to

metabolise oestrogen (Health24 2012). Genetic variants were chosen that are associated with hydroxylation, glucuronidation, methylation, sulfation and oxidative stress (DNAlysis 2014f). These are each described individually below.

3.4.1 Genetic variants associated with hydroxylation

Eliminating toxic compounds from the body, such as waste by-products of hormones and chemical processes, occurs in a two-phased process. The first stage, or phase I detoxification is predominantly driven through a process of hydroxylation by Cytochrome P450 enzymes (see Figure 3.1), that render the compounds more hydrophilic (DNAlysis 2014; Thomson and Potter 2013). This includes the hydroxylation of Estrone (E1) and Estradiol (E2).

Three Cytochrome P450 genes are screened in the DNAlysis *DNA Oestrogen* test (DNAlysis 2014f):

- Cytochrome P450 1A1 (CYP1A1): polymorphisms Msp1 T/C, and Ile462Val;
- Cytochrome P450 17A (CYP17A): polymorphisms T34C; and
- Cytochrome P450 1B1 (CYP1B1): polymorphism Val432Leu.

These are each discussed next.

3.4.1.1 Cytochrome P450 1A1 (CYP1A1):

This gene codes for the enzyme aryl hydrocarbon hydroxylase (AHH), which is predominantly expressed in epithelial tissues, and extra-hepatic tissues, such as the lung (Motovali-Bashi et al. 2012; DNAlysis 2014; Wu et al. 2013). The CYP1A1 enzyme catalyses the first step in the metabolism of polycyclic aromatic hydrocarbons (PAH), which are also present in tobacco smoke (Wu et al. 2013). This enzyme also exhibits important roles in the initial phase of metabolic activation of many other environmental carcinogens and xenobiotics, such as PAHs, aromatic amines, nitrosamines, and a small number of endogenous substrates, such as oestrogens (Sharma et al. 2014). These reactive electrophilic metabolites bind highly efficiently to DNA, leading to chemical modifications and adducts in the DNA that can precede mutation events (Motovali-Bashi et al. 2012; Wu et al. 2013).

While several important polymorphisms have been noted in the CYP1A1 gene, DNAlysis specifically screens for two mutations in the gene. The first includes the CYP1A1 *2A allele of the gene, otherwise known as the *Msp*I mutation, whereby a thymine to cytosine transition at nucleotide 1803, located in the 3' noncoding region of the gene introduces a new restriction site for *Msp*I endonuclease (Motovali-Bashi et al. 2012; Wu et al. 2013). This CYP1A1 *Msp*1 CC genotype has been associated with increased enzyme activity, resulting in heightened levels of activated metabolites and DNA damage (DNAlysis 2014f). Consequently, it has been linked to various

cancers, such as lung cancer, cervical cancer and gallbladder cancer (Wu et al. 2013; Sharma et al. 2014).

The second functional nonsynonymous polymorphism that is screened with the *DNA Oestrogen* test is a guanine to adenine point mutation (A4889G) within exon seven, which results in the codon for isoleucine (Ile) 462 being replaced by valine (Val)(Wu et al. 2013; Sharma et al. 2014). The Ile462Val polymorphisms have shown an increased risk for lung cancer, oesophageal carcinoma, leukaemia and prostate cancer (Wu et al. 2013).

According to Wu et al. (2013), ethnic variations have been observed for the *Msp*I and Ile462Val polymorphisms, with *Msp*I being more prevalent among Asian populations, and Ile462Val being observed in Asians and Caucasians.

In response to the presence of the C allele, or *2A allele (*Msp*I mutation), individuals are recommended to reduce their exposure to all environmental and pro-carcinogens, such as aromatic amines, nitrates, PAHs and all forms of smoking (DNAlysis 2014; Motovali-Bashi et al. 2012). In the presence of the G allele (Ile462Val mutation), individuals are recommended to reduce all pro-carcinogens, and in addition, to optimise their phase II detoxification (DNAlysis 2014f).

3.4.1.2 Cytochrome P450 17A (CYP17A):

This gene codes for the cytochrome P450c17α enzyme, which is active in the early stages of oestrogen biosynthesis and catalyses the 17α-hydroxylation of progesterone and pregnenolone into precursors of androgen and oestrogen, respectively (Ghisari et al. 2014). A common single base pair substitution, or the point mutation of thymine to cytosine, is often observed at position 1931 in the 5′ untranslated gene promoter region (Yager and Davidson 2006; Ghisari et al. 2014). The common T allele is denoted as A1, while the C allele variant is referred to as A2. The mutation in carriers of the A2 allele creates an additional SP1 promoter site, which although originally thought to up-regulate CYP17 transcription (Carey et al. 1994), this has been refuted (Kristensen and Børresen-Dale 2000), and the functional impact of the T/C point mutation is as yet, not fully known (Ghisari et al. 2014). The rare A2 allele is, however, observed to correlate with increased levels of various sex steroids, such as testosterone, progesterone, oestrone, and oestradiol (Ghisari et al. 2014; Kristensen and Børresen-Dale 2000).

According to Ghisari et al. (2014), individuals of differing ethnicities have different risks of breast cancer, relative to the presence of the different CYP17 variant alleles. For example, Greenlandic Inuit women with the CYP17 A2 allele have appeared to present a decreased risk of breast cancer, as have pre-menopausal Finnish women with at least one CYP17 A2 allele. In a 2010 study by Yao et al. (2010), no association was found between either the A1 or A2 alleles, and the risk for breast cancer, while conversely, postmenopausal Chinese women were found to be associated with increased risk of breast cancer compared to individuals with the A1/A1 genotype (Zhang et al. 2009).

In response to the results of the *DNA Oestrogen* test, individuals are recommended to exercise beneficial modulation of oestrogen levels, through diet and lifestyle interventions, which include consuming larger volumes of insoluble fibre, increasing phytoestrogen intake, avoiding refined carbohydrates, increasing exercise, and losing weight if overweight. Additionally, choice nutrients and micronutrients are recommended to reduce oestrogen load by promoting preferred oestrogen pathways (DNAlysis 2014f).

3.4.1.3 Cytochrome P450 1B1 (CYP1B1):

This gene codes for a key phase I xenobiotic metabolising enzyme, which places an important role in the metabolism of endogenous steroid hormones and detoxification of xenobiotics, by (in conjunction with CYP1A1) catalysing the conversion of oestradiol to the 2-hydroxyestrogen (2-OHE2) and 4-hydroxyestrogen (4-OHE2) catechol oestrogen metabolites, respectively (Ghisari et al. 2014). As 4-OHE2 is extremely estrogenic and carcinogenic in studied animal models, and the concentration ratio of 4-OHE2 to 2-OHE2 in breast cancer extract has been reported to be 4:1, this suggests a considerable role in carcinogenesis (Cerne et al. 2011).

The CYP1B1 enzyme metabolically activates several pro-carcinogens and environmental contaminants, such as PAHs, polyhalogenated aromatic hydrocarbons (PHAHs) and aryl amines, into reactive epoxide intermediates that may escalate the risk of oxidative stress and cancer (Sharma et al. 2014; Ghisari et al. 2014). The gene is also induced by some environmental chemicals, via the cellular aryl hydrocarbon receptor (AhR), such as dioxin (Kristensen and Børresen-Dale 2000; Safe 1995, cited in Ghisari et al. 2014).

An important genetic variant of the CYP1B1 gene is a cytosine to guanine point mutation at codon 432 in exon 3, which results in a substitution of the leucine amino acid with valine (Leu432Val), resulting in an increase in the 4-OH activity of CYP1B1 by up to three fold (Cerne et al. 2011; Ghisari et al. 2014; Yager and Davidson 2006). Cerne et al. (2011) also suggest that the G allele of CYP1B1 may also have heightened risk of cancer when in the presence of specific phase II detoxification gene variants.

Based on the results of the *DNA Oestrogen* test, individuals are recommended to reduce their exposure to all environmental and dietary pro-carcinogens, while focusing on promoting phase II detoxification (DNAlysis 2014f).

3.4.2 Genetic variants associated with glucuronidation

The glutathione S-transferases (GST) can be divided into five classes − alpha (A), mu (M), pi (P), theta (T) and zeta (Z) — based on chromosomal location and sequence homology — and are a family of cytosolic enzymes that play an important role by detoxifying potential carcinogens, and conjugating phase I metabolic by-products, such as oestrogens, with each class of GSTs encompassing several genes and isoenzymes (Ying et al. 2012; Abu-Amero et al. 2008). The

family of enzymes works by inactivating the endogenous end products and xenobiotics that are formed as secondary metabolites from oxidative stress (Ying et al. 2012; and Abu-Amero et al. 2008). This renders them more water-soluble (Mitrunen and Hirvonen 2003) and, therefore, more efficiently excreted from the body (phase I metabolic products should be swiftly removed from the body, especially where carcinogenic by-products have been produced) (DNAlysis 2014f).

Two glutathione S-transferase genes are screened in the DNAlysis *DNA Oestrogen* test (DNAlysis 2014f):

- Glutathione S-Transferase M1 (GST-M1) polymorphism: gene deletion; and
- Glutathione S-Transferase T1 (GST-T1) polymorphism: gene deletion.

Two major polymorphisms have been observed in the population, which involve the deletions of each of these genes, and the ‘‘null’’ genotypes result in the virtual absence of enzyme activity (Abu-Amero et al. 2008), as opposed to the “present” genotype (Ying et al. 2012). In humans, *GST-M1* and *GST-T1* deletion genotypes are associated with various pathologic processes, including certain ophthalmologic diseases (cataract and senile macular degenerations; Abu-Amero et al. 2008), laryngeal cancer (Ying et al. 2012) and breast cancer (Ghisari et al. 2014). These genotypes are each discussed next.

3.4.2.1 Glutathione S-Transferase M1 (GST-M1):

This is a gene that is located on chromosome 1p13.3; it is predominantly expressed in the liver, and codes for an enzyme that participates in the deactivation of the carcinogenic intermediates of polycyclic aromatic hydrocarbons, such as those that are present in tobacco (Ying et al. 2012). Approximately 50% of Caucasian and Asian populations have the null genotype, while in African populations, only around 27% contain the polymorphism (Mitrunen and Hirvonen 2003).

Based on a null genotype result in the *DNA Oestrogen* test, individuals are recommended to eat an antioxidant-rich diet, minimise their exposures to toxins, and increase their consumptions of allium and cruciferous vegetables (DNAlysis 2014f).

3.4.2.2 Glutathione S-Transferase M1 (GST-T1):

This gene is expressed in various tissues, including the lung, liver and in red blood cells (RBC). The null genotype is observed in approximately 60% of Asians, and 20% of Caucasians (Mitrunen and Hirvonen 2003). As shown in Figure 3.2, the GST-T1 null genotype is associated with lowered inactivation of quinones (the further oxidised metabolites of 4-hydroxyeostrogen, as shown in Figure 3.1), as well as reduced liver detoxification (Cerne et al. 2011).

Dietary recommendations for improving phase II detoxification include the consumption of cruciferous vegetables, such as cabbage and broccoli, or allium vegetables, such as onions and garlic, as the breakdown products of these food groups are proposed to induce the enzymatic

activities of GSTs. Broccoli consumption has also showed to have a protective effect against the incidence of colorectal adenomas (DNAlysis 2014f).

3.4.3 Genetic variants associated with methylation

Methylation is one of the first steps (in conjunction with hydroxylation) in the oestrogen degradative and excretory pathways, as shown in Figure 3.1 (Thomas and Potter 2013). Methylation is also one of the most important biological processes involved with preserving the integrity of DNA (DNAlysis 2014f).

Two methylenetetrahydrofolate reductase genes are screened in the DNAlysis *DNA Oestrogen* test (DNAlysis 2014f):

- Methylenetetrahydrofolate Reductase (MTHFR) polymorphism: C677T; and
- Catechol-O-Methyl Transferase (COMT) polymorphism: Val158Met.

These are each discussed next.

3.4.3.1 Methylenetetrahydrofolate Reductase (MTHFR):

This is an important enzyme that regulates the metabolism of folate and methionine, which are both important for DNA synthesis and methylation (Long et al. 2012). The enzyme catalyses the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is a co-substrate for homocysteine remethylation to methionine, and a dominant circulating form of folate (Spiroski et al. 2008; Long et al. 2012). The gene is localised on chromosome 1p36.3, and is composed of 11 exons (Spiroski et al. 2008).

Twelve alleles of human MTHFR have been identified so far (Spiroski et al. 2008); however, two common SNPs are known to affect enzyme function, and have clinical significance (Long et al. 2012). The most common mutation is a cytosine to thymine transition at nucleotide 677 in the fourth exon, which results in a substitution of alanine for valine that affects the enzyme's catalytic domain (Long et al. 2012). Carriers of the T allele present reduced enzymatic function, and lower metabolic activity by between 30 and 60% for homozygous variant 677 TT and heterozygous variant 677 CT genotypes, respectively, as compared to the wild-type 677 CC genotype (Kordas et al. 2009; Inoue et al. 2008).

In a meta-analysis by Taioli et al. (2009), the TT genotype of the MTHFR C677T polymorphism appeared to be associated with a reduced risk of colorectal cancer (CRC), though this appeared to vary depending on the population. An inverse association was observed in Caucasians and Asians, for example, but not in Latino or African populations (Taioli et al. 2009). The T-allele is, however, associated with an increased risk of breast cancer (Inoue et al. 2008). Studies have also been conducted on the link between the MTHFR T-allele and maternal folate intake, tibia lead and infant size at birth (Kordas et al. 2009), occlusive artery disease and deep venous thrombosis

(Spiroski et al. 2008), and cervical lesions (Long et al. 2012). Various authors (Osterhues et al. 2013; van der Put et al. 1998, cited in Long et al. 2012) have also observed links between this MTHFR polymorphism and neural tube defects (NTD).

In support of DNAlysis' recommendations for specific vitamin and mineral consumptions, relative to the results of the *DNA Oestrogen* tests, authors such as Inoue et al. (2008) have reported finding that green tea, or polyphenol (2)-epigallocatechin-3-gallate (EGCG) acts as a cancer preventive agent through folate pathway inhibition, whereby in T-allele carrier women with a low folate intake (less than 133.4 mg per day), daily and weekly green tea consumption was inversely associated with breast cancer risk compared to those with lower consumptions of green tea.

3.4.3.2 Catechol-O-Methyl Transferase (COMT):

This is a phase II enzyme involved in methylating and, thus, inactivating the hydroxyl-oestrogens by converting them to their non-genotoxic methoxy derivatives (Ghisari et al. 2014). This is quantitatively the most active conjugation pathway for hydroxyl-oestrogens (Cerne et al. 2011). In so doing, the 2- and 4-hydroxy groups on the oestrogen A-rings are converted to methoxy groups (Thomas and Potter 2013). The COMT protein exists in two forms, namely: a soluble s-COMT, which is composed of 221 residues, and membrane bound mb-COMT, which contains an additional 50 residues at its N-terminal end to facilitate binding to the cell membrane (Thomas and Potter 2013). A common polymorphism occurs at residue 108 in the soluble form of COMT, and at residue 158 of the membrane-bound form, where valine is replaced, through a missense mutation, with methionine, following a single base pair change from guanine to adenine (Ghisari et al. 2014; Yager and Davidson 2006).

Various disorders are associated with the rarer methionine polymorphism, or M-allele, due to reduced activity of the methionine residue, an increased range of conformational states, and greater instability from autoxidation, temperature fluctuations and the presence of denaturants (Cerne et al. 2011; Thomas and Potter 2013). Individuals carrying the M-allele are theorised to have a lower capacity to produce the anti-tumour compound 2-methoxyestradiol, thus producing an accumulation of the reactive catechol oestrogen intermediates that facilitate the proliferation of oestrogen-induced tumours, such as in breast cancer. This genotype also results in various neuropsychiatric disorders and a lower pain threshold (Thomas and Potter 2013). A side benefit has also been reported, though, which involves improved cognitive function and working memory (Thomas and Potter 2013). Mitrunen and Hirvonen (2003) also report a significant increase in risk for breast cancer in postmenopausal women with the COMT M-allele who have continued long-term use of oestrogen for more than 30 months, those who had an early menarche (before age 12), and those with post-menopausal obesity.

To counter the effects of the COMT M-allele, DNAlysis endorses certain vitamins and minerals, such as folate, which can promote the function of methylation enzymes (DNAlysis 2014f).

3.4.4 Genetic variants associated with sulfation

The human SULT1A subfamily of cytosolic sulfotransferases is part of a supergene family of enzymes that catalyse the relocation of a sulfonate group from 3'-phosphoadenosine 5'-phosphosulfate, or PAPS, to a variety of endogenous compounds and xenobiotics, such as steroids, drugs and carcinogens (Hempel et al. 2004). By transferring sulfo-groups to nucleophilic sites on oestrogens, they form biologically inactive and water-soluble oestrogen sulphates, which may be excreted into the urine or bile, thereby lowering their internal exposure to target tissues (Glatt and Meinl 2004). Unlike other species, the human SULT1A gene family contains more than one member, and each of the three variants (SULT1A1, SULT1A2, and SULT1A3) share more than 92% similarity at the amino acid level (Hempel et al. 2004). The three gene variants are also found in proximity to each other on chromosome 16 (16p12.1-p11.2), implicating their recent evolution from a gene duplication event (Hempel et al. 2004).

The SULT1A1 sulfotransferase gene is screened in the DNAlysis *DNA Oestrogen* test (DNAlysis 2014f), as discussed, next:

3.4.4.1 Sulfotransferase 1A1 (SULT1A1):

This is an important phase II xenobiotic metabolising enzyme that mediates the sulfonation of steroids, drugs and carcinogens (Hempel et al. 2004). It also leads to the protective conjugation of oestrogen metabolites that are formed in the body (Cerne et al. 2011). SULT1A1 protein is found in many tissue types, with the highest abundance in the liver (Yao-Borengasser et al. 2014).

SULT1A1 has been shown to contribute to increased cancer risk, including breast cancer (Yao-Borengasser et al. 2014), and while SULT1A1 activity may vary several-fold among individuals, the gene expression and protein activity levels of SULT1A1 have been seen to affect the efficacy of TAM treatment (Yao-Borengasser et al. 2014). SULT1A1 expression has also been seen to relate to the disease state, whereby there is virtually no expression in normal breast epithelia, but profuse protein expression in most breast tumours (Yao-Borengasser et al. 2014).

Studies relating to SNPs in the SULT1A1 promoter 3′-untranslated region (UTR) and coding regions have been shown to contribute to SULT1A1 availability and activity (Hempel et al. 2004); however, according to Yao-Borengasser et al. (2014), SNPs only account for a small proportion of the variation of SULT1A1 activity, and even doubling SULT1A1 copy numbers has not shown to double its activity. Therefore, factors other than copy number determine the activity of SULT1A1, and while SULT1A1 has traditionally been considered as a non-inducible enzyme, authors such as Hempel et al. (2004) have reported transcription factor (TF) regulation of SULT1A1 by compounds such as Sp1 and GA binding protein (GABP).

One common polymorphism exists in exon 7 of the SULT1A1 gene, due to the substitution of a histidine residue for an arginine residue at position 213 (Thomas and Potter 2013; Mercer et al.

2010). This polymorphism, termed the SULT1A1*2 allele results in the production of an enzyme with considerably lower catalytic activity and reduced thermal stability (Mercer et al. 2010).

Jiang et al. (2010) report that while the SULT1A1*2 allele produces no exact increased risk for breast cancer, postmenopausal women who are dominant carriers of the allele have been shown to have an increased risk of breast cancer. So, too, was a significant increase in breast cancer risk reported among Asian women, though not in recessive Caucasian women. In a study by Yang et al. (2005) on Chinese women, the authors found that women who had the SULT1A1*2 allele and a high body mass index (BMI), or a long menstruation (over 30 years), were between 3.6 and 4.0 times more likely to develop breast cancer, respectively, as compared to individuals with the wild type allele.

3.4.5 Genetic variants associated with oxidative stress

Reactive oxygen species (ROS) are produced as a consequence of the oxygen-rich atmosphere in which we live, and are by-products of oxygen metabolism (Fridovich 1978, cited in Holley et al. 2012). Low levels of ROS are important mediators for various cellular processes, including immune responses, cell adhesion, apoptosis, intracellular signalling, cell growth and differentiation (Holley et al. 2011). Excessive production of ROS, though, may cause DNA damage, inhibit the normal activity of cellular enzymes, and induce cell death through the activation of caspase cascades and kinases (Miao and St. Clair 2009), resulting in numerous diseases, including cancers and several neurological disorders (Waris and Ahsan 2006, cited in Holley et al. 2011).

The superoxide dismutase (SOD) enzyme family is dedicated to eliminating superoxide anion radicals that are derived from within the mitochondrial matrix as by-products of the metabolism of oxygen through electron transport chains, as well as extracellular stimulants, such as oxidative insults and ionising radiation (Miao and St. Clair 2009) into oxygen and hydrogen peroxide (Fukai and Ushio-Fuka 2011). Three SOD isoforms have been characterised in mammals. These are the cytosolic copper-zinc superoxide dismutase (Cu/ZnSOD), manganese superoxide dismutase (MnSOD) and extracellular superoxide dismutase (ECSOD), which are encoded by the genes, *sod1, sod2 and sod3*, respectively (Fukai and Ushio-Fuka 2011; Miao and St. Clair 2009).

The manganese superoxide dismutase gene is screened in the DNAlysis *DNA Oestrogen* test (DNAlysis 2014f), as discussed next.

3.4.5.1 Manganese Superoxide Dismutase (MnSOD or SOD2):

This is an antioxidant enzyme that is localised in the mitochondrial matrix, and is essential for the survival of aerobic life (Holley et al. 2012). It is also an evolutionarily conserved enzyme, and is found in a variety of organisms, including *Escherichia coli, Saccharomyces cerevisiae* (yeast) and *Porphyridium cruentum* (red algae) (Holley et al. 2012). The enzyme is composed of a 96 kDa homotetramer, and is coded by a gene of five exons and four introns localised to chromosome

6q25 (Cai et al. 2004). A manganese ion at the active site of MnSOD serves to catalyse the disproportionation of superoxide to oxygen and hydrogen peroxide (Fukai and Ushio-Fuka 2011).

Numerous cancer cell types have been shown to present reduced levels of antioxidant enzymes, especially MnSOD, and an elevated expression of MnSOD has been seen to suppress malignant phenotypes of breast cancer (Mitrunen and Hirvonen 2003), suggesting its link as a tumour suppressor gene in breast cancer.

Various genetic variants of MnSOD have been identified (Fukai and Ushio-Fuka 2011; Miao and St. Clair 2009). One genetic polymorphism that is screened in the *DNA Oestrogen* test is a thymine to cytosine substitution in the mitochondrial targeting sequence of MnSOD (amino acid 16 in the mitochondrial signalling sequence (Miao and St. Clair 2009), where the amino acid codon at position–9 in the signal peptide (base-28) is changed, through a missense mutation, from alanine (GCT) to valine (GTT) (Ambrosone et al. 1999). This polymorphism alters the secondary structure of the protein, and the transportation of MnSOD within the mitochondria (Cai et al. 2004). The wild type (Ala16) variant has a partial α-helical structure, can smoothly enter the mitochondrial matrix and has a higher activity than the Val16 variant, which instead adopts a β-sheet structure; and remains embedded in the inner membrane (Holley et al. 2011).

Studies have suggested links between the C(-28)T SNP and risks for ovarian cancer, lung cancer, prostate cancer (Holley et al. 2011), and breast cancer (Ambrosone et al. 1999).

A second important polymorphisms in the SOD2 gene involves a transition of isoleucine 58 (Ile58) to threonine in exon 3 of MnSOD (Cai et al. 2004). This affects the stability of the tetrameric interface of the protein molecule and lowers its volume and enzyme activity (Cai et al. 2004), as well as increases its thermal sensitivity (Holley et al. 2011). The reduced enzyme activity of the Thr58 variant lowers its tumour-suppressive ability in human breast cancer (Holley et al. 2011).

In response to the *DNA Oestrogen* test, recommendations are made to increase the dietary intake of anti-oxidants, such as from vegetables and fruits (DNAlysis 2014f). A study by Ambrosone et al. (1999), for example, showed that breast cancer risk was most pronounced among women who consumed less-than-median amounts of fruits, vegetables, dietary ascorbic acid and α-tocopherol, while those whose diets were rich in these foods showed little increase in risk.

3.5 METHODOLOGIES

Numerous laboratory techniques are utilised for the observation of gene polymorphisms (Ying et al. 2012; Loo et al. 2012). Otherwise known as genotyping, typical techniques include:

- Polymerase chain reaction (PCR);
- Hybridisation to DNA microarrays or beads;
- Restriction fragment length polymorphism (RFLP);
- Amplified fragment length polymorphism (AFLP);

- Random amplified polymorphic detection (RAPD);
- Allele specific oligonucleotide (ASO) probes; and
- DNA sequencing.

Variations of the above techniques have been described, such as Microfluidic Capillary Electrophoresis-based Restriction Fragment Length Polymorphism (µCE-based RFLP) (Zhang et al. 2013); multiplex PCR (Abu Amero et al. 2008), and PCR-based RFLP. Two of the most common techniques that are referred to in the literature, when genotyping mutations in human genes, involve multiplex PCR and PCR-RFLP (Markoulatos et al. 2002; Abu Amero et al. 2008; Cerne et al. 2011).

3.5.1 Multiplex PCR

While conventional PCR uses thermal cycling with two DNA primers to amplify a DNA sequence, so that detailed nucleotide sequences may be detected, multiplex PCR describes a variant of PCR in which two or more target sequences are amplified simultaneously in the same reaction mixture, using more than one pair of DNA primers (Markoulatos et al. 2002). Originally described in 1988 (Chamberlain et al. 1988), this technique has the potential to considerably reduce effort and time in the laboratory by combining multiple tests into a single thermocyclic amplification.

Executing an efficient multiplex PCR often requires strategic planning and several attempts to optimise the conditions of the reaction, such as the concentration of the PCR buffer, the balance between the deoxynucleotide concentrations and magnesium chloride, the cycling temperatures, and the amounts of DNA polymerase and template DNA (Markoulatos et al. 2002).

Abu Amero et al. (2008) present an example of analysing polymorphisms of GSTM1 and GSTT1 (the two genetic variants associated with glucuronidation that are screened by the DNAlysis DNA Oestrogen test) using multiplex PCR. In the methodology of the paper, the following primers were used:

- *GSTT1* forward primer 5`-TTC CTT ACT GGT CCT CAC ATC TC −3`;
- *GSTT1* reverse primer 5`-TCA CCG GAT CAT GGC CAG CA −3`;
- *GSTM1* forward primer 5`- GAA CTC CCT GAA AAG CTA AAG C −3`; and
- *GSTM1* reverse primer 5`- GTT GGG CTC AAA TAT ACG GTG G −3`.

Each 25 µl PCR reaction was produced with 10 ρmol of each primer, 2.5 µl of 10X reaction buffer, including $MgCl_2$ (the concentration was not specified, but Yang et al. (2005) presented a similar reaction with 2.5mM $MgCl_2$), 100 ρmol/µl of deoxynucleoside triphosphates (deoxyATP, deoxyguanosine triphosphate, deoxycytidine triphosphate, and deoxythymidine triphosphate), 1 unit of HotStar *Taq* DNA polymerase, and 100 ng of genomic DNA template in Tris-HCl buffer. The annealing temperature was 58°C, over 40 cycles, and the PCR products were separated using 2%

agarose gel electrophoresis at 100V for 50 minutes. Two bands at 209 bp for *GSTM1 and* 459 bp for *GSTT1* were observed in the case of the T1M1 genotype, while the T0M1 genotype showed only one band of 209 bp and the T1M0 genotype showed only one band of 459 bp. The T0M0 null genotype was recognisable through the absence of bands, and in such cases, a β-globin internal positive control was used to negate any false positives through the incorrect operation of the PCR reaction (Abu Amero et al. 2008).

3.5.2 PCR-RFLP

Polymerase chain reaction (PCR)-based restriction fragment length polymorphism (RFLP) includes the combining of two methodologies: PCR and RFLP detection.

Cai et al. (2004) present an example of analysing polymorphisms in MnSOD genotypes for the Val-9Ala polymorphism, and the Ile58Thr polymorphism using the PCR-based RFLP method (the two genetic variants associated with oxidative stress for the Manganese Superoxide Dismutase (MnSOD) gene that are screened by the DNAlysis DNA Oestrogen test). In the methodology of the paper, the following primers were used for the Val-9Ala polymorphism:

- Forward primer 5`- ACCAGCAGGCAGCTGGCGCCGG −3`; and
- Reverse primer 5`- GCGTTGATGTGAGGTTCCAG −3`.

The following primers were used for the Ile58Thr polymorphism:

- Forward primer 5`- AGCTGGTCCCATTATCTAATAG −3`; and
- Reverse primer 5`- TCAGTGCAGGCTGAAGAGAT −3`.

Each 20 µl PCR reaction was produced with 0.5 µmol of each primer, 1xPCR buffer including 1.5 mmol/l $MgCl_2$, 0.16 mmol/l of each dNTP, 1 unit of HotStar *Taq* DNA polymerase, and 5 ng of genomic DNA template. The denaturation temperature was initially 95°C for 15 minutes, followed by 35 cycles of 30s at 94°C, 30s at 60°C and 30s at 72°C, before a final extension cycle at 72°C for 7 minutes.

The second phase of the PCR involved restriction digestions by the *Ngo*MIV restriction endonucleases for the Val-9Ala polymorphism, and *Eco*RV for the Ile58Thr polymorphisms. The DNA fragments were then separated on 3% agarose gel, and visualised with ethidium bromide under UV (Cai et al. 2004).

In the case of the Val-9Ala polymorphism, a 107bp PCR product from carriers of the C-allele (Ala) was digested into two fragments of 89 bp and 18 bp each with *Ngo*MIV, while DNA from carriers of the T-allele (Val) was unable to be cut by the *Ngo*MIV, resulting in a single 107bp band. In the case of the Ile58Thr polymorphism, an 139bp PCR product from carriers of the T-allele (Ile) was digested into two fragments of 117bp and 22bp each with *Eco*RV, while DNA from carriers of the

C-allele (Thr) was unable to be cut by the *Eco*RV enzyme, resulting in a single 139bp band (Cai et al. 2004).

Figure 3.3 shows a photograph of an agarose gel electrophoresis of the MnSOD genetic polymorphism (Ala-29Val) that was observed by Ambrosone et al. (1999) using PCR-RFLP analysis. The 29Ala/29Ala genotype, for example (lane A), was observed by a band at 87bp, while the 29Ala/29Val genotype (lane B) was evident by two bands at 87bp and 93bp. The homozygous 29Val/29Val genotype (lane C) was evident by a single band at 93bp.

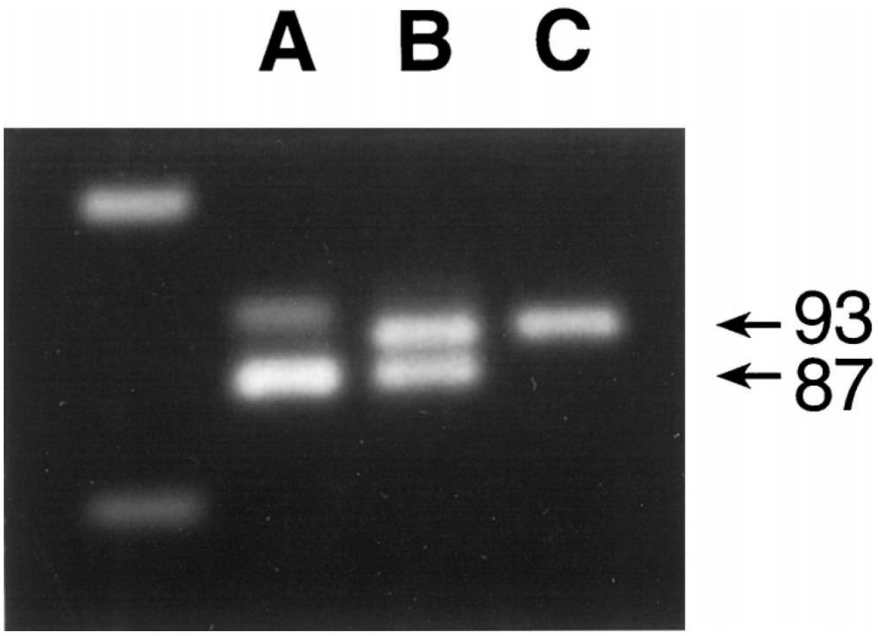


Figure 3.3 Photograph of an agarose gel electrophoresis of the MnSOD genetic polymorphism, as determined using PCR-RFLP analysis. Genotypes include 29Ala/29Ala (lane A), 29Ala/29Val (lane B), and 29Val/29Val (lane C).

Source: Ambrosone et al. 1999

Cerne et al. (2011) also present an example of analysing polymorphisms using a PCR-based RFLP method. In the methodology of the paper, the authors identify a polymorphism of cytosine 1294 for guanine, in the same Leu432Val polymorphism screened by the DNAlysis *DNA Oestrogen* test (DNAlysis 2014f). Although they do not describe the primers, or PCR reaction conditions used, to identify the allelic variations, Cerne et al. (2011) conducted a restriction digestion of the PCR fragments with *Eco*57I restriction endonuclease in the second phase of the PCR-RFLP reaction, and separated and visualised the DNA fragments by electrophoresis on polyacrylamide gels. Outcomes of the restriction digestion showed bands similar in nature to Figure 3.3 by Ambrosone et al. (1999).

3.6 CONCLUSION

This concludes the scientific review of some of the principles and contexts involved in the commercialisation of a successful biomedical technology venture in South Africa, with a specific review of the *DNA Oestrogen* test from DNAlysis. Each of the nine genes, and 11 genetic polymorphisms was discussed individually, along with their associated maladies. The chapter ended with a discussion on some of the methodologies that are noted in the literature to observe these particular genetic polymorphisms, with a focus on two that are repeatedly applied: Multiplex PCR, and PCR-based RFLP.

This case study has reiterated that detailed scientific principles can be applied successfully in South Africa for the sake of financial and humanitarian gain, thereby linking science to a commercial need. Ultimately, therefore, there is scope in the country for commercially employing scientific techniques and concepts. However, simply basing a company on scientific principles is not enough to ensure success; and indeed, evaluating the scientific principles of a South African HTV is insufficient to allow a full understanding to be drawn on the features and characteristics that SME-scale HTVs require to succeed and be sustainable in South Africa. To do so necessitates a detailed analysis of the commercial and core functional characteristics of the HTVs throughout the country, thereby observing any correlations or patterns that may exist between the majority of the HTVs and the types of core functional techniques that they have used; examining the challenges that advanced HTVs have faced in South Africa; discerning any correlations that may exist between the start-up spending, technology type, size, location, production method, and activity state or sustainability of the companies; and in essence, identifying what constitutes success to the HTVs across South Africa. This was therefore the aim of this study.

The methods employed for the purpose of this dissertation, and to answer these research questions, are discussed next.

CHAPTER 4
METHODS

4.1 INTRODUCTION

This chapter covers the methods of the dissertation. Two phases of research were performed to complete the research objectives and answer the research questions of the study, termed Phase 1 and Phase 2. The first phase was a small-sampled mixed-methods (qualitative and quantitative) study, while the second phase was a larger, purely quantitative study. The chapter begins by discussing the research philosophy and the concepts that were deliberated for each phase of the study. Next, the research design of the study is presented, which involves the framework that was applied for collecting and analysing the data.

In discussing the research design of this study, the target population is introduced, followed by the two samples that were approached for each of the study's phases. The research instruments are then presented in detail, along with the survey and data capturing methods that were employed to obtain the data for the study. Thereafter, the techniques of analysing the data are discussed, whereby the appropriate data analysis procedures that were applied to extract the necessary information from each of the qualitative and quantitative data sets, are explained.

The chapter ends with a deliberation of the aspects that pertained to this study regarding issues of bias, the ethical considerations of the study, the limitations, and the delimitations of the study. The chapter begins, next, with the research philosophy.

4.2 THE RESEARCH PHILOSOPHY

Rubin and Rubin (1995) argue that a research paradigm or research philosophy can be considered within two schools of thought: phenomenology and positivism. Saunders et al. (2009), instead, consider the research philosophy within a broader spectrum of perspectives which they term positivism, realism, interpretivism and pragmatism.

The Rubin and Rubin (1995) concepts of positivism and phenomenology both apply to this research, and correspond to the two branches described by Saunders et al. (2009) of positivism, and interpretivism. Researchers who use quantitative methods and tools for measuring and counting through a scientific approach are termed positivists, while phenomenologists employ qualitative methods of observation through questioning and describing. Positivists and phenomenologists differ in their beliefs of what is important in a study. Positivists believe that there is only one external reality, which is fixed, knowable, and directly measurable. Conversely, phenomenologists argue that there are multiple versions of reality, whereby reality continually changes; and this change can be indirectly observed through interpretation by people.

In this study, two phases of research were conducted. The first was based on a mixed-methods approach, involving both qualitative (phenomenological) and quantitative (positivist) research methods. The second was based on a purely positivist approach, involving quantitative research methods. According to Rosnow and Rosenthal (2005), qualitative research is most suitable when conducting studies on organisational management, although Adams et al. (2007) highlight that "qualitative data are numerically nonmeasurable", and argue that in many applications, quantitative techniques should be applied with data that can be measured numerically. Therefore, in order to gain a fuller understanding of the South African health technology environment, dual methodologies were performed in the first phase to gain a deeper understanding of the human perspective, while in the second phase, a primarily quantitative approach was followed to gain a scientific understanding of the South African macroenvironment. The overall structure of the study could therefore be classified as a mixed-method study, which is discussed in the literature by authors such as Tashakkori and Teddlie (2003).

The first phase of the study was conducted in order to satisfy the following objectives:

- To examine the challenges that advanced biomedical ventures face in South Africa as compared to other developing and developed countries;
- To determine what constitutes success in an HTV, such as its profit, sustainability, number of people treated, overall improvement to society or otherwise; and
- To assist in considering the proportion of HTVs that are successful or sustainable, compared to the number of ventures started, and thereby to aid in concluding what has made these biomedical ventures a success in the South African environment.

The second phase of the study was performed to satisfy the following objectives:

- To aid in examining the challenges that advanced HTVs face in South Africa as compared to other developing and developed countries;
- To identify the types of costs involved with advanced HTVs in South Africa, and whether there is a correlation between the start up spending, technology type, size, location, production method, and activity state (sustainability) of the companies;
- To observe any correlations or patterns between the majority of HTVs and the types of techniques that they are using; and
- To consider the proportion of HTVs that are successful or sustainable, compared to the number of ventures started, and thereby to aid in concluding what has made these biomedical ventures a success in the South African environment.

4.3 RESEARCH DESIGN

Bryman and Bell (2007) define the research design as the structure for guiding the implementation of a research methodology and the examination of any subsequent data. Cheek (2008) describes

the research design as the technique that is applied to convert a research concept into a research plan, which can then be performed in practice. As explained previously, this research consisted of two phases, involving both quantitative and qualitative analyses. The framework for collecting and analysing the data, therefore, involved practices corresponding to each of these methods of data collection and analysis. The samples that were drawn from the target population, the research instruments, and the data analysis techniques employed are each described in detail next.

4.3.1 Target population

An important task for any research is to clearly define the sample of the study (Tashakkori and Teddlie 2003). The population or "universe" of a study constitutes all the possible elements that can be incorporated into a study, and may consist of an entire community, class of individuals, selection of events or range of cultural rituals (Given 2008).

The target population for this study involved all of the medically related 'health technology' ventures (HTVs) that have been in existence in South Africa within the past ten years, that were within the size and business scale of standard SMEs. This included companies from the categories of vaccines; biogenerics; therapeutics; nutraceuticals; reagents; diagnostics products and equipment; medical devices; biotools; contract services; and public services. Companies were classified into these categories based on the definitions presented in Chapter 1.

The sampling frame for a study is a complete list of all the cases in the population from which a sample will be drawn (Given 2008; Saunders et al. 2009). For this study, a sampling frame of 184 HTVs was compiled based on the parameters of the target population, by:

- Drawing from lists on government publications, such as the Technology Innovation Agency (TIA Report 2012; Department of Science and Technology 2013);
- Drawing from publications from previous researchers on health technology in South Africa (Al Bader et al. 2009; Chakma et al. 2010; Masum and Singer 2010; Uctu and Essop 2013);
- Referring to various online resources (University of Cape Town 2014a; University of KwaZulu Natal 2009; BioSA 2006; University of Cape Town 2014b); and
- Browsing through company websites and material in the internet public domain.

4.3.2 Sample

The sample of a study comprises the selected members of the population or universe that are included in the research, in order to generate a conclusion based on that population (Adams et al. 2007). Sampling is, therefore, the technique or process of selecting a suitable sample from the population (Given 2008).

As noted by Adams et al. (2007), researchers should "always try to draw a representative sample to draw any conclusion about the 'real world'". A common concern in research, therefore, relates to

how representative a target population's sample is, whereby sample size is an important aspect of sampling — an adequate sample should be derived to provide a tolerable margin of error, and confidence in the results (Saunders et al. 2009).

Two basic sampling techniques are applied in research: probability and non-probability sampling (Adams et al. 2007). As noted by these authors, a probability sample is one in which "every element of the population has an equal chance of being selected." Conversely, a non-probability sample is one that is "selected on the basis of personal judgement." Within a non-probability sampling approach, convenience sampling, purposive sampling (which involves judgement or quota sampling), snowball, network or chain sampling may be used (Saunders et al. 2009; Adams et al. 2007).

Conversely, as noted by Saunders et al. (2009), probability or representative sampling "is most commonly associated with survey-based research strategies where you need to make inferences from your sample about a population to answer your research question(s) or to meet your objectives." Within a probability sampling approach, a simple random sample; stratified random sample; systematic (quasi-random) sample; cluster (multistage) sample; or sequential (multiphase) sample may be accumulated (Saunders et al. 2009; Adams et al. 2007). Different sampling techniques were used for each of the samples of the project as discussed next.

4.3.2.1 Sample 1: Small-sample mixed-methods phase

Non-probability sampling was applied in the first phase of the study. Judgement sampling was performed, whereby a cross-section of the population was selected following judgement by the researcher regarding organisations that conformed to the inclusion criteria of the research objectives. As noted by Saunders et al. (2009), "purposive or judgemental sampling enables you to use your judgement to select cases that will best enable you to answer your research question(s) and to meet your objectives." In line with this approach, a range of potential companies was chosen by counting through the listed sampling frame of potential candidates and selecting cases that would have been particularly informative for answering the research questions.

As shown in Figure 4.1, a sample of 21 companies (referred to here as Sample 1) was approached for the first phase of the study. This included, by numbers, predominantly medical device companies, followed by biogenerics, diagnostics and contract service organisations. Two vaccine companies were also approached. In terms of the headquarter locations, 95% of the companies involved in Sample 1 were based locally, with only one company being based abroad. In addition, the majority of companies were from the Western Cape, followed by Gauteng and KwaZulu Natal, as shown in Figure 4.1. Respondents from the companies were either owners, directors, CEOs, or in rare cases, from middle-to-upper management.

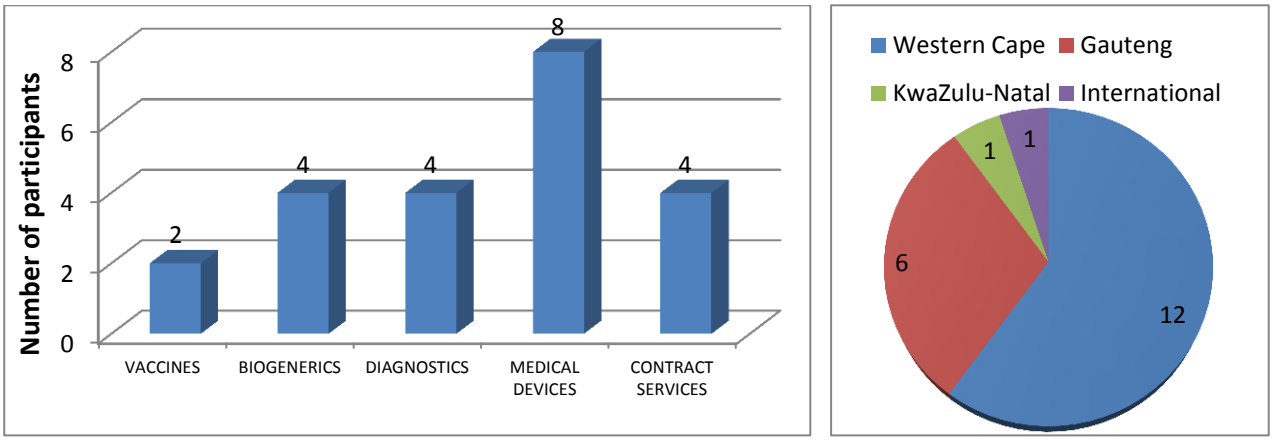


Figure 4.1 The organisations approached for Sample 1, including their core function (left) and headquarter locations (right)

The geographical split of organisations may, at first, seem biased, since the Gauteng region, which is an economic hub, had fewer organisations participating than the Western Cape. However, Cape Town has been recognised in the literature (van Zyl 2014; 2015) for its technology and life science growth prospects, with van Zyl (2015) stating that Cape Town has become a major hub for life sciences and technology start-ups. A study by Brandeis International Business School and consulting firm T3 Advisors also listed Cape Town as "one of seven cities across the globe poised for significant growth in technology and life sciences" (van Zyl 2015). Moreover, the focus of this study was on SME-scale ventures, and the Gauteng region is home to many corporate-scale or multinational organisations that were larger than the criterion for this study. Thus, it could be argued that the Sample 1 of this study was indeed a true representation of the geographical split of the SME-scale HTVs in South Africa, and not a bias. Furthermore, Sample 2, which was a far larger (randomised) sample, also reflected this regional split in organisations, providing further validation of the geographical distributions of the companies in the study.

4.3.2.2 Sample 2: Larger, quantitative phase

Probability sampling was applied in the second phase of the study. While each of the sampling techniques have advantages (Adams et al. 2007), a systematic or quasi-random sample was selected for this phase of the study to ensure that a thorough sample was procured, and units were not sampled more than once. In line with this approach, a sample of potential companies was chosen by counting through the listed sampling frame of potential candidates and selecting every available unit. As shown in Figure 4.2, of the maximum 184 companies in the sampling frame, 107 companies were accessible, and therefore included in Sample 2, consisting predominantly of medical device companies, diagnostics organisations, and companies with core functions in multiple categories.

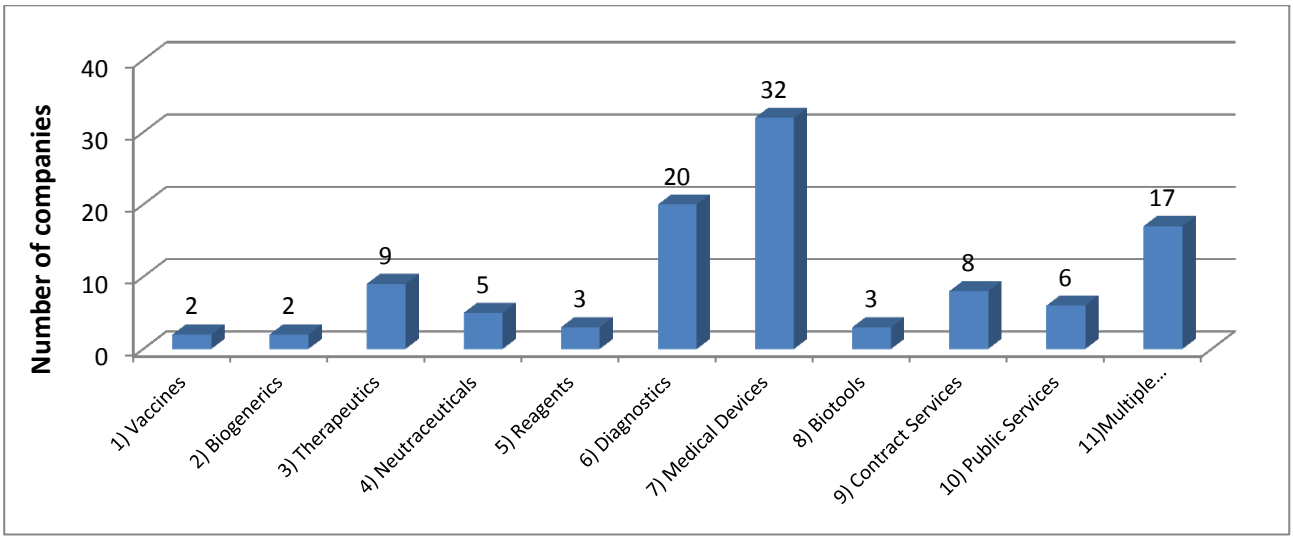


Figure 4.2 Core functions of the organisations approached for Sample 2

Of the companies approached, 72% responded, 7% declined to provide information, and 21% were unavailable — especially in the case of defunct companies, which consequently required additional research to be conducted in the form of a desktop study, as discussed later in the chapter. In addition, of the companies included in the Sample, 38.3% were head-quartered (HQ) in Cape Town, followed by 26.2%, 14.0% and 9.3% in Johannesburg, Pretoria and Durban, respectively. Other regions were scarcely observed as HQ locations; except Stellenbosch, which presented a hub of health technology development by comprising 6.5% of the Sample 2 companies, as shown in Figure 4.3.

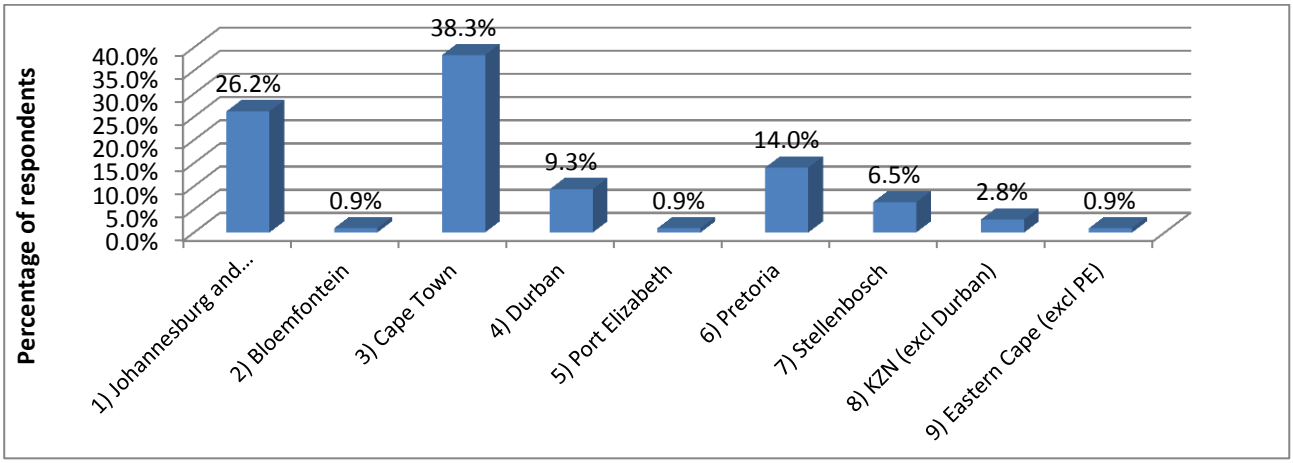


Figure 4.3 Head office locations of respondents

4.3.3 Research instruments

Data collection techniques for a research project may be from many sources. According to Yin (2003), there are six primary methods of data gathering: interviews, archival records, direct observations, participant-observations, physical artefacts and documentation. Adams et al. (2007) state that to obtain information from people, one should either question them face-to-face, conduct

questionnaires or perform telephonic surveys. Adams et al. therefore argue that surveys are potentially the most broadly employed technique of data collection in organisational research.

Saunders et al. (2009) concur that a survey is typically associated with deductive studies, and is a popular strategy in organisation research; whereby it is most often used to answer questions of the form who, where, what, how much and how many. It is, thus, popular for descriptive and exploratory research, as surveys allow the collection of large amounts of data in a "highly economical way" and from "a sizeable population" (Saunders et al. 2009).

Surveys may be considered within two broad categories: questionnaires and interviews (O'Leary and Miller 2008). Questionnaires are often paper-and-pencil instruments that are completed by the respondents, and the data is directly recorded by the participant. Conversely, interviews are completed through the instruction of the interviewer in a face-to-face conversation or telephonic survey, whereby the interviewer typically records the data on the participant's behalf (Adams et al. 2007).

In the first phase of this project, a participant-observation was conducted in the form of an online questionnaire survey, while in the second phase of the study, three data gathering techniques were applied: direct observations in the form of a desktop study; participant-observations in the form of an email-based questionnaire survey; and interviews in the form of short telephonic consultations. Details of these research instruments are explained next.

4.3.3.1 Phase 1: Small-sample mixed-methods study

In the first phase of the study, a survey of the 21 individuals of Sample 1 was performed with the use of an online questionnaire, using a combination of both structured and unstructured questions. Initially, respondents were contacted telephonically and introduced to the background and implications of the study. The respondents were then emailed a link to the online questionnaire platform, where they were directed through a sequence of questions relating to their organisations and their experiences of the South African macroenvironment. Note that both existing and defunct company owners were contacted. As in the case of existing companies, contact details of the owners of former or defunct companies were researched from the internet, where possible, and individuals were contacted in the same manner as active-company owners. The cell-phone numbers and email addresses of such individuals were often still active. This was done to provide insight into companies that were not only successful, but also ones that had failed.

The questionnaire for this study was designed with no time limit, and the participants were able to close the web page and return to it at a later time, via the same link and computer if they were unable to complete it all at once. Respondents were also able to add or adjust information, and alternate between pages as much as they wished until they decided to submit the survey or quit the process. The questions asked during the online questionnaire may be observed in Appendix II.

Data from the online questionnaire was downloaded and captured using Microsoft Excel for analysis and presentation in the results chapter of the dissertation.

4.3.3.2 Phase 2: Larger, quantitative study

As note by Saunders et al. (2009), a survey-based strategy allows the collection of data that can be analysed quantitatively using both descriptive and inferential statistics. Furthermore, data collected from surveys can be used to suggest possible reasons for relationships between variables and to generate models pertaining to these relationships. As in the first phase of the project, a survey was used again for the second phase of the study but a different approach was undertaken to generate data that could be used for more detailed statistical analysis of the data.

Berg (1995, cited in Struwig and Stead 2001) argues that in semi-structured discussions, structured questions are presented to each participant in a consistent and orderly manner. However, the participants should also be afforded the opportunity to discuss any matters outside of the confines of the questions if they desire. Therefore, a system of semi-structured consultations was applied during the second phase of the study to allow concise answers to be generated for the statistical correlation analysis, but to afford opportunity for the collection of additional material, wherever forthcoming from the respondents, to supplement the phenomenological aspects of the study. The questions asked during Phase 2 may be observed in Appendix II. The variables generated from these questions were directly related to the current situational aspect of the business, without interrogating very personal data, and thereby minimising the cause for any company participants to decline to answer. The current state of activity, location, start-up spending, classification, size, and mode of production were considered the point-specific details of any business that could be compared, and which directly pertained to the research objectives of this study.

For initial data collection, a direct observation of any available information was conducted in the form of a desktop study, which included researching all obtainable resources in the public domain. This covered company websites, publications, public articles and open source documents. This was especially necessary in the case of companies that had been closed down or become defunct at the time of the study. Thereafter, participant-observation was conducted in the form of an email based questionnaire survey. Sample 2 individuals were contacted via email with an introductory explanation to the background and implications of the study, along with six semi-structured questions to which the respondents were asked to reply via email. Due to the nature of the study, many of the Sample 2 participants were forthcoming with supporting commentary in their response emails; which, although not required for, or used in the quantitative data analysis portions of the study, did provide supplementary material to complement the phenomenological aspects and discussion chapter of this dissertation.

As a third form of data collection technique, short telephonic interviews were conducted with any remaining Sample 2 respondents, and information to the six variables was captured manually by the researcher. Saunders et al. (2009) note that in many cases, a respondent will respond better following the establishment of personal contact, and this was apparent during the interview phase of this study. Data from the emailed survey and telephonic interview was captured in a Microsoft Excel Spreadsheet, and analysed according to the principles indicated in Section 4.3.4, before presentation in the results chapter of the dissertation.

4.3.4 Data analysis

Appropriate techniques were applied to analyse the qualitative and quantitative data from each of the two phases of this study.

4.3.4.1 Phase 1

In order to analyse the quantitative (numerical) data from the first phase of the study, two techniques were applied. The first was a descriptive statistical analysis to observe the immediate frequency tables and statistical information from the data. The second technique involved a scoring system, whereby responses from each of the respondents were graded and averaged on a ten-point scale. Companies were awarded an individual score between zero and ten in each of the categories relating to the production process, company citizenship, financial operations, competitor profile, market profile, sustainability profile, and strength and weakness (SWOT) profile. On this scale, ten constituted an all-positive answer and zero an all-negative answer. Positive and negative answers were graded in relation to a tendency of local (South African) advantage, as shown in Table 4.1.

Each company was awarded a total score per category and the scores of each company were averaged to present a total score for the sample, where a maximum possible score of 260 points among the sample constituted a fully locally-centric macro-environment, with all strengths and no weaknesses. This method of generating a combined points system was devised specifically for this study, but studies employing points and ranked data are described widely in the literature (Woodside 2010; Agresti 2007).

For the qualitative portion of the Phase 1 data analysis, a third technique was performed, involving a common qualitative research approach termed thematic analysis, which can be used as an analytical method for recognising, analysing and reporting on themes or patterns among qualitative data (Braun and Clarke 2006). In order to formulate themes, Guest et al. (2012) refer to a process of ‘coding’. This refers to the process of combining data into ideas, themes and categories, and then coding the similar themes of text with a label that can be accessed for further comparison and analysis at a later stage.

Table 4.1 Score table for use in the quantitative portion of Phase 1 of the study

		[Each item is awarded points on a scale of 0 - 10 where 10=100% / True / Yes]					
Process	**Subcategory**	**Positive Answer**	**Points Awarded**	**Negative Answer**	**Points Awarded**	**Maximum Points**	**Totals**
Production Process (Production is highly South Africa-centric)	Products manufactured locally	All	10	None	0	10	40
	Products / raw materials sourced locally	All	10	None	0	10	
	Products researched / developed locally	All	10	None	0	10	
	Products supplied locally (or exported)	Local	10	Exported	0	10	
Company Citizenship (Company staff basis is highly South Africa-centric)	Company owned by South Africans	All	10	None	0	10	50
	Company started by South Africans	All	10	None	0	10	
	Company operated by skilled South Africans	All	10	None	0	10	
	Company operated by unskilled South Africans	All	10	None	0	10	
	Company based locally	TRUE	10	FALSE	0	10	
Financial Operations (Financial operations are strongly in shareholders' favour)	Company start-up was funded by local capital / funding (vs international / foreign)	All	10	None	0	10	40
	Company start-up was funded by private capital / funding (vs government investment)	All	10	None	0	10	
	Company start-up was funded by equity capital / funding (vs debt investment)	All	10	None	0	10	
	Gross margin percentage	100%	10	0%	0	10	
Competitor Profile (There are no direct local competitors)	Similar local goods or services in SA market	None	10	Large scale	0	10	40
	Similar foreign goods or services in SA market	None	10	Large scale	0	10	
	Threats of local entrants to SA market	None	10	Large scale	0	10	
	Threats of foreign entrants to SA market	None	10	Large scale	0	10	
Market Profile (Market size is large enough for the number of business competitors)	Local demand for new local goods or services	Large scale	10	None	0	10	60
	Local demand for new foreign goods or services	Large scale	10	None	0	10	
	Local demand for wider range of local goods or services	Large scale	10	None	0	10	
	Local demand for wider range of foreign goods or services	Large scale	10	None	0	10	
	International demand/capacity for goods or services	Large scale	10	None	0	10	
	International demand for SA goods or services	Large scale	10	None	0	10	
Sustainability Profile (The company is fully	Number of years in operation (1 point/year)	10 years or more	10	Less than 1 year	0	10	20
	Company operation is self-sustainable	TRUE	10	FALSE	0	10	
SWOT Analysis (There are many strengths, relative to	Ratio of strengths to weaknesses	High strengths, low weaknesses	10	Low strengths, high weaknesses	0	10	10
				TOTAL FOR OPTIMUM POSSIBLE COMPANY			**260**

The following six steps were performed for the thematic analysis, as per the procedural indications of Braun and Clarke (2006):

- Become familiar with the data, and note any initial ideas;
- Generate initial codes by capturing patterns that have any meaningful gain;
- Search the data for themes, and analyse the combinations of codes to form themes;
- Review the themes;
- Define and name the current themes; and
- Write the final report.

An example of the points awarded for the factors noted in the competitor and market profile questions of the questionnaire (see Appendix II) is presented in Table 4.2.

Table 4.2 Answers and points awarded for the competitor and market profile questions

Factors	1) Similar local goods and/or services (G&S)	5) Local demand for new local G&S
	2) Similar foreign G&S	6) Local demand for new foreign G&S
	3) Threat of entry by local G&S	7) Local demand for more local G&S
	4) Threat of entry by foreign G&S	8) Local demand for more foreign G&S
		9) Intl. demand for foreign G&S
		10) Intl. demand for South African G&S
Potential Answers	**Points in the case of competitor factors (factors 1-4 above)**	**Points in the case of market demand factors (factors 5-10 above)**
No, not at all.	10.000	0.000
Yes, but just from our goods or services	7.500	2.500
Yes, from a few other SME companies	5.000	5.000
Yes, from many other SME companies	2.500	7.500
Yes, from large scale or corporate pharmaceutical or biotechnology firms	0.000	10.000

4.3.4.2 Phase 2

In order to analyse the quantitative data from the second phase of the study, two techniques were applied: descriptive and inferential statistical analyses. As noted by Adams et al. (2007), inferential statistical analysis generates “inferences as to the nature of effects between elements in the data”, thereby allowing observations on how one element could influence another, and facilitating a fuller understanding of the complexity of a situation.

In the first step of the data analysis, as recommended by Agresti (2007), the data sets were coded with numerical values according to the corresponding answers to each of the six questions. For example, in response to Question 1 (on the company classification type), companies that responded in the category of ‘vaccines’ were coded with the numerical value 1, ‘biogenerics’ with the numerical value 2, and so on, as shown in Appendix III. By analysing the data with inferential statistical methods, answers to the following broad spectrum of concepts were sought:

- Does the classification correlate or associate with the activity state?
- Does the classification correlate or associate with the start-up spending?
- Does the classification correlate or associate with the size?
- Does location correlate or associate with the classification?
- Does location correlate or associate with the activity state?
- Does the location correlate or associate with the spending?
- Does the production type correlate or associate with the activity state?

- Does the production type correlate or associate with the spending?
- Does the production type correlate or associate with the size?
- Does the spending correlate or associate with the activity state?

A central aspect that was sought from the data was to observe, using the 'activity level' of the companies as the dependent variable for the multiple logistic regression, whether any or all of the variables were associated with, and perhaps 'influenced' the success or sustainability of the companies. This was achieved by considering the active company states as a sign of sustainability, and closure or sale of the companies as a sign of unsustainability.

In order to observe the above correlations and associations, statistical tests such as Pearson's Chi-Square, Analysis of Variance (ANOVA), bivariate correlation, linear regression, logistic regression and multinomial logistic regression were performed on the Sample 2 data, with details in Appendix III of which tests were performed for each analysis.

Contingency tables and Chi-Square (χ^2) analyses: These are performed to determine if categorical variables are associated (Adams et al. 2007). It, thus, allows a researcher to determine if the values in several categories differ from their predicted values (Agresti 2007), or as noted by Saunders et al. (2009), to test whether two variables that are grouped into discrete classes are associated. One specific test, the Chi-Square Test of Independence of Categorical Variables is used to determine whether the outcomes of one variable are dependent on the value of another variable, whereby the null hypothesis is stated as follows (Elevers 2014a):

H_o: The two variables are independent of each other
H_1: The two variables are not independent of each other

These hypotheses are represented by the equations:

H_0: $$\sum\sum(\boldsymbol{O}-\boldsymbol{E})^{\mathbf{2}}=\mathbf{0} \quad \textbf{[1]}$$

H_1: $$\sum\sum(\boldsymbol{O}-\boldsymbol{E})^{\mathbf{2}}\neq\mathbf{0} \quad \textbf{[2]}$$

Where:

O is the observed frequency; and
E is the expected frequency.

ANOVA: As noted by Elevers (2014b), ANOVA is an inferential statistical test that allows the researcher to test and observe if any of several means are different from one other. As explained by Saunders et al. (2009), it is a method of testing whether three or more groups or categories of data are different, by analysing the spread of data values or variance within and between the groups of data from their means. The *F* ratio or *F* statistic is the outcome of these differences, whereby a large *F* ratio, with a probability (p-value) of less than 0.05, indicates that the likelihood of any difference between groups occurring by chance alone is very low (Saunders et al. 2009). It

should be noted that central to ANOVA is that dependent variables (DV) should be continuous, since data continuity allows the mean to be calculated. Conversely, independent variables (IV) should be categorical (Adams et al. 2007). However, to allow for ordinal data to be analysed, a standard procedure is performed in social research, which allows ordinal data to be treated as continuous, provided the interval between each ranked level is uniform (Saunders et al. 2009).

There are three other primary assumptions for ANOVA, which are that the observations are independent, that the sample data sets have a normal distribution, and that the scores in different groups have similar variances (Saunders et al. 2009). The null hypothesis for ANOVA is stated as follows (Elevers 2014b):

H_o: There is no difference between the means of the different groups or categories
H_1: There is a significant difference between the means of the different groups or categories

These hypotheses are represented by the equations:

H_0: $$\mu_a = \mu_b = \mu_c = \mu_d \quad [3]$$

H_1: $$\mu_a \neq \mu_b \neq \mu_c \neq \mu_d \quad [4]$$

Where:

μ_a is the mean of the DV corresponding to group (a) of the IV
μ_b is the mean of the DV according to group (b) of the IV … and so on.

In order to conduct One-Way ANOVA tests on the data (one IV and one DV), the 'activity state' variable was ranked on an ordinal scale of one to six relative to sustainability, with the least sustainable option of 'closed before operation began' ranked lowest, and 'in general operation' ranked highest. Codes used in the analysis are presented in Appendix III. In order to satisfy the requirements of ANOVA, the difference in magnitude between the numerical values of one and two were assumed to be the same as between the values two and three, or the rank difference in sustainability between 'closed before operation began' and 'closed or no longer in operation' was considered to be the same as between 'in R&D phase' and 'ready to launch'.

Furthermore, while the sale, exit, or globalisation (transfer) of an organisation out of the country is arguably not a failure of the organisation (and indeed the goal of many entrepreneurs), for the sake of this study, such a company was regarded as no longer being within the category of a locally sustainable company. For the purpose of this study, it was assumed that, had South Africa been the most optimum location for the company, it would have continued to be based in South Africa, even after the sale and while under new ownership; thereby, continuing to expand into the international market from South Africa. For the sake of this dissertation, sale out of the country was thus assumed to mean that a local requisite was not being fulfilled. The rank of this category was positioned between 'closed or no longer in operation', and 'still in R&D phase'. Based on this assumption, the 'activity state' variable was analysed in the ANOVA tests.

Bivariate correlation: This may be used to conclude whether two ranked or numerical variables are linearly related to one another (Elevers 2014c). The Pearson's Product Moment Correlation Coefficient (PMMC), 'r', is a system of measurement that observes the degree of linear association between variables, by calculating a value between +1 and -1 (Saunders et al. 2009). An 'r' value close to +1 indicates a strong positive association, while an 'r' value close to –1 indicates a strong negative association (Adams et al. 2007). As described by Saunders et al. (2009), if both variables contain numerical data, PMCC can be used to assess the strength of a relationship; while if one or both of the variables contain ranked data, a different correlation coefficient should be used that factors ranked data, such as Spearman's Rank Correlation Coefficient (Spearman's rho, ρ) or Kendall's Rank Correlation Coefficient (Kendall's tau, τ). For this study, PMCC was calculated for the numerical data, and both Spearman's rho and Kendall's tau were calculated for the ranked data.

Linear regression: This form of regression is generally used as an inferential statistical technique to help to explain the changes that may result in one phenomenon as a result of one or more other influencing variables (Adams et al. 2007). Elevers (2014d) explains it simply as a technique of specifying the nature of the relation between two variables, whereby if the value of one variable (the IV) is given, the value of some other variable (the DV) can be predicted. It is therefore a major tool of statistical modelling. In contrast to the correlation coefficient (r), the regression coefficient r^2, or coefficient of determination, allows the strength of a relationship between a numerical DV and one or more numerical IVs to be assessed, based on a score between 0 and +1 (Saunders et al. 2009). The linear regression equation typically takes the form (Elevers 2014d):

$$\mathbf{DV} = \beta \times \mathbf{IV} + \alpha \qquad \textbf{[5]}$$

Where:

DV is the predicted or dependent variable;
IV is the predictor or independent variable;
α *is the regression constant or Y-intercept of the linear graph; and*
β *is the slope coefficient of the independent variable.*

Logistic regression: For variables containing categorical data, linear regression is not possible, and logistic regression or multinomial logistic regression are conducted instead (Adams et al. 2007). Also known as the logit model, logistic regression is used to model dichotomous outcome DVs, while multinomial logistic regression is used to model DVs with multiple values (Institute for Digital Research and Education 2014). In such statistical analyses, the regression coefficient r^2 does not exist; however, various "pseudo R-Square" values have been devised in order to fulfil its function, such as the Cox and Snell R-Square, and the Nagelkerke R-Square (Agresti 2007; Institute for Digital Research and Education 2014).

In this study, logistic regression and multinomial logistic regression were performed with a goal of observing whether the 'activity state' (DV), and therefore sustainability of the companies in Sample 2, had been affected or influenced by any of the other variables (IV). Activity level was analysed with multinomial logistic regression using the standard six coded categories, while for the logistic regression it was further coded into two (dichotomous) states of either active (locally sustainable) or inactive (locally unsustainable), considering the states of 'in general operation' as a sign of attaining sustainability, and all other traits as being outside of the state of sustainability in South Africa (see Appendix III).

All data for the quantitative phase of the study were analysed using the IBM statistical analysis software SPSS, as recommended by Adams et al. (2007), and explained by Elevers (2014a; 2014b; 2014c; 2014d) and the Institute for Digital Research and Education (2014).

4.4 BIAS

The purpose of this study was an academic reflection of the existing climate of health technology in South Africa, and all data collection was carried out exclusively as a factual observation of the industry, devoid of any political motivations, biases, private views or personal opinions.

According to Saunders et al. (2009), refusals to respond to both individual questions and entire questionnaires or interview schedules, present a form of bias. This is due to the refusal by respondents to respond; the inability to locate a respondent; ineligibility of the respondent to respond; and the ability to locate a respondent, but inability to make contact with them. Each of these was a factor in this research, particularly in the second phase of the study. Additionally, survivorship bias (formed by having a lower chance of contacting information on individuals or companies that have not 'survived' and a higher chance of locating information on individuals or companies that have), was certainly a factor, where locating individuals from defunct companies, at times, proved challenging.

To minimise any bias due to the inability to locate a respondent (thus, limiting survivorship bias and maximising the study's validity), information on Sample 2 was researched as thoroughly as possible from the desktop study research instrument to acquire as reliable information as possible for the data. This was also supported with any direct data that could be acquired from the former shareholders. A surprisingly large amount of information was still available in the public domain, even on companies that were no longer in operation; and as mentioned previously, the cell-phone numbers and email addresses of former company owners were often still active, thereby aiding to minimise the survivorship bias. To eliminate the potential for bias from non-response (of all companies, including active ones), the researcher was thorough in attempting to approach the sample, and assured the respondents of the confidential nature of the study. Due to the potentially delicate nature of the information, though, non-response was a factor of bias that had to be considered for this study.

4.5 ETHICAL CONSIDERATIONS

4.5.1 Private business

The information that was discussed was typically of a private business nature, and could therefore have had implications for the respective companies involved. Due to the fact that actual company brands and private undisclosed company information were analysed, there was an ethical duty on the part of the researcher to consider the repercussions of publishing such information. Furthermore, there was a duty to inform the respective companies involved in the study that this was an academic study for non-commercial purposes, and it was also necessary to define which logistical and strategic company information could be openly divulged (as it was in the public domain), and which should be treated as confidential. Furthermore, there was an ethical obligation to uphold the trust of any information that was presented for the study, and respect the wishes of the individual company shareholders to treat the information as strictly confidential. It was ethically necessary to remove the names of companies, and to use numerical codes for companies instead of actual names, since company names and the names of shareholders were inconsequential to the overall results and objectives of the study.

Respondents were provided complete information about the study at all times, and during all communications. Respondents were provided a letter of informed consent via email during all interactions, and respondents were informed of their rights not to answer, or to withdraw from the study at any time if they so wished.

4.5.2 Resulting effect of the study

It was important to consider the resulting effect that any information from this study could have had on the biomedical and biotechnology environment and, therefore, the patients and public consumers in South Africa. The study was completed in such a manner that there should be no repercussions that could harm the reputations of individual companies, any sectors of the biotechnology industry, any types of goods and services used, any types of research being conducted, or the availability of these goods and services to the patients and consumers who use them.

4.5.3 Environmental impact

The study was carried out with a minimal negative impact/cost on the environment. Where possible, printing of emails, documents, faxes and any other correspondence was kept to an absolute minimum. Transportation, such as air- and overland-travel for the purposes of data collection, scientific advice and thesis compilation was only conducted when absolutely necessary, and wherever possible, research was conducted via telephone, email, video conference, social media and other environmentally responsible means.

4.6 LIMITATIONS OF THE STUDY

There were various limitations that the researcher faced during the study, which hindered the extent and scope of the study. Some of the significant issues included:

Location: The researcher was based in Tehran during the course of the study, while the scope of the study covered companies and organisations all over South Africa. As a result, it proved complex to harness the necessary information from all areas in equal detail and reliability. Strict quality demands and effort were needed to overcome any limitations in this regard. Being based internationally did, however, allow an even national perspective of the country to be drawn, without bias due to a proximity to companies in any one city.

Confidentiality: Due to the nature of the information that was gathered for the study, such as private company financial data, debt and liability statistics, details of funding providers and loan contracts, patented technical scientific property, as well as any other data of a confidential nature, it proved difficult at times to acquire the necessary information from many of the companies.

Data availability: Due to the relatively recent development of the commercial health technology sector in South Africa, data records on many companies were not fully up to date, or were incompletely represented in the literature. This required a thorough desktop study before companies could be approached in order to verify the legitimacy of the information from the desktop study.

4.7 DELIMITATIONS OF THE STUDY

This study focused on commercial health technology ventures in South Africa, which were within the size and business scale of standard SMEs; and it covered companies involved in health biotechnology, ‘high-tech’ medicine, and the remediation of human disease. Companies in support of these outcomes were categorised into the following groupings: vaccines; biogenerics; therapeutics; nutraceuticals; reagents; diagnostics products and equipment; medical devices; biotools; contract services; and public services. Companies or venture types that did not fit into these categories, or that were not specifically involved in the remediation of human disease, were excluded from the study. Industry types that were excluded thus covered the following:

- Agricultural, plant-based, environmental and industrial biotechnologies;
- Producers and suppliers of health technology for non-human recipients.
- Producers and suppliers of products for general health and wellness, such as vitamins and dietary supplements; and
- Producers and suppliers of general medical equipment and materials (such as hospital equipment, wound dressings, and so on).

During the correlation analysis phase of this study, the sizes of the companies were calculated using the number of employees as the determinant of size. Annual turnover was not included as a parameter, since many companies still in R&D phase or prior to launch may not have had an annual turnover, while still being sizeable ventures. While balance sheet total may have presented a different means of measuring financial size to include, this was also not included, since financial statistics are withheld or unavailable by respondents more frequently than employee numbers, and accruing more data on employee numbers was perceived as better than accruing less data on financial figures.

4.8 CONCLUSION

This ends the methods section of the dissertation. As discussed during this chapter, two phases of research were conducted. The first was based on an approach involving both qualitative and quantitative research methods, and the second was based on a positivist approach, involving almost exclusively quantitative research methods. Two samples were approached for each phase of the study, whereby a sample of 21 companies (Sample 1) was included in the first phase of the study, and 107 companies were included in Sample 2.

In the first phase of the project, a participant-observation was conducted in the form of an online questionnaire survey, while in the second phase, three data gathering techniques were applied: surveys, interviews and a desktop study. The data analysis techniques were also discussed. As explained, the study involved descriptive statistical analysis, data scoring and thematic analysis in the first phase, and descriptive and inferential statistics in the second. Each of the aspects of bias, ethics, the limitations and delimitations of the study were also discussed. The dissertation continues, in Chapter 5, with the results of the data analysis.

CHAPTER 5
RESULTS

5.1 INTRODUCTION

A detailed analysis of the data was performed in each of the two phases of this study. This chapter presents the results of that analysis. The chapter is structured in two parts, relating to the first and second phases of the study, respectively. It begins with the results of the first phase of the study, and the section is separated among the findings that were derived from the scoring system, and the thematic analysis. These findings pertain to the production process, company citizenship, financial operations, competitor and market profile, sustainability profile and the strength-weakness-opportunity-threat (SWOT) analysis of the companies in Sample 1. The section also includes the findings on the thematic analysis, which covers aspects such as the additional training that South African academic institutions should provide to enhance the country's HTV sector, as well as how the Sample 1 respondents perceived success, and an introduction to the aspects that were highlighted as keys for success in the South African macroenvironment.

The second part of the chapter presents the results of the second phase of the study, and provides a detailed overview of the results of the descriptive statistics, and the inferential statistical analyses that were performed. The inferential statistics included tests such as Pearson's Chi-Square, ANOVA, bivariate correlation, linear regression, logistic regression and multinomial logistic regression.

The chapter begins, next, with the results of the first phase of the study.

5.2 RESULTS OF PHASE 1: SMALL-SAMPLE MIXED-METHODS STUDY

In the first phase of this study, a general profile of questions was posed to the Sample 1 of HTVs to answer a range of questions pertaining to the general profile of the South African environment. As shown in Table 5.1, the general categories in the operational environment that were determined included the 'production process', 'company citizenship', 'financial operations', 'competitor profile', 'market profile', 'sustainability profile', and the 'SWOT analysis'; whereby, as explained in the methodology, responses from each of the respondents were graded and averaged on a ten-point scale to quantify how locally-centric the macro-environment was. Thus, points were awarded to indicate how much each function had been achieved locally, or by South African or independent means. For example, 100% in any category would have indicated that *all* of these actions had been achieved locally or by South African or independent means. This was not to say that local- or independent-means were necessarily 'better', but just that outside assistance had not been needed or acquired.

The category of ‘company citizenship’ appeared to present the strongest of South Africa’s company processes, where the average company citizenship was at 87.7% of the maximum possible (full ownership), as shown in Figure 5.1. The ‘production process’, ‘financial operations’ and ‘sustainability profile’ were all at analogous levels, of 61.0%, 67.5% and 63.5% of maximum, respectively, while the ‘competitor profile’ and ‘market profile’ were each around half of optimum for the country.

Table 5.1 General profile of the South African health technology environment

	[Each item is awarded points on a scale of 0 - 10 where 10=100% / True / Yes]							
Process	**Subcategory**	**Positive Answer**	**Points Awarded**	**Negative Answer**	**Points Awarded**	**Actual Points**	**Totals**	**Percentage of Maximum**
Production Process (Production is highly South Africa-centric)	Products manufactured locally	All	10	None	0	7.857	24.416	61.0%
	Products / raw materials sourced locally	All	10	None	0	4.619		
	Products researched / developed locally	All	10	None	0	7.190		
	Products supplied locally (or exported)	Local	10	Exported	0	4.750		
Company Citizenship (Company staff basis is highly South Africa-centric)	Company owned by South Africans	All	10	None	0	8.100	43.826	87.7%
	Company started by South Africans	All	10	None	0	8.650		
	Company operated by skilled South Africans	All	10	None	0	9.050		
	Company operated by unskilled South Africans	All	10	None	0	8.526		
	Company based locally	TRUE	10	FALSE	0	9.500		
Financial Operations (Financial operations are strongly in shareholders' favour)	Company start-up was funded by local capital / funding (vs international / foreign)	All	10	None	0	8.474	26.998	67.5%
	Company start-up was funded by private capital / funding (vs government investment)	All	10	None	0	7.588		
	Company start-up was funded by equity capital / funding (vs debt investment)	All	10	None	0	5.250		
	Gross margin percentage	100%	10	0%	0	5.686		
Competitor Profile (There are no direct local competitors)	Similar local goods or services in SA market	None	10	Large scale	0	7.656	20.067	50.2%
	Similar foreign goods or services in SA market	None	10	Large scale	0	2.679		
	Threats of local entrants to SA market	None	10	Large scale	0	6.875		
	Threats of foreign entrants to SA market	None	10	Large scale	0	2.857		
Market Profile (Market size is large enough for the number of business competitors)	Local demand for new local goods or services	Large scale	10	None	0	3.036	33.067	55.1%
	Local demand for new foreign goods or services	Large scale	10	None	0	5.769		
	Local demand for wider range of local goods or services	Large scale	10	None	0	4.167		
	Local demand for wider range of foreign goods or services	Large scale	10	None	0	6.429		
	International demand/capacity for goods or services	Large scale	10	None	0	7.500		
	International demand for SA goods or services	Large scale	10	None	0	6.167		
Sustainability Profile (The company is fully sustainable)	Number of years in operation (1 point/year)	10 years or more	10	Less than 1 year	0	6.912	12.701	63.5%
	Company operation is self-sustainable	TRUE	10	FALSE	0	5.789		
SWOT Analysis (There are many strengths, relative to weaknesses)	Ratio of strengths to weaknesses	High strengths, low weaknesses	10	Low strengths, high weaknesses	0	3.659	3.659	36.6%
	TOTAL FOR OPTIMUM POSSIBLE COMPANY		**260.000**			**TOTAL FOR AVERAGE SOUTH AFRICAN COMPANY**	**164.733**	

As represented in Figure 5.1, the lowest category was the SWOT analysis with a rating of 36.6%, indicating that the ratio of strengths and opportunities to weaknesses and threats, by number, was relatively low for the average company in South Africa. Results of each category are presented in detail in the following subsections.

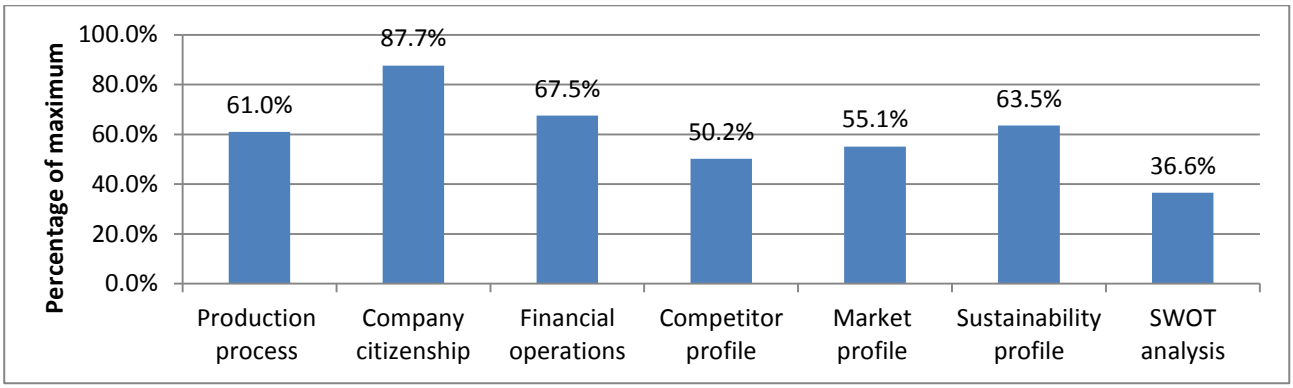
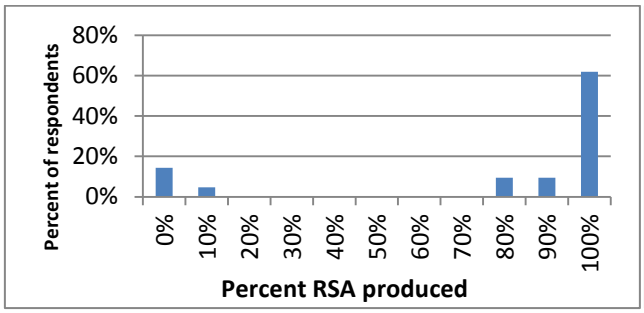


Figure 5.1 Profile of Sample 1 companies relative to maximum possible locally-centric values

5.2.1 Production process

On average, most companies noted that their goods and/or services (G&S) had either been researched or developed locally, and that their goods and/or services had been manufactured or produced locally. These were observed by score ratings of 7.190 and 7.875, respectively, out of a possible 10.000; whereby, a score of 10.000 would have signified that 100% of the companies had fully researched or produced their goods and services locally, as shown in Figure 5.2 and Figure 5.3.



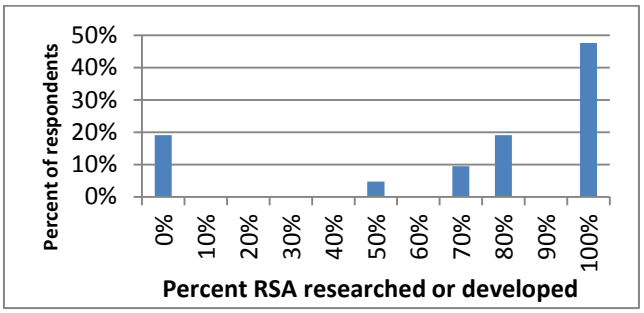
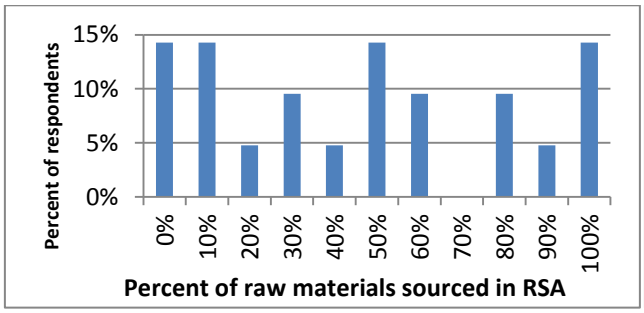


Figure 5.2 (Left) Percent of G&S produced in RSA by Sample 1
Figure 5.3 (Right) Percent of G&S researched or developed in RSA

The raw materials and supply of the products was far more internationally-focused for South African HTVs, whereby, as shown in Figure 5.4 and Figure 5.5, relatively even proportions of the sourcing of raw materials and distribution of the goods and services resulted in average scores of 4.619 and 4.750, respectively, out of a possible 10.000.



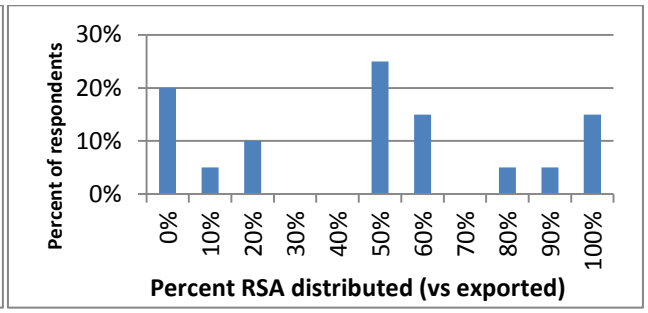


Figure 5.4 (Left) Percent of raw materials sourced in RSA by Sample 1

Figure 5.5 (Right) Percent distributed in RSA (as opposed to exported) by Sample 1

Thus, as noted in Table 5.1, the scores for the 'production process' in South Africa, which represent a measure of how locally-centric the company production is, totalled 24.416 out of a maximum 40.000, suggesting that production was at 61.0% of the optimum potential for the companies interviewed in Sample 1.

5.2.2 Company citizenship

The analysis of South Africa's 'company citizenship' strategy for HTVs included an analysis of five primary factors of the company, as shown in Table 5.1. Once again, respondents were asked to rate each of the aspects on a scale between 0% and 100%, where 0% meant they were all owned, started, or operated by foreign citizens, and 100% meant these actions were done locally or by South African citizens.

The average company indicated a relatively high company citizenship score, whereby the average score out of 10.000 for each of the five factors observed were all above 8.100, as shown in Table 5.1. Current company ownership was rated with a score of 8.100 in favour of South African citizens, and 8.650 for having been started by South African citizens. Thus, on average, 86.5% of companies from Sample 1 were started, and 81% were still currently owned by South African citizens.

A score rating of 9.050 out of 10.000 was observed for the proportion of South African citizens employed as technical or skilled staff, as opposed to foreign technical staff, and the proportion of unskilled staff was also relatively high, at 8.526. These figures suggest that, on average, 90.5% of the skilled tasks in the HTVs from Sample 1 were completed by South African citizens, and 85.26% of the unskilled tasks. The graphical distribution of the responses for this study are shown in Appendix IV.

Thus, as noted in Table 5.1, the scores for the company citizenship, which observed how South Africa-centric the staff basis was, totalled 43.826 out of a maximum 50.000. As stated previously, this formed the most optimum of the company categories, at 87.7% of optimum.

5.2.3 Financial operations

The analysis of South Africa's 'financial operations' strategies for Sample 1 HTVs included an analysis of four primary factors, as shown in Table 5.1. To observe the funding strategy of the company start-ups, respondents were asked to rate each of the above factors on a Likert-scale of 'all', 'mostly', 'moderately', 'equally', 'slightly', or 'none', while in order to observe the average profit margin as a percentage, respondents were asked to note what percentages of the selling price of their goods or services were spent on the costs of their goods or services.

The results of each of the first three factors of the 'financial operations' are shown in Figure 5.6. Most of the companies were able to source funding locally, instead of abroad (blue line); whereby, 84.2% of companies were either fully or mostly funded locally. This funding trend plateaued with only 5.3% of companies being either equally, slightly or not-at-all funded by local means during their start-ups. The trend for private versus government funding (red line) was similar to the local versus foreign funding trend, but leaned towards a need for government funding. In this category, 70.6% of the South African companies approached were either all or mostly privately funded, and 29.4% had received some government involvement, with 23.5% being equally (or more) funded by government investment. The third and final factor observed, which considered the ratio of equity to debt investment (green line), presented a far more even curve. Half of companies were either equally, or more funded through debts or liabilities, and half were moderately, mostly or fully funded through equity investment by the shareholders. The difference between all equity and all debt was 31.3% and 18.8%, respectively.

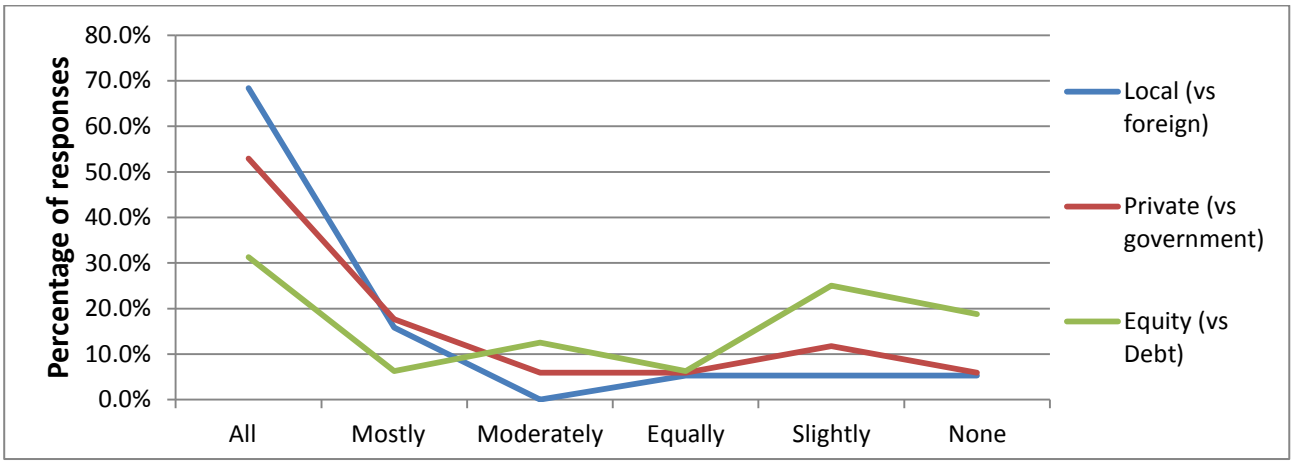


Figure 5.6 Funding sources for the companies in Sample 1 by local, private or equity means

To rate each of the 'financial operations' categories into a scale comparable to the other company processes (on a 10.000-point system), the Likert-scale responses were allocated points as follows: all (10 points); mostly (8 points); moderately (6 points); equally (5 points); slightly (2 points); and none (0 points). As shown in Table 5.1, the local funding category received an average rating of 8.474, the private funding category received a rating of 7.588, and the equity/debt category received a rating of 5.250, out of a possible 10.000.

Companies mostly noted that between 20% and 50% of their selling prices were spent on costs for their goods or services, as shown in Figure 5.7; with a few outliers in the case of companies that had relative costs as low as 12%, and as high as 75% of their selling prices, respectively.

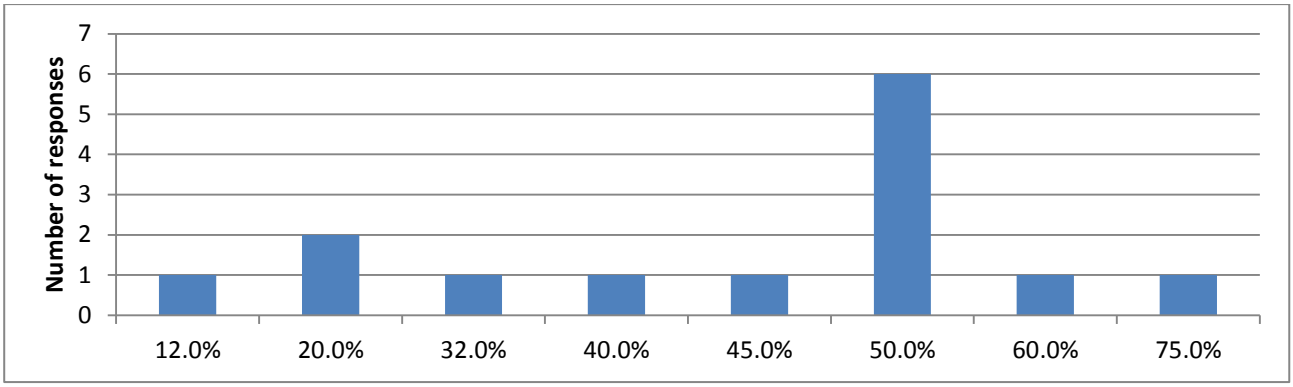


Figure 5.7 Percent of the selling price of goods or services spent on costs for these goods or services

Based on the equation for calculating profit margin (PM) as a percentage, as follows, the average profit margin for the research sample could be calculated:

$$\boldsymbol{Profit\ Margin\ (PM) = Total\ Sales\ Revenue\ (TSR) - Cost\ of\ Sales\ (CS)} \quad \textbf{[6]}$$

The average profit margin for the research sample would, therefore, be:

$$\boldsymbol{Average\ PM = Average\ TSR - Average\ CS} \quad \textbf{[7]}$$

Where:

$$\boldsymbol{Average\ PM\ (as\ a\ percent) = 100\% - \frac{\sum(All\ respondent\ CS\ as\ a\ percentage)}{Number\ of\ respondents}} \quad \textbf{[8]}$$

Thus:

$$\begin{aligned} Average\ PM\ (as\ a\ Percent) &= 100\% - \frac{604\%}{14} \\ &= 100\% - 43.1\% \\ &= 56.9\% \end{aligned} \quad \textbf{[9]}$$

The average PM of 56.9% by the companies suggests that on average, more than half of the selling price of the goods and services of the companies approached constituted profit. Converting this into a score out of 10.000, an average PM of 59.6% implied a score of 5.960. Therefore, as noted in Table 5.1, the scores for 'financial operations' totalled 26.99 out of a maximum 40.000 for the Sample 1 companies, suggesting that companies were at 67.5% of their optimum potential scores.

5.2.4 Competitor and market profile

To present an overview of each of the Sample 1 competitor and market demand profiles, respondents were asked to rate ten factors on a Likert-scale, as shown in Table 5.1, and these were converted to a numerical value according to the points system described previously, in Table 4.2. The purpose of this was to attempt to quantify the amount of direct local competition faced by the companies; and secondly, to determine whether the market size and potential was large enough for growth. Rather than grouping all of the company information together, individual variations were observed between different types of companies. This was done to allow different profiles to be drawn for each type of company function, and thereby to determine any variations between them. The companies were grouped into the three main categories, based on the nature of their business: diagnostic and medical devices; vaccines and biogenerics; and public and contract services; for example, where public and contract services included companies that provided services such as bio banking or stem cell banking.

As shown in Figure 5.8, vaccine and biogenerics companies showed very little competition from similar local goods or services compared to either the diagnostics and medical devices, or public and contract services, respectively; but, they showed the highest competition from similar foreign goods and services compared to the other company types. Vaccines and biogenerics also showed more drastic fluctuations between the threats of entry by local and foreign products, but the highest average scores for business potential in the international market. Public and contract services showed a generally lower risk of competition in South Africa due to either local or foreign threats, compared to the other company types; but, the lowest average potential for business in South Africa or abroad compared to the other groups. The diagnostics and medical devices showed a moderate threat of competition in South Africa, but also a moderate-to-high potential for local and international business, with the average potential for South African products on the international market rated as highly as the vaccines and biogenerics products.

All the company types noted relatively higher values (and, therefore, lower competitor threats) from similar existing local goods and services, or even from the entry of similar local goods and services, compared to the presence or entry of foreign products. This suggests that the companies were more concerned about the entry of foreign products to their markets than about the South African products currently existing in, or entering into the market. The average scores of 7.000 and 1.250 for vaccines and biogenerics, for example, relating to the threat of entry of local and foreign goods and services, respectively (factors three and four), implied that very few South African firms were likely to start forming directly competitive products; but foreign entrants — of the magnitude of large scale corporate pharmaceutical or biotechnology firms — were likely to enter the South African market. Similarly, however, scores of 8.000 and 8.125 for the international demand of foreign and South African products (factors nine and ten), respectively, implied that vast potential

also existed on the global market for South African vaccines and biogenerics products — also of the magnitude of large scale corporate pharmaceutical or biotechnology firms.

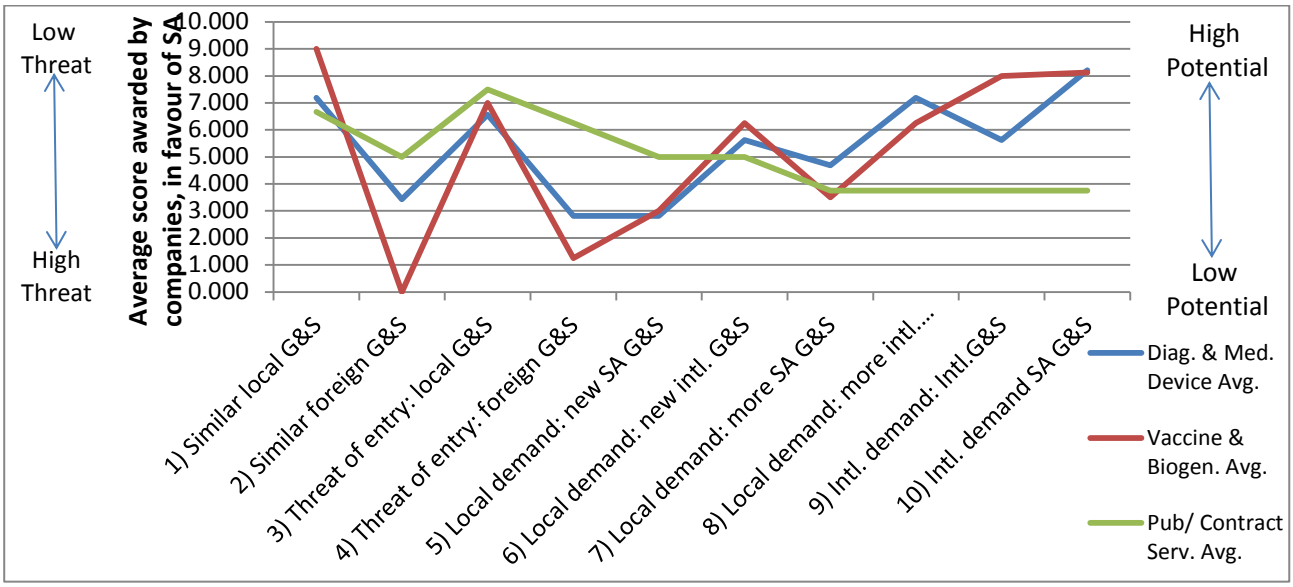


Figure 5.8 Average scores of the competitor threats and market potential for either diagnostics and medical devices, vaccines and biogenerics, or public and contract services, rated in favour of the South African market

The points in the general profile (Table 5.1), which considered all values from each of the companies, combined, suggested that while there were typically few similar local products currently in South Africa, considerable similar foreign products were currently available. The threat of new foreign products was also above average. Local demand for new local products appeared to be low throughout all of the categories, but higher when foreign products were being considered. In each of the categories, combined, international demand was higher than local demand; and while the international demand for foreign goods and services rated higher than the international demand for South African goods and services, a score of 6.429 for South African products abroad suggested a considerable overall potential for goods and service export. Overall, the competitor environment among the sample was rated at 20.067 out of a maximum 40.000, or 50.2% of its optimum potential score; while the demand was rated at 33.067 out of a maximum 60.000, or 55.1% of its optimum potential score.

5.2.5 Sustainability profile

The sustainability of Sample 1 companies in South Africa's health technology market was observed as a measure of whether the companies were able to operate as independent, fully sustainable ventures. Two factors were observed, as shown in Table 5.1, which included the number of years that the company had been in operation (1.000 point awarded per year, up to a maximum of 10.000), and whether the company's operations were self-sustainable (10.000 points awarded for 'Yes', 0.000 points awarded for 'No').

Companies presented answers with an average score of 6.912 to depict their number of years in operation, and 5.789 to depict their level of self-sustainability. On average, therefore, companies in Phase 1 of the study had been in operation for nearly seven years, and slightly over half had reached a level of sustainability (9 out of the 19 who furnished an answer for this question). One of the companies, for example, noted that sustainability would be reached

> *"Within 3 years, subject to the requested fund from Government funding agencies" (Company N).*

A significant number of the respondent companies highlighted that they were never able to reach a level of sustainability, and had been forced to close down. Sustainability was considered in further detail in the second phase of the study.

5.2.6 SWOT analysis

In the final points-rated category of this study, Sample 1 organisations were asked to rate the greatest opportunities or strength dynamics of the South African health technology industry, and its most significant weaknesses or threats, thereby presenting a SWOT profile.

5.2.6.1 Market strengths

The respondents from the Sample 1 concurred in their opinions of the strengths of the South African health technology market. The most commonly noted strength was in the category of South Africa's market opportunities (MKT OPPRTY); whereby, as shown in Figure 5.9, 23.3% of respondents noted this as one of the country's key strengths. The table in Appendix IV presents the variations of comments that were noted within each of the respective categories; and in the MKT OPPRTY category, strengths from "large domestic markets for products in HIV and TB" (Company I), access to the "developing markets" (Company U), and "increasing [international] exposure" (Company Q) were all noted by the respondents. One respondent, for example, noted "There are great market opportunities, both in SA and internationally" (Company C).

Support by the government (GOVT) was rated as the second-most-frequent category of strengths by respondent companies, being noted 16.7% of the time, or by five different companies. This category included comments such as support from "The government as the major customer in healthcare" (Company N), "Government tenders and R&D tax rebates" (Company U), "SA [being] open for biotech advances (e.g. GMO regulation and perception) compared to Europe" (Company B), and the Department of Trade and Industry having "programmes to assist exporters" (Company C).

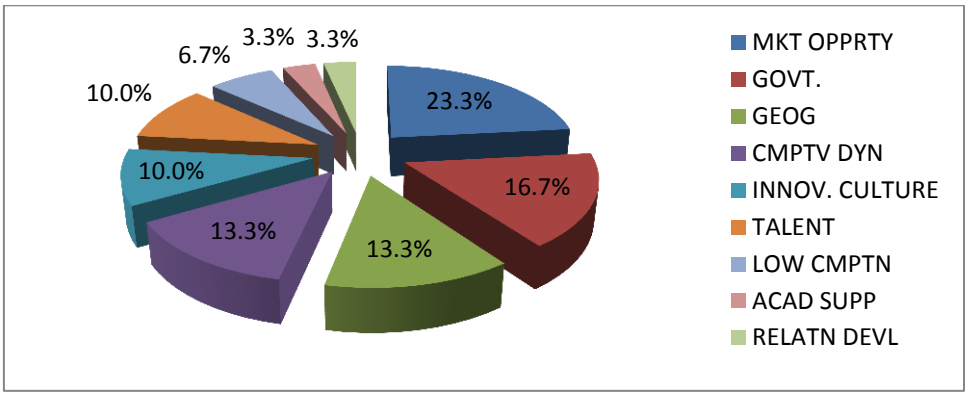


Figure 5.9 Strengths in RSA's health technology market, by percentage recurrences

South Africa's geographical location (GEOG) and competitive dynamics (CMPTV DYN) were each noted with a frequency of 13.3% of responses, and covered aspects such as South Africa's central global location, its "opportunity to service and serve as [a] gateway to [the] growing African market" (Company K), and its natural resources. The competitive dynamics covered aspects such as "Competitive pricing" (Company A) – relative to the developed markets, its "Relatively cheaper R&D costs" (Company L), its "High price of imported drugs that the public has to pay for" (Company N), and "Cheap labour rates relative to international [countries]" (Company D).

While noted with a lower frequency, other strengths were noted, such as South Africa's innovative, entrepreneurial culture (INNOV CLTR); the quality of the country's universities and scientific research (TALENT); academic support (ACAD SUPP); few competitors (LOW CMTN); and the scope to develop business through relationship building (RELATN DEVL).

5.2.6.2 Market weaknesses

A proportionally higher number of weaknesses were noted by the respondent companies, though, relative to the quantity of strengths described. For example, while 30 individual strengths were highlighted across nine categories, 52 types of weaknesses were highlighted across 13 categories of factors. This presented a ratio of 1:1.73, with a point rating of 3.659 for the company process in Table 5.1, out of a possible 10.000.

The primary weakness that was listed by the respondent companies included the lack of financial backing (FUNDS). This included a "Lack of early-stage funding" (Company B), "Insufficient venture capital for start-ups" (Company C), "[poor] foreign investor confidence (economic stability)" (Company K), and a "limited, risk averse venture capital pool" (Company K). The problem of a lack of funds was listed 12 times by the respondent companies, constituting 23.1% of the combined list of weaknesses in the South African environment, as shown in Figure 5.10 and Appendix IV. Although they were rated as independent categories, problems with foreign currency (FOREX) and costs of operation (COSTS) were each listed in recurrence by the respondents in 9.6% (n=5) and 5.8% (n=3) of cases, respectively, which when combined with the country's financial issues, formed the most significant barrier to company operations, at 38.5% of the country's shortcomings.

The second-most-frequently listed country weakness was a lack of skills (SKILL) in the country; whereby problems, such as “limited expertise and networks enabling global market penetration” (Company K), “Scarce skills” (Company U), “Shortage of foreign skilled workers” (Company I), and “Insufficient human resource capacity and skills” (Company I), were listed more than eight times. While other less-frequently-noted weaknesses also existed, one weakness that was highlighted repeatedly was the aspect of weaknesses in South Africa’s market (MKT).

This referred to issues with “Market size” (Company A), corporate monopolies, Chinese imports, and overcoming long-standing network alliances between brands.

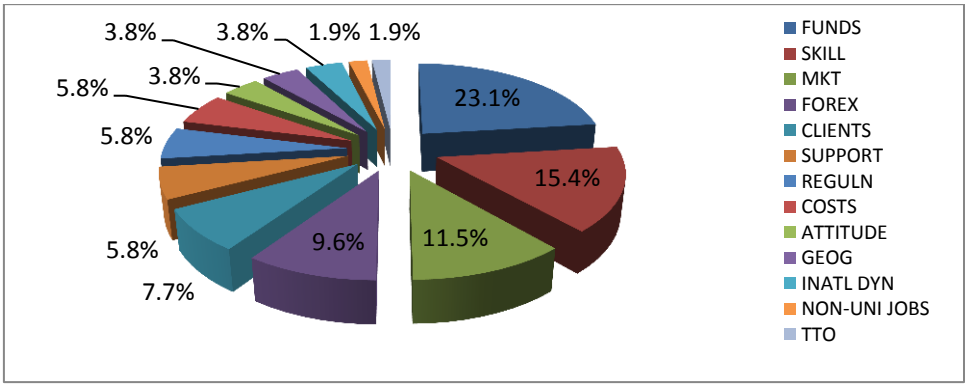


Figure 5.10 Weaknesses in RSA’s health technology market, by percentage recurrences

5.2.7 Company growth

Company growth was observed as an indication of changing sustainability over recent years. Five main characteristics were observed: growth in the number of product types or services (Figure 5.11), growth in the number of staff employed (Figure 5.12), growth in the number of dealers or branches (Figure 5.13), growth in the number of products sold or clients (Figure 5.14), and growth in the companies’ turnovers (Figure 5.15). Each of these characteristics was observed as a *percentage growth*, over the years 2010 to 2013, with each year presented as a percentage increase or reduction relative to its preceding year. As shown in Figure 5.11, any movement below the X-axis constituted negative growth (recession), while on-or-above the X-axis represented no change, or growth, respectively. For example, Company P (a contract services company) observed no growth between 2010 and 2011, but a 150% growth from 2011 to 2012 when it’s two service types were expanded to five. Between 2012 and 2013, Company P’s five services remained unchanged, represented by a percentage growth of 0% in 2013. In the case of Company Q (a medical devices company), though, eight product types in 2010 saw a 50% reduction between 2010 and 2011 to only four product lines. This remained unchanged until 2013, when the company was closed, and its reduction of four product lines to zero was represented by a further 100% negative growth. It should be noted that an increase of 10 to 20 (100% growth) would have seemed similar to an increase of 100 to 200 (also 100% growth), thus allowing growth in relatively smaller SMEs to be equated to growth in larger ones.

Figure 5.11 Percentage growth in the number of product types or services

As shown in the figures, most of the companies from Sample 1 saw considerable growth in each of the five categories between the years 2010 and 2012. The numbers of product types, for example, showed either a consistent number, or no growth from 2010 to 2011, but growth between 2011 and 2012. Companies that had seen a negative growth between 2010 and 2011, showed a slowdown in percentage reduction between 2011 and 2012.

However, 2013 appeared to be a slow year for company growth (based on annual reports and company figures from the respondents at the time of the study), with most companies showing either a slow-down in their percentage growth, or (in the case of Company Q) a negative growth. The highest average percentage growth for the number of product types or services, average number of products sold or clients, and average company turnover categories were at 40.5%, 19.6% and 43.6%, respectively, in 2012. Conversely, 2011 showed the highest percentage growth for the number of staff employed and the numbers of dealers, or branches and outlets, at 42.3% and 97.5%, respectively. After the 0% baseline percentage of 2010, 2013 showed the poorest percentage growth, with three of the categories — number of product or service categories, number of staff employed, and the number of clients or products sold — showing negative growths of -9.4%, -2.7% and -25.9%, respectively.

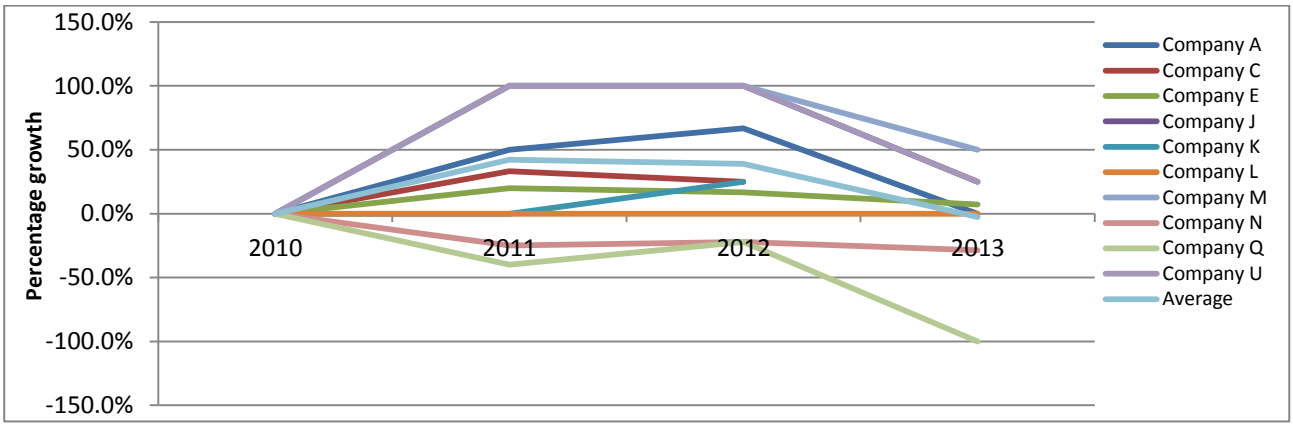


Figure 5.12 Percentage growth in the number of staff employed

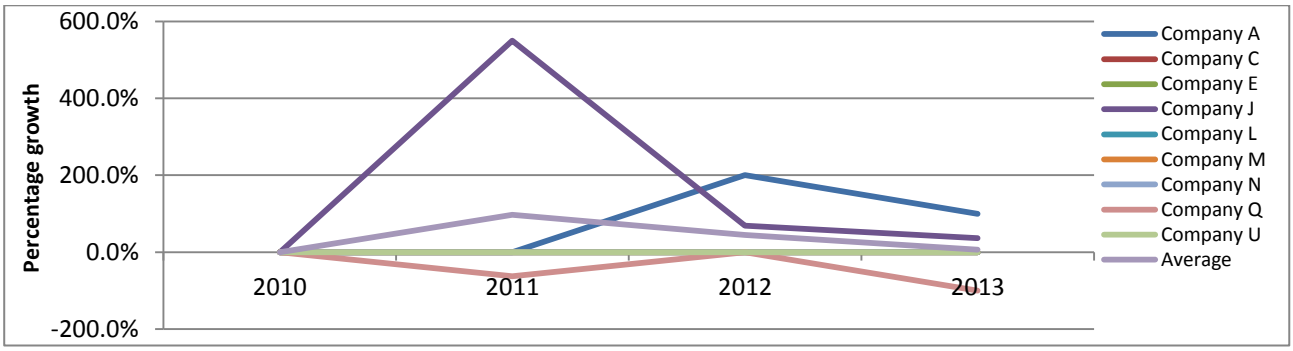


Figure 5.13 Percentage growth in the number of dealers or branches

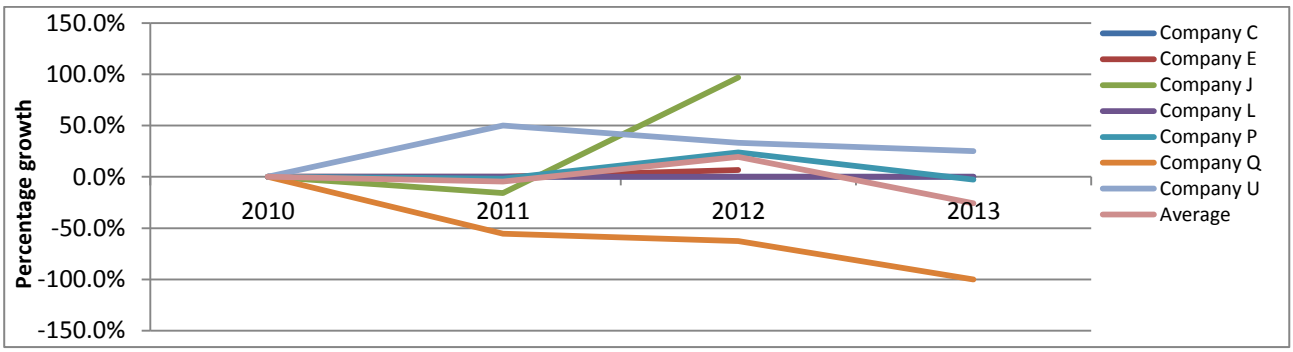


Figure 5.14 Percentage growth in the number of products sold or clients

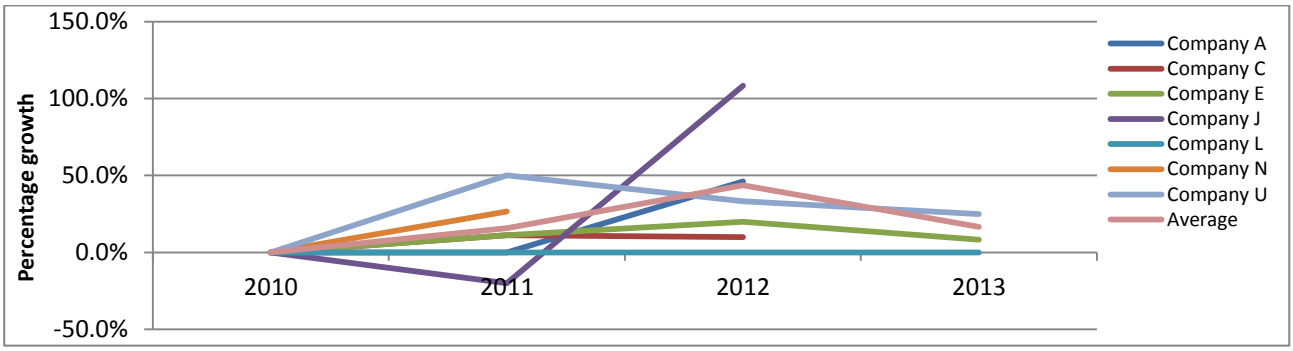


Figure 5.15 Percentage growth in the companies' turnovers

5.2.8 Additional training for South African universities

When asked what additional training South African academic institutions should offer to better prepare students for the South African job market, three primary categories of answers emerged: 'inter-disciplinary training', 'practical or industry experience', and 'academic institution changes'. The vast majority of answers (62.8%) fell within the category of inter-disciplinary training, as shown in Figure 5.16.

Respondents noted that students should receive training (apart from scientific training) in commerce (COMMR); entrepreneurship (ENTREP); finance (FIN); business and business management (BUS); law (LAW); marketing (MKT) and sales (SALES); intellectual property management (IP); medical technology and BTech (TECH) and various "Cross-discipline technical skills (mechatronics, IT, life sciences)" (Company K). This was exemplified by two statements:

"Combine life science degrees with training in business skills and entrepreneurship" (Company B); and “[training on] how to start their own business" (Company C). The graphical distribution of all answers is shown in Figure 5.17.

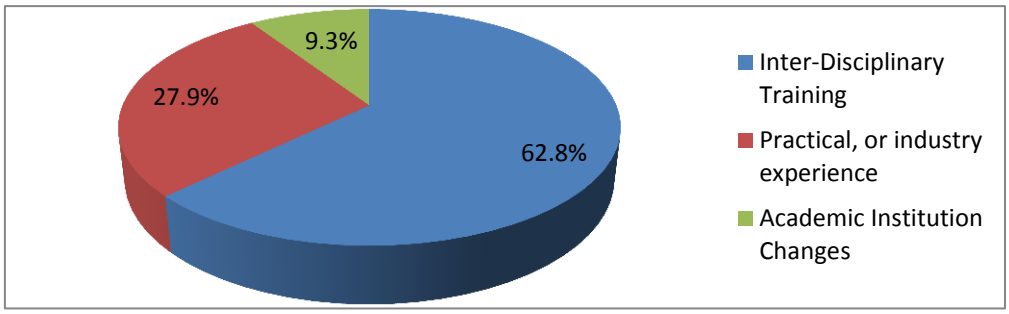


Figure 5.16 Changes that should be made in RSA’s universities, by percentage repeats

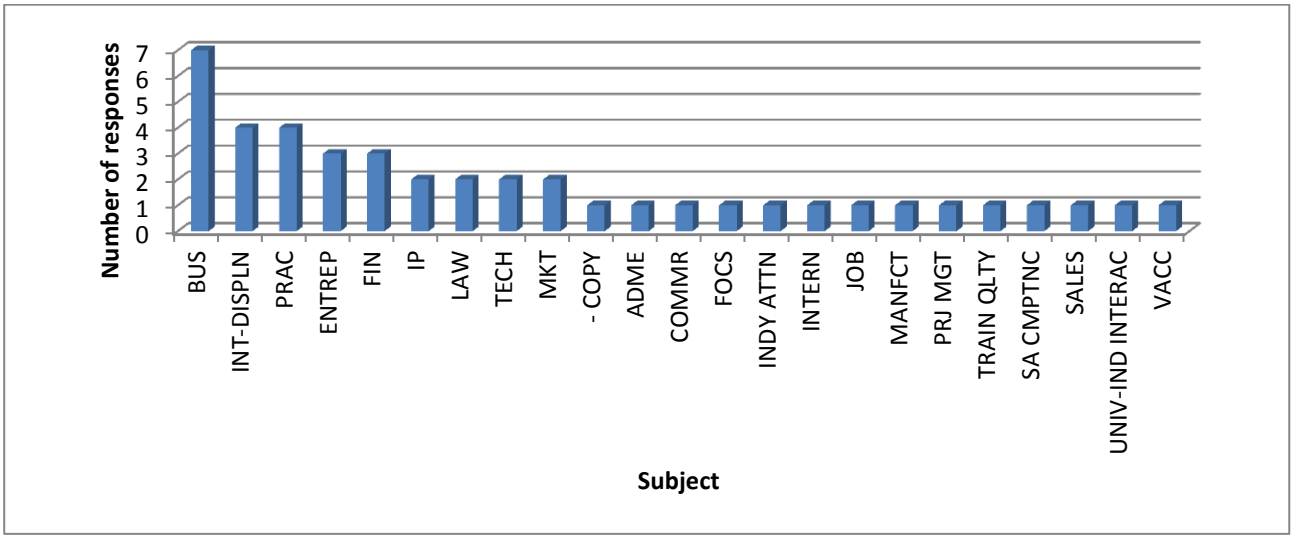


Figure 5.17 Profile of changes that South African universities should make to better prepare students

Suggestions that related to practical or industry-related experience included “more practical experience” (Company P), “more industrial focus / practice knowledge” (Company E), “QA and QC training including GMP codes as applied to manufacturing” (Company N), “training in ADME for drug development” (Company H); and “attention to [the] vaccine industry and requirements” (Company E).

While academic institution changes constituted the smallest of the response categories, one respondent made a suggestion for universities to introduce “Internships for scientists and engineers with business mentors” (Company L). Another respondent suggested (Company U):

> *“"Inter-faculty courses should be offered to equip graduates with the necessary skills to enter the job market, e.g. scientist also having a law and business elective".*

5.2.9 Determinants of success

When asked to distinguish what constituted the primary determinants of success for the companies in the study, a relatively even distribution was evident between 'human factors', and 'financial factors'. Human factors included aspects, such as humanitarian benefit, skills development, organisational growth, quality of products, and "Reaching [a] scientific and commercial proof-of-concept" (Company L).

Financial factors outweighed the human factors in a ratio of 1.2:1, though, and most respondents listed return on investment (ROI), profit, international business and the "Trade sale [at] EXIT" as the primary determinants of success of their organisations, as shown in Figure 5.18 and Figure 5.19, respectively. ROI was the single-most-noted factor, whereby one of the participants was honest in stating "[it is] given as humanitarian benefit, but really [it is] ROI" (Company R).

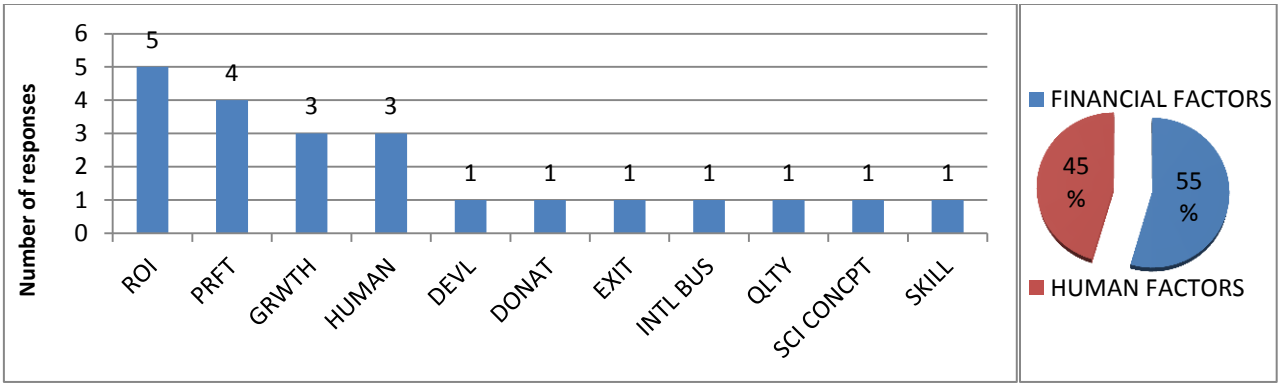


Figure 5.18 (Left) Profile of factors that constitute success for the companies in this study
Figure 5.19 (Right) Proportions of factors constituting success

5.2.10 Keys for success

A final question that was asked of the Sample 1 respondent companies was to describe their suggestions for success, such as 'what had made their company a success'. Respondents were forthcoming with various, primarily qualitative answers. It is of value to present and deliberate these during the discussion and conclusions of the dissertation (Chapter 6).

5.3 RESULTS OF PHASE 2: QUANTITATIVE, OR POSITIVIST STUDY

In order to analyse the quantitative data from the second phase of the study, two techniques were applied: descriptive and inferential statistical analyses. To do so, Pearson's Chi-Square, Analysis of Variance (ANOVA), bivariate correlation, linear regression, logistic regression and multinomial logistic regression were performed on the Sample 2 data. The results of these tests are described, next.

5.3.1 Descriptive statistics

The results of the descriptive statistical analyses of the Sample 2 data revealed a fuller overview of the general climate of the health technology sector in South Africa, since a wider number of companies from the sector was studied compared to Sample 1. In terms of the production style of the companies, the most popular method of production of the goods and services for the companies in Sample 2 was by developing, manufacturing, and/or producing the goods and/or services in-house (42.1%). This proportion reduced considerably as the amount of responsibility was transferred to third party developers and manufacturers, and only a very small minority (less than 2%) of companies studied had developed their products in-house, but transferred their manufacturing responsibilities to a third party. In some cases, especially where more than one product or service was offered by the company, multiple production formats had been employed, as shown in Figure 5.20.

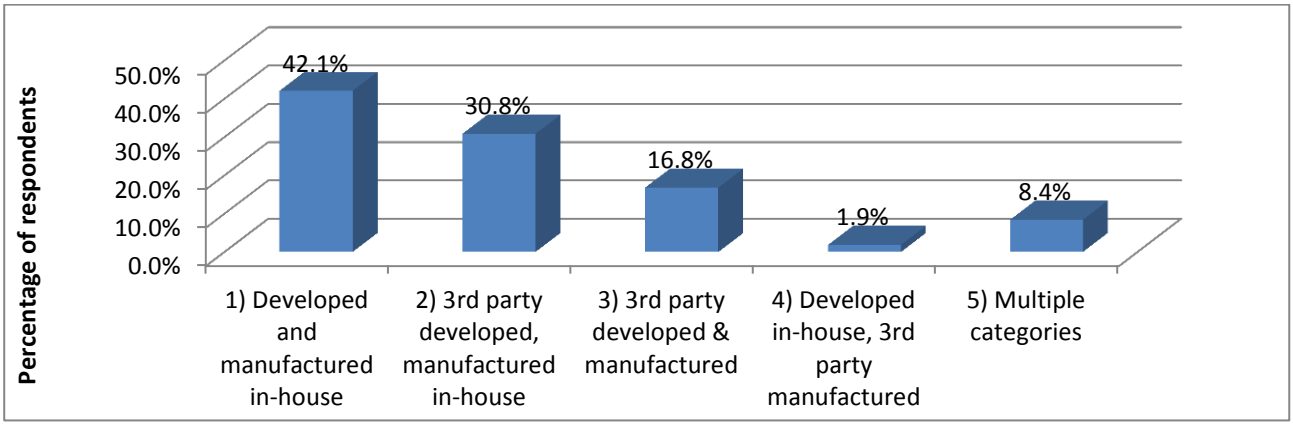


Figure 5.20 Production format of Sample 2 companies

Nearly two thirds of the companies were in a state of general operation, as shown in Figure 5.21, while approximately 20% were either sold, or closed down. The remaining 10% of companies were in a state of 'in R&D phase', or 'ready to launch'.

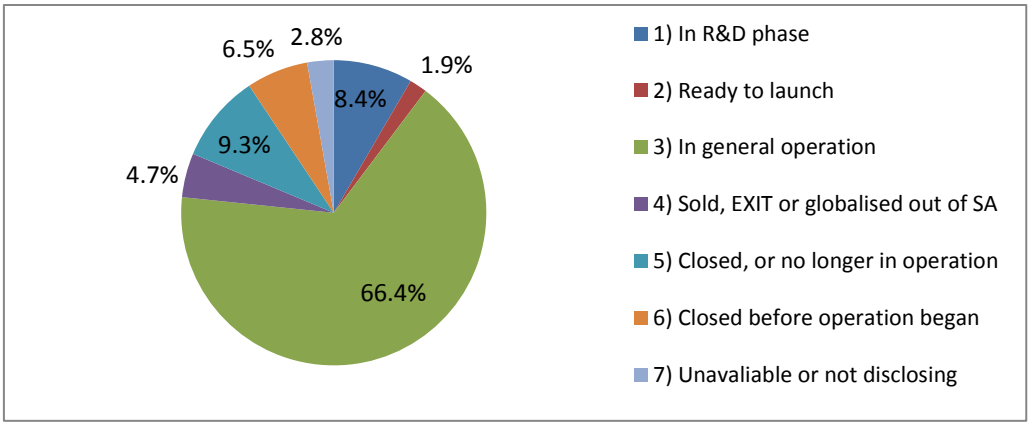


Figure 5.21 Percentage of respondents relative to their activity state

The start-up and R&D costs of the Sample 2 companies showed a distribution across a wide scale (see Figure 5.22), with most companies requiring between R1 million and R11.7 million for their R&D and start-up, and outliers at around R65,000 and upward of R78 million. A modal cost of R5 million was apparent from the data. All figures were corrected to their present values, in South African Rand (ZAR), by factoring in South Africa's Cost Price Index (CPI) for inflation on an annual basis since the capital had been spent.

Sizes of the companies tended to be smaller (calculated in terms of the number of staff working more than 20 hours per week, paid or unpaid), with companies ranging from zero, in the case of closed or defunct companies, to some companies that had had in excess of 350 employees. The median number of staff for the companies studied was six people, as shown in Figure 5.23.

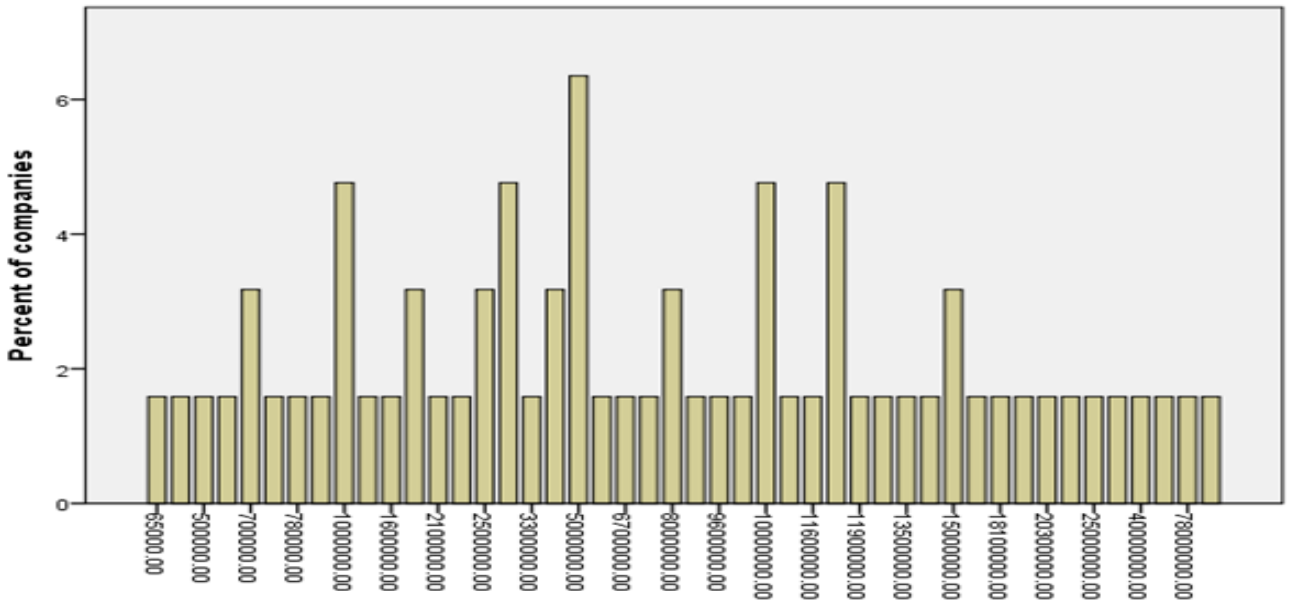


Figure 5.22 Start-up or R&D spending required for Sample 2 companies, in ZAR

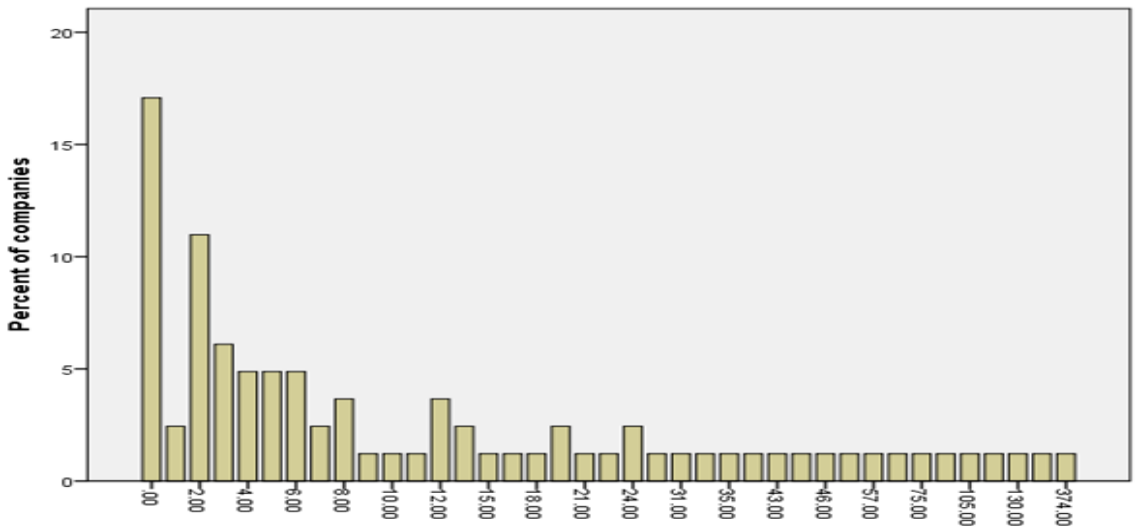


Figure 5.23 Sample 2 company sizes

When grouping the data based on their HQ locations, the ‘activity state’, and start-up ‘spending’ could be observed. There was no clear difference between the start-up and R&D spending requirements of companies relative to their HQ locations, and companies from each of the cities had R&D and start-up spending requirements that spanned across the cost spectrum, between R65 000 and R200 million, corrected for inflation to rates in December 2014.

As shown in Table 5.2, while most HTVs in the study Sample 2 were from Cape Town, Johannesburg had the highest proportion of companies in a state of sustainability or ‘in general operation’ (85.7%) compared to those that had not (14.2%). Cape Town had the highest proportion of HTVs that had not reached a state of sustainability (42.1%), but had a considerable development of new companies that were ‘in R&D phase’ or ‘ready to launch’. This was a further validation of the ‘hot-spot’ nature of Cape Town for HTV start-ups, as described in Section 4.3.2.1 (van Zyl 2014; 2015). Pretoria and Johannesburg had a very low proportion of companies ‘in R&D phase’ and ‘ready to launch’, indicating a lower rate of new initiative growth. The ‘other’ cities, which included the remainder of the country, had a moderate proportion (61.5%) of companies that had reached sustainability, but the highest relative proportion of companies that were ‘in R&D phase’, indicating a considerable amount of new growth in these regions.

Table 5.2 Variations in the activity states of HTVs, relative to their HQ locations

Activity or sustainability state	Jhb	Pta	Cpt	Dbn	Other
Closed before operation began	7.1%	13.3%	13.2%	0%	0%
Closed or no longer in operation began	7.1%	0%	5.3%	30.0%	7.7%
Sold, EXIT, or globalised our of SA	0%	13.3%	5.3%	0%	7.7%
In R&D phase	0%	0%	13.2%	10.0%	23.4%
Ready to launch	0%	0%	5.3%	0%	0%
In general operation	85.7%	73.3%	57.9%	60.0%	61.5%
Unsustainable (not reached sustainability yet)	14.2%	26.7%	42.1%	40.0%	38.5%
Sustainable	85.7%	73.3%	57.9%	60.0%	61.5%
Sample size (N)	28	15	38	10	13

It was useful to consider the ‘activity states’ of the companies further, relative to their R&D or start-up ‘spending’, ‘size’, ‘production type’, and core functional ‘classification’. These results are shown in Table 5.3.

Variations could be observed in the overall rate of sustainability for companies, considering the state of ‘in general operation’ as having reached sustainability, and all other states (including companies exclusively in ‘R&D’ or ‘ready to launch’) as having not yet reached a level of sustainability. The ‘spending’ category with the highest proportion of sustainability was of companies that had spent between R20m and R30 million; whereby, 77.8% of companies had

reached sustainability. The lowest were among each of the categories that had spent R1 million to R5 million, and R5 million to R10 million, with 66.7% having not reached sustainability yet.

Table 5.3 Variations in the activity state of the Sample 2 HTVs, relative to their spending, size, production type and classification

Variable	Categorisation	Unsustainable (Not yet reached sust.)	Sustainable (in general operation)
Spending	R0 to R1m	40%	60%
	R1m to R5m	66.7%	33.3%
	R5m to R10m	66.7%	33.3%
	R10m to R15m	36.4%	63.6%
	R15m to R20m	45.5%	54.5%
	R20m to R30m	22.2%	77.8%
	R30m+	26.4%	73.6%
Size	0 people	100%	0%
	1 to 5 people	21.7%	78.3%
	6 to 20 people	22.7%	77.3%
	Over 20 people	4.5%	95.5%
Production type	Developed and manufactured in-house	46.7%	53.3%
	3rd party developed, manufactured in-house	21.9%	78.1%
	3rd party developed and manufactured	25%	75%
	Developed in-house, 3rd party manufactured	0%	100%
	Multiple methods	11.1%	88.9%
Core functional classification	Vaccines	0	100%
	Biogenerics	50%	50%
	Therapeutics	33.3%	66.7%
	Nutraceuticals	60%	40%
	Reagents	33.3%	66.7%
	Diagnostics	47.4%	52.6%
	Medical devices	40.6%	59.4%
	Biotools	0%	100%
	Contact services	16.7%	83.3%
	Public services	0%	100%
	Multiple categories	11.8%	88.2%

The category of ‘size’ formed a suitable control variable for the data, especially in the inferential statistics section, next, because as was to be expected, companies that were in a state of ‘general operation’ were relatively quite large, while of course companies that had closed (and were therefore unsustainable), had zero staff members. This was evident when classifying the data by

'size', whereby those with zero staff were 0% sustainable, and the largest companies were almost always (95.5%) 'in a state of general operation'.

When grouping the variable of 'activity state' according to 'production type', the mode of production with the lowest sustainability was companies that had 'developed and manufactured their products in-house', while the highest sustainability was from those that had 'developed in-house, but manufactured externally'. This statistic should be observed with caution, though, due to the low sample size in some of the categories, as shown previously in Figure 5.20. Finally, the companies with the classification types of 'vaccines', 'biotools', and 'public services' had the highest proportion of companies that were in the sustainable category (100%), while the 'classification' category with the highest proportion not yet in a state of sustainability was the 'nutraceuticals'.

Observing the company 'classification', 'location', 'production type', 'spending' and 'size' in order to determine the company type that would be most likely to succeed in the South African macroenvironment, the above descriptive statistics were converted to a probability, and compounded as follows:

$$\boldsymbol{PS_{MAX} = P_c \times P_l \times P_p \times P_{Sp} \times P_{Si}} \qquad \textbf{[10]}$$

Where:

PS_{MAX} is the highest probability of sustainability;
P_C is the highest classification category probability of sustainability;
P_l is the highest location category probability of sustainability;
P_p is the highest production type category probability of sustainability;
P_{Sp} is the highest spending category probability of sustainability; and
P_{Si} is the highest size category probability of sustainability;

Based on this, calculating the company type with the maximum probability of reaching sustainability was calculated from the 'classification', 'location', 'production type', 'spending', and 'sizes' with the highest probabilities; whereby, the highest percentage sustainability was converted to a probability, as follows:

$$\boldsymbol{PS_{MAX} = 1.000 \times 0.857 \times 1.00 \times 0.778 \times 0.955}$$

$$\boldsymbol{= 0.637} \qquad \textbf{[11]}$$

The company type that was found to be most likely to succeed was a 'vaccines', 'biotools' or 'public services' company located in Johannesburg, that had developed its products in-house, but manufactured them externally; that had spent between R20 million and R30 million on its R&D or start-up; and that had employed at least 20 employees. Such a company was found to have a 63.7% probability of reaching sustainability, based on the statistical observations of the companies in this study.

Conversely, in order to observe the company 'classification', 'location', 'production type', 'spending' and 'size' that would be least likely to succeed in the South African macroenvironment, the same equation above could be used, but instead inserting the lowest probability from each variable:

$$PS_{MIN} = 0.400 \times 0.579 \times 0.533 \times 0.333 \times 0.773$$

$$= 0.032 \quad \textbf{[12]}$$

The company type that was found to be least likely to succeed, based on the participants in Sample 2 of this study, was a nutraceuticals company based in Cape Town that had developed and manufactured its products in-house; that had spent between R1 million and R10 million on its R&D or start-up; and had between six and 20 employees. Such a company had a 3.2% chance of reaching sustainability, based on the statistical observations in this study.

It should be noted that the model proposed in Equation [10] is a probability model, based on the statistical occurrences of each of the traits in the Phase 2 of the study. It did not assume that there were specifically any relationships between the traits (although these are presented later in the chapter), but only what the chances of success or failure would have been for a company with a specific set of traits, based on actual observations of the Sample 2 companies. Deliberation of the significance of this, in relation to the future South African environment (considering the size of the sample and the efforts that were taken, as noted in Section 4.4, to minimise survivorship bias), are presented in Chapter 6.

5.3.2 Inferential statistics

Due to the nature of the data generated for Sample 2, different inferential statistical tests were applied, as explained in the methods chapter. Pearson's Chi-Square, ANOVA, bivariate correlation, linear regression, logistic regression and multinomial logistic regression were performed on the Sample 2 data, where appropriate.

5.3.2.1 Results of the Chi-Square tests

Following the Chi-Square tests of Independence of Categorical Variables, it was found that various associations did exist, as shown in Table 5.4. As indicated by the p-values that were less than or equal to α (0.05), it was found that the association between 'classification' and 'production type', was statistically significant at a 5% confidence level. This test resulted in an overall Chi-Square value of 23.252 with 12 degrees of freedom (df). The significance (p) of 0.026 meant that the probability of the values occurring by chance alone was less than 0.026. Thus, in deciding whether to reject the null hypothesis H_0, it could be concluded that the relationship between 'classification' and 'production type' was extremely unlikely to be explained by chance factors alone, and the null hypothesis could be rejected in favour of the hypothesis. Alternatively, it could simply be stated that

the two variables of ‘classification’ and ‘production type’ were not independent (χ^2 = 23.525, df = 12, p < 0.05).

Table 5.4 Results of the Chi-Square tests on categorical data

Variable Type		Pearson Chi-Square Result			Association and confidence
Variable 1	**Variable 2**	**Value**	**Deg. freedom (df)**	**Asymp. Sig. (2-sided)**	
Classification	Activity state	8.405	8	**0.395**	No significant assoc.
Classification	Production type	23.252	12	**0.026**	Association at 5% significance.
Location	Classification	13.750	16	**0.617**	No significant assoc.
Location	Activity state	10.815	6	**0.094**	Association at 10% significance.
Production type	Activity state	14.475	8	**0.070**	Association at 10% significance.
Production type	Spending	13.847	8	**0.086**	Association at 10% significance.
Spending	Activity state	3.360	4	**0.500**	No significant assoc.
Size	Activity state	71.696	6	**0.000**	Association at 5% significance.

The variables of ‘size’ and ‘spending’, although discrete and continuous data, respectively, were grouped into categories as categorical data, and they were also found to have an association with some of the variables. ‘Size’ and ‘activity state’, which presented the control test for the data, indicated a significant association at a 1% level of confidence, as was to be expected (χ^2 = 71.696, df = 6, p < 0.01). This high degree of association for the control test arose because large companies would have been expected to be in a state of ‘general operation’, while companies that had closed would have had zero staff members — a statistic that was precisely testable in the case of the second phase of this study as a control test.

Although not statistically valid since they only occurred at a 10% confidence level, it could be argued that there was some evidence to reject the null hypotheses for the Chi-Square tests between ‘location’ and ‘activity state’ (χ^2 = 10.815, df = 6, p < 0.1); ‘production type’ and ‘activity state’ (χ^2 = 14.475, df = 8, p < 0.1), and ‘production type’ and ‘spending’ (χ^2 = 13.847, df = 8, p < 0.1). At a 10% confidence level, it could be argued that each of the pairs of variables were not independent, however, this could not be statistically proven, since they were not within the standard α (0.05). None of the other associations showed any significant association in the remaining Chi-Square tests.

It should also be noted that, due to the limited size of the data set, each of the Chi-Square tests flagged cells that had had expected counts of less than five, whereby the minimum expected cell

count for Chi-Square tests should be five. Thus, one of the assumptions of Chi-Square analysis was violated indicating that the results “may not be meaningful” (Elevers 2014a).

5.3.2.2 Results of the ANOVA

Results of the ANOVA are shown in Table 5.5. As explained by Elevers (2014b), in deciding whether to reject the ANOVA hypothesis H_0 for the data, “if the p-value associated with the F ratio is less than or equal to the α level, then you can reject the null hypothesis that all the means are equal.” Thus, most of the ANOVA tests were unable to reject the hypotheses that the means were equal; however, in the case of the ‘size’ versus ‘activity state’; ‘classification’ versus ‘spending’; and ‘production type’ versus ‘size’, the null hypotheses could be rejected with sufficient evidence to conclude that their means were not equal. The results of each of these ANOVA tests were $F(3, 77) = 71.451$, $p = 0.000$; $F(10, 52) = 71.451$, $p = 0.000$; and $F(5, 76) = 2.830$, $p = 0.021$, respectively.

As in the case of the Chi-Square tests, the analysis of ‘size’ versus ‘activity state’ presented a suitable control test. It presented a significant difference in means between the large and small size groups, as shown in Figure 5.24. However, in the case of the association between ‘classification’ and ‘spending’, a high *F* ratio accompanied by a low p-value indicated that there was also a significant difference in the means of ‘spending’ in relation to the core function (‘classification’) of the companies. In addition, while it was not a very high *F* ratio, there was a significant p-value difference between the variables of company ‘size’ in relation to the ‘production type’ of the companies.

It should be stated that The Test of Homogeneity of Variances (HOV) output, which tests the null hypothesis (H_0) that the variances of each of the variables are equal, is an important assumption made by ANOVA (Elevers 2014b). If the p-value of HOV (sig.) is below the α level for the test (0.05), the H_0 should be rejected, and a conclusion drawn that the variances are not equal. In relation to the results of this study, in each of the cases where there appeared to be a significant difference in means at a 5% confidence level, the HOV p-value was also below 0.05. Thus, since the variances were not equal, one of the assumptions of the ANOVA analysis was violated indicating that the results “may not be meaningful” (Elevers 2014b). Results of the remaining ANOVA tests are presented in Appendix V.

In order to observe the associations between each of the variables and the ‘activity state’ of the companies, it was useful to consider the plots of the mean values of the ‘activity states’ of the companies from the ANOVA tests, relative to their ‘sizes’, ‘production types’, start-up ‘spending’, ‘classification’ and head office ‘locations’, as shown in Figure 5.24, Figure 5.25, Figure 5.26, Figure 5.27, and Figure 5.28, respectively. Considering ‘activity state’ as a sign of sustainability in the companies, it could therefore be observed that companies in a spending category of between R15million and R20million had had the lowest average sustainability, represented on the graph by a mean value of 3.33, on a scale between one and six. In addition, companies that had spent less

than R1million for their start-up had had the highest overall sustainability rating, with an average of 5.67 for the category.

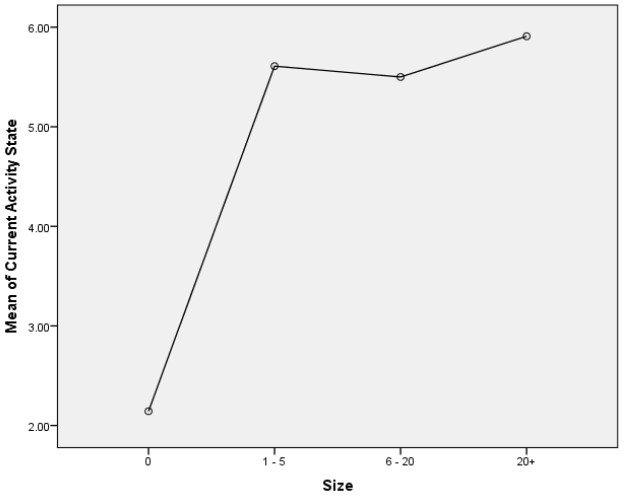
Table 5.5 Results of the ANOVA tests on the ordinal and numerical data

Variable type		One-way ANOVA result				Association and confidence
Independent variable	**Dependent variable**	**HOV sig.**	**Mean Square (MS) Error**	**F ratio**	**Sig. (p value)**	
Classification	Activity state	0.000	2.886	1.154	**0.332**	No difference in means
Location		0.048	2.981	0.775	**0.626**	No difference in means
Production type		0.132	2.942	0.906	**0.480**	No difference in means
Spending		0.015	2.137	1.633	**0.155**	No difference in means
Size		0.001	0.682	71.451	**0.000**	Significant diff. in means at 5% confidence.
Classification	Spending	0.001	1.844E+14	20.521	**0.000**	Significant diff. in means at 5% confidence.
Location		0.133	7.892E+14	0.796	**0.594**	No difference in means
Production type		0.000	6.931E+14	2.282	**0.058**	No difference in means
Classification	Size	0.232	2542.549	0.859	**0.575**	No difference in means
Production type		0.000	2244.702	2.830	**0.021**	Significant diff. in means at 5% confidence.

The production method with the lowest overall sustainability was among companies whose goods and services had been developed and manufactured in-house (average ‘activity state’ = 4.58), while companies whose goods and services had been developed in house, but manufactured by a third party, had experienced an average sustainability of 6.00. However, it should be noted that the latter of these two categories had had the smallest number of cases (N=2), indicating that the reliability of this statistic may be in question due to the small number of values in the group.

Companies located in the Eastern Cape, including Port Elizabeth had shown the lowest mean sustainability rating, while those located in KwaZulu Natal (excluding Durban) were observed with the highest average sustainability rating.

Biogenerics presented the core classification with the lowest average sustainability rating (average ‘activity state’ = 3.50), while vaccines, biotools and public services were the three classification categories with the highest average sustainability ratings each (average ‘activity state’ = 6.00, respectively). Each of these classification categories did, however, have small sample numbers of participants (N=2, N=2, N=3, and N=6, respectively).



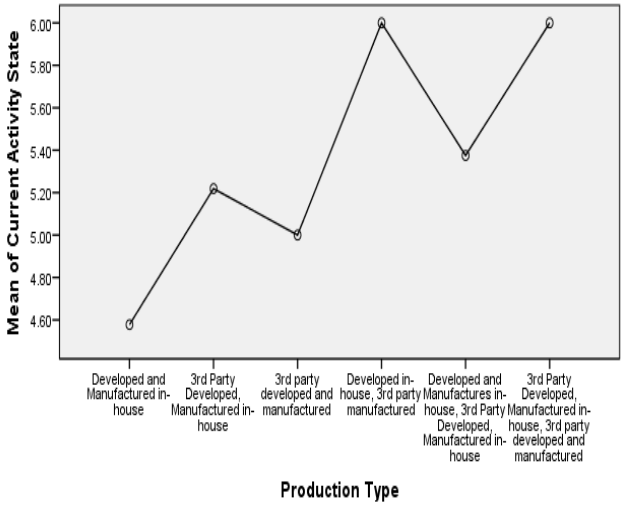
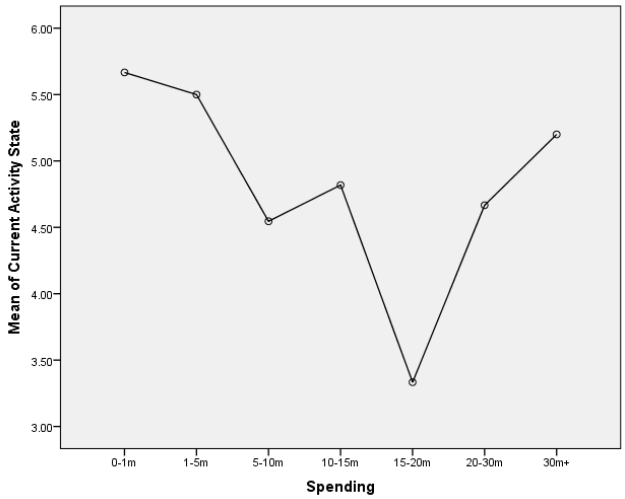


Figure 5.24 (Left) Mean values of activity state relative to the size

Figure 5.25 (Right) Mean values of activity state relative to the production type



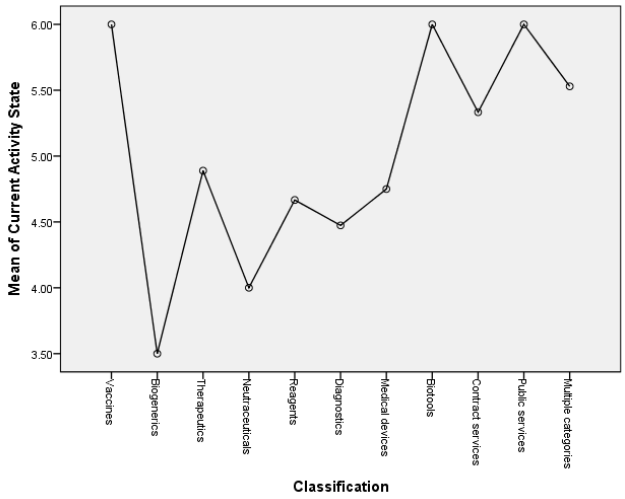


Figure 5.26 (Left) Mean values of activity state relative to the spending

Figure 5.27 (Right) Mean values of activity state relative to the classification

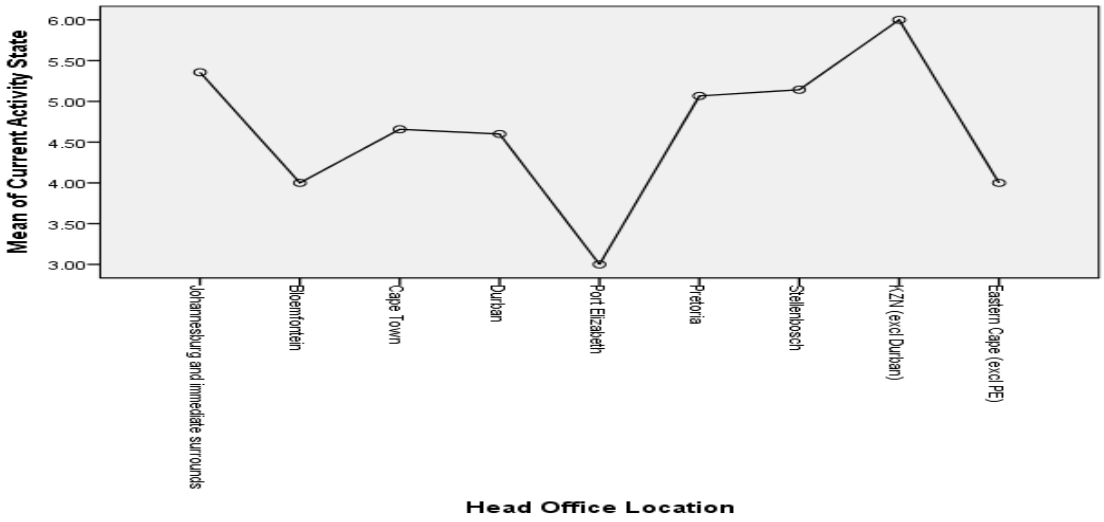


Figure 5.28 Mean values of activity state relative to the head office location

5.3.2.3 Results of the correlation analysis

The two numerical variables from the Sample 2 data set ('size' and 'spending') were correlated using Pearson's Product Moment Correlation Co-efficient (PMCC). As shown in Table 5.6, an *r* value of 0.506 was observed, indicating that there was a moderate-to-strong positive correlation between the sizes of the companies, and the amount that had been spent to date on their R&D and or start-up costs, which was statistically significant ($r = .506, p < .01$).

Table 5.6 Results of the correlation analysis on the numerical data variables

		Spending	Size
Spending	Pearson Correlation	1	0.506**
	Sig. (2-tailed)		0.000
	N	63	62
Size	Pearson Correlation	0.506**	1
	Sig. (2-tailed)	0.000	
	N	62	82
**. Correlation is significant at the 0.01 level (2-tailed).			

Based on an overlapping data size (N = 62), the significance indicates that it is improbable that an *r* value this large would have been possible by chance, if there was not a relation between the variables. While this result is somewhat intuitive, the result statistically supports that there was a moderate-to-strong positive correlation between 'size' and 'spending', suggesting that the larger the companies had grown (in terms of employee numbers), the more had been required for their R&D and start-up. Considered alternatively, the more that had been spent on R&D and start-up, the larger the companies had become.

Since ranked data cannot be used for PMCC, the correlation coefficients of Kendall's tau and Spearman's rho were calculated instead, relative to the numerical variables of 'size' and 'spending', using the 'activity state' variable on a ranked scale. As shown in Table 5.7, 'size' was shown to have a moderate-to-strong positive correlation with the 'activity state', whereby the Kendall's tau correlation co-efficient of 0.503 ($p < 0.01$), and Spearman's rho correlation coefficient of 0.618 ($p < 0.01$) were observed. This was in line with expected correlation values of the 'size-activity state' control test, as described previously.

Of interest from these correlation analyses was the relation between 'spending' and 'activity state', which was shown to have a partial-to-weak negative correlation ($P < 0.05$). This indicates that there was a statistically significant partial-to-weak negative correlation between the amount spent to date on the companies' R&D and or start-up costs, and the activity states of the companies. The result was re-iterated by similar Kendall's tau ($\tau = -0.209, p < 0.05$) and Spearman's rho values ($\rho = -0.275, p < 0.05$), respectively.

Table 5.7 Results of the correlation analysis between size, spending and activity state

			Size	Current activity state
Kendall's tau	Size	Correlation Coefficient	1.000	0.503**
		Sig. (2-tailed)	.	0.000
		N	82	81
	Current activity state	Correlation Coefficient	0.503**	1.000
		Sig. (2-tailed)	0.000	.
		N	81	104
Spearman's rho	Size	Correlation Coefficient	1.000	0.618**
		Sig. (2-tailed)	.	0.000
		N	82	81
	Current activity state	Correlation Coefficient	0.618**	1.000
		Sig. (2-tailed)	0.000	.
		N	81	104
			Spending	**Current activity state**
Kendall's tau	Spending	Correlation Coefficient	1.000	-0.209*
		Sig. (2-tailed)	.	0.036
		N	63	63
	Current activity state	Correlation Coefficient	-0.209*	1.000
		Sig. (2-tailed)	0.036	.
		N	63	104
Spearman's rho	Spending	Correlation Coefficient	1.000	-0.275*
		Sig. (2-tailed)	.	0.029
		N	63	63
	Current activity state	Correlation Coefficient	-0.275*	1.000
		Sig. (2-tailed)	0.029	.
		N	63	104

*. Correlation is significant at the 0.05 level (2-tailed). **. Correlation is significant at the 0.01 level (2-tailed).

5.3.2.4 Results of the linear regression

Due to the nature of the data, linear regression could only be performed on the two numerical variables ('size' and 'spending'), since the remaining variables constituted categorical data. The variables analysed in the linear regression were 'size' as the DV, and 'spending' as the IV. The purpose of the test was to determine whether the amount spent for R&D and start-up were related to the overall size of the companies. The linear regression equation was of the form:

$$\mathbf{Spending} = \beta_1 \times \mathbf{Size} + \alpha \qquad \textbf{[13]}$$

Where:

α *is the regression constant or Y-intercept of the linear graph; and*

β_1 *is the slope coefficient of the 'spending' variable.*

Results of the linear regression are shown in Table 5.8, and based on these results, the equation can be rewritten as follows:

$$\mathbf{Spending} = \mathbf{271262} \times \mathbf{Size} + \mathbf{6815730} \qquad \textbf{[14]}$$

Table 5.8 Linear regression based on the association between size (IV) and spending (DV)

R	R Square	Adjusted R Square	Std. error of the estimate
0.506[a]	0.256	0.244	24238699.58820

Unstandardized coefficients		Unstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. Error	Beta		
	(Constant)	6815725.154	3389387.128		2.011	0.049
	Size	271261.900	59662.001	0.506	4.547	0.000

The r^2 value of this linear regression was 0.256, adjusted to 0.244 ($P < 0.01$) due to the single IV used in this equation. The probability of this coefficient occurring by chance alone was also approximately 0, and it could be concluded that 24.4% of the variation in the R&D or start-up spending of the companies could be explained by the number of people that were currently employed at the organisation (their size).

5.3.2.5 Results of the logistic regression and multinomial logistic regression

Finally, logistic regression and multinomial logistic regression were performed in order to analyse whether any relation could be observed between the categorical variables, and specifically to analyse whether the value of any of the variables could be used to predict the 'activity state' or sustainability of the companies. 'Activity state' was analysed as the DV in its standard six categories using multinomial logistic regression, and as a dichotomous variable in the logistic regression, as shown in Table 5.9 and Appendix III.

Table 5.9 Results of the multinomial logistic regression for activity state (DV) and size (IV)

Model (Size)	Model Fitting Criteria	Likelihood Ratio Tests			Pseudo R-Square	
	-2 Log Likelihood	Chi-Square	df	Sig.	Cox and Snell	0.574
Intercept Only	90.365				Nagelkerke	0.649
Final	21.236	69.129	15	0.000	McFadden	0.395

Table 5.10 Results of the logit regression for activity state (DV) and size (IV)

a. Variable(s) entered on step 1: Size.		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I.for Exp (B)	
								Lower	Upper
Step 1[a]	Size	1.264	0.392	10.381	1	0.001	3.538	1.640	7.630
	Constant	-1.228	0.601	4.174	1	0.041	0.293		

No significant association was observed between any of the variables and 'activity state', when analysed together as a multivariate analysis, as shown in the results table of Appendix V. An association was observed in the control test between 'size' and 'activity state', when analysed during individual multinomial logistic and logit regressions, as was to be expected. These results are shown in Table 5.9 and Table 5.10, respectively. None of the other variables indicated any

significant results with a p-value above 0.05, so it could be concluded that any coefficients of association, or Pseudo R-squared values between the variables were not statistically reliable since they could have occurred by chance alone.

5.4 CONCLUSION

This concludes the results of the dissertation. The category of ‘company citizenship’ appeared to present the strongest of South Africa’s company processes, where the average company citizenship was at 87.7% of maximum. The lowest rating was the SWOT analysis, at 36.6%, indicating that the ratio of strengths and opportunities, to weaknesses and threats, by number, was relatively low for the average company in South Africa. The general profile suggested that while there were typically few similar local products currently in South Africa, considerable similar foreign products were also available. The threat of new foreign products was also above average. International demand, however, suggested a considerable overall potential for goods and services export from South Africa. Regarding additional training by South African academic institutions in order to benefit the South African HTV sector, it was observed that most change should be within the category of inter-disciplinary training.

In the second phase of the study, the results of the inferential statistical analysis on Sample 2 were revealing. From the Chi-Square tests it was found that the association between ‘classification’ and ‘production type’ was statistically significant at a 5% confidence level, as was the analysis of the control test between ‘size’ and ‘activity state’. From the ANOVA tests, there was a significant difference in the means of ‘spending’, in relation to the core function (‘classification’) of the companies, along with the means of company ‘size’, in relation to their ‘production type’. From the correlation analyses, there was a moderate-to-strong positive correlation between ‘size’ and ‘spending’, and a partial-to-weak negative correlation between the ‘spending’ and ‘activity states’ of the companies. From the linear regression, it could be concluded that 24.4% of the variation in the ‘spending’ of the companies could be explained by their ‘size’. Finally, no significant association was observed between any of the variables and the companies’ ‘activity states’ (sustainability), when analysed together as a multivariate logistic regression analysis; however, an association was observed between the control variables ‘size’ and ‘activity state’ during the multinomial logistic regression of the ranked form of the ‘activity state’ variable. These results are discussed and concluded in the next chapter, along with the conclusion and recommendations of the study.

CHAPTER 6
DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

This final chapter of the dissertation presents the discussion, conclusion and recommendations of the study. The first stage of the study is dedicated to a presentation and critical discussion of the results of the study, pertaining to each of the objectives that were laid out in Chapter 1. The first section reviews the objective relating to the core functions of the HTVs, and presents a deliberation and conclusion of the findings from the study. The second section reviews the objective relating to the challenges that are faced by HTVs in South Africa, compared to other developing and developed countries. In discussing this objective, each of the most significant issues relating to financial shortages, skills shortages and competition issues are presented, along with supporting considerations from the literature and Sample 1 and 2 respondents.

For the third objective, the results of the inferential statistical analysis are presented, relating to each of the aspects of the Pearson's Chi-Square, ANOVA, bivariate correlation, linear regression, logistic regression and multinomial logistic regression that were performed on the Sample 2 data. Finally, the fourth objective is discussed, relating to the perceptions, proportions and keys to success that have been observed throughout this study, along with the suggestions that have been presented by the professionals in the HTV sector.

Before concluding the chapter, a short section on recommendations is presented, which introduces some additional or future research that may be conducted to supplement any gaps in this research, or to present additional material that may enhance the knowledge base.

The chapter begins, next, with the discussion and conclusion on the first of the four objectives of this study.

6.2 OBJECTIVE I. THE TYPES OF CORE FUNCTIONS BEHIND THE HTVS IN SOUTH AFRICA AND THEIR SCIENTIFIC THEORIES

This section of the study attempted to present a clear profile of the classes of HTVs that are being offered to the South African market. In so doing it hoped to determine the class of biomedical products that were most likely to succeed in South Africa. It also considered the biological principles of the scientific techniques incorporated at an organisation, with an explanation of their modes of operation and the scientific processes or pathways that they had involved.

As shown in the methodology of this dissertation, 107 companies were included in Sample 2, and the systematic approach to the sampling methodology resulted in a relatively complete profile of the HTVs that have been active in South Africa in the past decade (including active, inactive, and defunct companies). From the sample, the general profile of the core functional classifications of

the majority of companies in South Africa could be observed, since the sample size was large enough to generalise across the entire sector (Saunders et al. 2009). It could, thus, be concluded that, at the time of submitting this dissertation, the most active subcategory of HTVs in South Africa is the medical devices subcategory, followed by diagnostics, therapeutics and contract services. In many cases, companies have also tried to diversify among multiple categories.

Based on the largest sample included in this study (Sample 2), which was an exhaustive method of data sampling, the most frequent HQ location for HTVs in South Africa is Cape Town, which has been responsible for more than one third of the SME-scale HTV start-ups. This has been supported in the literature. As noted in Chapter 4, Cape Town has been recognised in the literature for its technology and life science growth prospects, with Cape Town having grown into “a major hub” for start-ups; not only in the life sciences sector, but in all the various technology sectors (van Zyl 2014; 2015). It should be reiterated, though, that this study did not consider companies that were larger than the size and business scale of standard SMEs, and this could explain the lower relative proportion of companies in Pretoria and Johannesburg, which may instead be home to the larger corporations and foreign products.

When grouped by HQ location, a higher proportion of companies from Johannesburg were in a state of general operation or sustainability (85.7%), compared to those that had not yet reached a state of sustainability. The proportion of companies in a state of R&D was highest in the ‘other’ cities, indicating that while only 61.5% of the companies in the other cities had reached a level of sustainability, they showed a relatively higher rate of growth and development of new initiatives. Of the four main cities in the study, the city with the lowest proportion of companies that had reached sustainability was Cape Town, with only 57.9% of companies having reached sustainability. However, the high number of companies in R&D phase and ready to launch, along with the proportionally higher number of companies in the sample size (38), indicates, again, that Cape Town was the most active location for HTV growth and development in the Country.

It is worth deliberating why Cape Town has advanced in the field of HTV start-ups, compared to the other cities in South Africa. Van Zyl (2014) presents a variety of factors that have allowed Cape Town to “stand out” in the development of technology start-ups in general, which includes the overall favourable business climate of the region, an excellent infrastructure, and favourable costs of rent, when considered in the global contexts; and indeed in relation to Johannesburg. Rental in Cape Town, for example, is noted by van Zyl (2014) to be approximately a quarter of the rental cost in the San Francisco Bay area. Other factors also include a skilled talent base, particularly in the fields of science and engineering, proximal location to numerous high quality universities, and an “emerging start-up culture” (van Zyl, 2014). Furthermore, relating to the life sciences, van Zyl notes that “Cape Town ranks highly because the University of Cape Town (UCT) and Stellenbosch University have concentrations of students with a combination of medical training (UCT Medical School) and engineering skills that can be tapped by companies looking for that talent.”

Conversely, based on the results of this study, Durban was in a relatively poor state of HTV development, with a ratio of 4:6 between those not yet in general operation, and those that were in general operation. In addition, the high percentage of companies that had closed or were no longer in operation, and the low percentage of companies in R&D phase indicates that the rate of HTV initiatives and growth in Durban was lowest, compared to the rest of the country. Indeed, Jackson (2015) asserts that there has been an "exodus of entrepreneurial talent from KwaZulu-Natal to the likes of Cape Town and Johannesburg"; apparently, in search of better co-working space, enterprise support, and mentorship. Jackson argues that this exportation of Durban's talent has caused a shortfall in the available expertise in the KwaZulu Natal region. Perhaps, as new initiatives are created, such the new Durban Innovation Hub (TDIH) that was launched in August 2014 to develop skills and knowledge for entrepreneurship and technology innovation — with a focus on training for previously disadvantaged community members (Jackson, 2015) — this poor HTV ranking in the region will be reversed.

6.2.1 The scientific review

Chapter 3 of this dissertation was dedicated to a thorough examination of the theoretical elements of some of the scientific techniques that have been used at one of South Africa's currently successful HTVs. The *DNA Oestrogen* test offered by DNAlysis was based on thorough scientific principles, and it is valuable to deliberate — in line with the first objective of this study — whether there may have been any correlations or patterns between these scientific principles, and the success of the company, to date. It is clear, for example, that DNAlysis has utilised core scientific principles, and a business model that has fitted into the South African environment to overcome the challenges that have existed in the country.

Fundamentally, it should be noted that a clear underlying need for the DNAlysis products existed. As noted by Joffe (2012, cited in Health24 2012), breast cancer is the most frequently diagnosed cancer in women, globally, constituting 16% of all cancers in females; and in South Africa, one in 29 women is affected with the condition. The need for cancer-related products was, thus, well established; and the supply of products that helped to target such needs, was sound business practice. Clearly, at the root of any business, including health technology ventures, is matching the demand to a solution, and targeting a sizeable potential market (Azevedo and Leshno 2014).

At their core, it is clear that the DNAlysis products were devised on techniques and principles that relied on advanced science (Motovali-Bashi et al. 2012; Wu et al. 2013; Miao and St. Clair 2009). Of course, organisations that function at a quintessential biological level to target diseases — using principles that are only now becoming fully understood — must be founded on updated learning. As shown in the DNAlysis review chapter, continuous research and development was performed on the products and services in order to keep up with the latest findings in the field; thereby,

progressively incorporating new gene profiling tests into the company's product offering (DNAlysis 2014d).

Another important observation of DNAlysis, which may have related to its success, was the translation of the science to the public in a useable manner. For example, based on the results of the *DNA Oestrogen* test, individuals were recommended to reduce their exposure to all environmental and dietary pro-carcinogens, while focusing on promoting Phase II detoxification (DNAlysis 2014f). In the case of DNAlysis, therefore, by offering people dietary and lifestyle recommendations to reduce their risks for cancer (DNAlysis 2014f), the science was converted to financial sustainability by generating a tangible product that applied to the market in a useable manner. The scientific principles were, therefore, being applied in a manner that had made the company sustainable in South Africa's modern environment.

6.2.2 Conclusion of the objective

The most active subcategory of HTVs in South Africa is the medical devices subcategory, followed by diagnostics, therapeutics and contract services. In many cases, companies have also tried to diversify among multiple categories. The most frequent HQ location for SME HTVs in South Africa in recent years is Cape Town, which has been responsible for more than one third of the SME-scale HTV start-ups; although Cape Town also has the highest proportion of companies that are not-yet-in, or otherwise outside of a state of sustainability.

Companies like DNAlysis, which manufactures and supplies the *DNA Oestrogen* test for genetic profiling of breast and other cancers, are among the HTVs that have reached sustainability in South Africa. It is not clear whether the specific scientific principles of the DNAlysis company, specifically, have led to its success, but its fundamental business and scientific principles, such as satisfying a need, applying modern research to target a widespread need, translating scientific benefits to the society in a tangible manner, and being able to respond to the challenges of the South African environment, have certainly assisted the company to do so.

6.3 OBJECTIVE II. THE CHALLENGES FACED BY HTVS IN SOUTH AFRICA, COMPARED TO OTHER DEVELOPING AND DEVELOPED COUNTRIES

This objective included an in-depth review of the South African entrepreneurial climate, with a specific look at the commercialisation of advanced HTVs, and the difficulties that are faced therein. It also attempted to compare the potential sources of funding for the ventures; thereby, offering a profile of the financial landscape of new HTVs.

Based on the first phase of the study, there appeared to be considerable challenges for the HTVs in Sample 1. This was initially observed from the general profile that was drawn up on these companies' macroenvironments, whereby the rating of 36.6% for the SWOT analysis indicated that

the ratio of strengths and opportunities, to weaknesses and threats, by number, was relatively low for the average company.

For the strengths and weaknesses report, a proportionally higher number of weaknesses were noted by the respondent companies, relative to the quantity of strengths described; whereby, 52 types of weaknesses were highlighted across 13 categories of factors, relative to 30 strengths across nine categories. The primary weakness that was listed by the respondent companies included the lack of financial backing. Since it was such a significant issue, this concept of capital shortage is deliberated in detail, next.

6.3.1 Financial shortage

The single most commonly noted challenge faced in South Africa was the issue of capital. This included a shortage of early-stage funding, insufficient capital for start-ups, poor confidence by foreign investors, a limited venture capital pool, and risk aversion by venture capital firms. Other problems observed were related to foreign currency (in terms of a shortage of forex inflow or high exchange rates), and the high costs of operation in South Africa.

Based on the results of this study, it was apparent that the majority of funding for the HTVs was provided locally (as opposed to by foreign sources) and by private (as opposed to by government) sources, while an even distribution of funding was provided via debt and equity means. Although much is noted in the literature about the efforts of the government to support and proliferate local biotechnology (Chakma et al. 2010; TIA Report 2012; Wild 2013), the data presented by the HTVs in this study painted a different picture. Less than 30% of the companies had received any government support, and a considerable grievance amongst the respondents of both Samples 1 and 2 was the lack of government support from funding.

Finances are, thus, a fundamental barrier in the country, and a number of companies in this study described this as a problem; whereby, only those who had been able to overcome this through creative means had been able to succeed in the long term. According to supplementary material that was generated following the collection of data from Sample 2, Sample 2 Anonymous Respondent B (2014b) argued:

> *"The government organisations that provide funding are not helping as they should in theory. The strict review process, share ownership implications, and insufficient funds all render the funding system rather ineffective. In order to land the funding to upgrade our manufacturing facility, we needed to acquire only new equipment (as opposed to cheaper 2nd hand equipment), and we had to pay upfront ourselves in order to be considered eligible for reimbursement. Then, the TIA would only refund back one third of the amount, after the facility was in full operation."*

Discussing the aspect of costs of production, another of the email interviewees was forthcoming with a list of issues relating to costs (Sample 2 Anonymous Respondent C 2014):

> *"With regards to the sustainability of my industry in South Africa, I really do not think that any new company will be able to survive here. My company does ~5% of its business within South Africa (due to non-payment by government) – the balance is all export, which is getting more and more impossible due to the following reasons:*
>
> - *Productivity is poor; wages are too high;*
> - *Power shortages and cost thereof; cost of electricity far too high – they compare us to countries overseas, but they are earning in Euro's or Dollars and this is never taken into consideration;*
> - *Cost of freight, especially sea freight is some 80 – 100% higher than our competitors countries costs;*
> - *Banking services are getting worse and making it difficult to do export business;*
> - *SARS can delay repayment of VAT for up to 12 months forcing companies with poor cash-flow to shut down;*
> - *Competitors' pricing is lower than my production costs. As a result, we have lost some 80% of the business we had 3 years ago. We were supplying some 12% of the worlds [… diagnostic …] tests, we are now down to some 2% and falling.*
>
> *Not a pretty picture. We have been in business in this industry for >25 years and have seen 5 other companies enter this market locally and then disappear. The latest one is [company X] who will close their doors at the end of this month. South Africa just cannot compete with the real world and it is getting worse."*

Another company owner presented a different perspective (Sample 2 Anonymous Respondent A 2014), by stating that the funding problems were:

> *"Mostly True. I say mostly because there are too many opportunists that just want a free ride for a year or two until they find something better to do. I don't think people will mind to go through strict review processes with all the paperwork involved, as long as they can get proper consistent funding for the duration of the project."*

One company, which had received funding from the IDC and TIA, remarked (Sample 2 Anonymous Respondent A 2014):

> *We have secured funding from both the IDC in the form of a SPII grant and from the TIA in the form of a loan from their "Idea Development Fund". We are very grateful for this funding as it has been instrumental in us reaching this advanced stage of the project. We request that both of these organisations will officially give us permission to seek International*

> *opportunities to find a partner or willing buyer of our technology. If we are not allowed to investigate this option it is, unfortunately, likely that the IP will be lost through lack of final registration or inability to maintain it through the payment of future patent fees.*

While funding was a central aspect of the challenges faced by the HTVs in this study, it should be noted that various authors indicated that this is a problem that exists across all industries throughout South Africa, and not just in the health technology sector (Atieno 2009; Pretorius and Shaw 2004). Maas and Herrington (2006), for example, suggested that the lack of financial support has been the "second major contributor to the low Total Entrepreneurship Activity (TEA) rate in South Africa". The TEA is an indication of the number of people aged between 18 and 64 who are involved in the start-up or operation of a business that is less than 3.5 years old (Maas and Herrington 2006). Furthermore, Pretorius and Shaw (2004) observed that inadequate capital structures or 'resource poverty' could have been the root cause of a large percentage of the failed entrepreneurial ventures in the country; across all industries.

Sample 2 Anonymous Respondent A (2014) provided a comparison between South Africa and the international bioincubators, stating that:

> *"The bio-incubator we visited in Paris provided support on all levels. They financed all aspects involved with setting-up or growing of a company - personal funding (living wage), office space, accounting services, intellectual property registration, HR, IT etc. In [that] environment you can allocate some shareholding because you had access to all these functions without paying for it. They only get rewards once your company is profitable. In our environment they are quick to sign shareholding etc., but in the end it is still up to you to make it work and you end up paying for all these services with the little funding you get".*

Within South Africa, the amount of funding is also on a far lower scale than in the developed world. As noted by Sample 2 Anonymous Respondent A (2014):

> *"Our budget for research is almost non-existent compared to the big players. A few years ago … they had a discussion on how far behind the EU was with regards to biotech research. As far as I can recall the EU (public and private) spent something like $20 billion/annum while the US spent over $100billion on biotech research."*

This has been corroborated by authors such as Sherwin (2007), and Huggett (2012), as noted in the literature review chapter of this dissertation (see Table 2.6, and Figure 2.5), but with slight corrections to the amounts noted by the respondent. It should also be highlighted that the figures noted by the respondent would have been for the corporate-scale public sector biotechnology firms (Huggett 2013b), and in the private sector, even in the developed countries, available funding is far lower. Huggett (2012), for example, noted Europe's private sector funding from VCs alone to be second only to the US in 2011, at more than $700 million; while private sector VC capital in the US

in 2011 was approximately $2.5 billion. When compared to the US and European, though, funding for start-ups typically received by South African biotechnology companies is a fraction of what would be received in the US or in European countries (Pillay and Uctu 2013).

Indeed, the aspect of generating funding from foreign sources in the country is a significant issue. While it was noted as a problem by the respondents in Sample 1 (and by support material offered from the respondents in Sample 2), authors such as Al Nasser (2010) concur that foreign direct investment (FDI) plays an important role in contributing to a country's economic growth. In the paper by Al Nasser, it was shown that there is a positive causal link between FDI and economic growth; and in the South American countries, this causal link has even been seen to "go both ways", whereby economic growth in turn appears to attract more FDI. As shown in Figure 6.1, below, though, Africa has remained far behind the other developing regions of the world in terms of FDI. Al Nasser asserts that inflation, trade, receiving a school education and telephone lines are the most important determinants of location decisions for foreign investors. Such infrastructural developments should therefore be concentrated on by the South African government in order to boost the flow of FDI into the country.

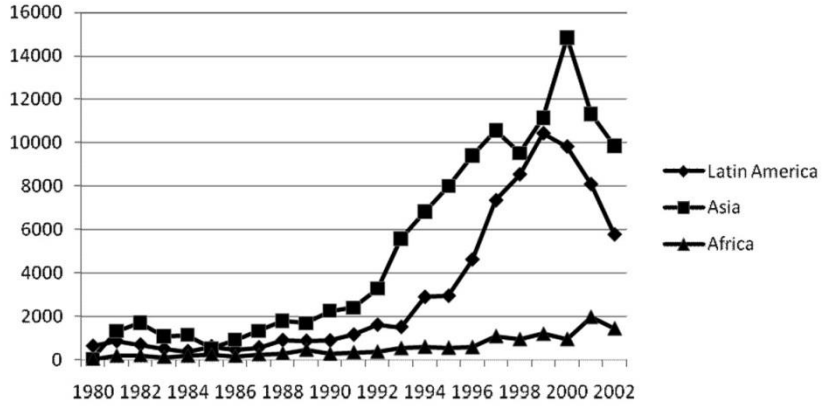


Figure 6.1 FDI inflows per region, in millions of dollars, between 1980 and 2003

Source: Al Nasser 2010

It is clear, therefore, that within the South African market, generating alternative forms of capital and funding that do not rely on FDI, is a significant factor that must be considered by health technology start-ups. As noted in the results of Phase 2 of this study, the start-up and R&D of HTVs in South Africa would typically require between R1 million and R11.7 million in financial capital; and although outliers existed (as low as R65 000, and upward of R78 million), a modal cost of R5 million suggests that most often, around R5 million would be required for start-up at today's currency value. Although this would of course fluctuate, depending on the mode of production, core functional classification and size (although as noted in the results, location would not be expected to have any outcome on the costs), it is to be expected that an HTV in South Africa would require considerable financial resources.

Generating funds in creative and innovative ways is currently a ‘hot topic' in the entrepreneurial literature. According to Lehner (2014), crowdfunding (CF) presents a new and different opportunity of financing for young ventures. Instead of approaching the traditional financial sources, such as venture capital funds (Huggett et al., 2012, 2013a), banks or business angels, various ventures have found success by generating capital from the public, through web and multi-media based platforms that act as intermediaries and money collectors from the community — otherwise referred to as the ‘crowd’ (Mitra 2012).

Crowdfunding is being seen increasingly as an alternative to the traditional forms of financing and funding, especially in the early stages of a company start-up. As noted by Lehner (2014), “the crowd is a heterogeneous, highly dispersed and large-numbered source that is open to providing capital when the risks outweigh the potential gains for banking institutions and venture capital funds” (Lehner 2014). While the contributions from the crowd vary from pre-payments and simple donations to more formal debt and equity investments, such funds are almost always small in comparison to the traditional forms of investment, but can ultimately add up to large sums.

Lehner (2014) suggests that the intentions of individual crowd members for providing capital to new start-up ventures is contrastingly different to the intentions of the traditional funding institutions, since the crowd often choses the start-ups for being “highly desirable social ventures that have little prospect for economic gains”. It could be argued, therefore, that in order for an HTV to attempt to source crowdfunding, it may require different approaches and logics on how the business should be structured, in order to win the appeal of the public for funding.

It is also useful to consider a recent trend that has proliferated in the global economy that is based on the concept of ‘social entrepreneurship’ (Lombard 2012). Although the term has only quite recently flourished, it is agreed that its underlying concept has existed for some time. Social entrepreneurship is the concept of combining “the traditional characteristics associated with business entrepreneurs with a vision for social change.” Dees (1998:1, cited in Lombard 2012) asserts that social entrepreneurship “combines the passion of a social mission with an image of business-like discipline, innovation, and determination commonly associated with, for instance, the high-tech pioneers of Silicon Valley”.

A primary difference between social entrepreneurship and business entrepreneurship is its use and purpose of wealth. In social entrepreneurship, capital is perceived as “a means to an end”, while to business entrepreneurs, wealth creation is a means of measuring the success of the venture, and therefore, its value creation (Lombard 2012).

Finally, while capital in the form of funding is one form of resource, it is of value to consider Bourdieu’s (1986) four forms of ‘capital’, as capital in its different forms is central to venture success. Bourdieu originally offered three distinct types of capital: economic capital (EC) or material property; social capital (SC) or networks of social connections; and cultural capital (CC) or “objectified cultural competence”. Bourdieu (1989) later added a fourth type – symbolic capital

(SYMC) to better differentiate between CC and SYMC, by including aspects such as legitimacy, prestige and charisma.

One of the central notions of Bourdieu's (1986; 1989) "economies of practices" is the concept that capital is transferable between each of the four forms of capital; whereby, costs in one form may result in profits in another, and that all forms of capital are transferable from–and–to EC. Bourdieu also strongly related the aspects of SYMC, such as charisma and prestige, to SC and CC; asserting that the aspects of legitimacy, reputation, and trust have a "transformative power". Considered alternatively, therefore, the HTVs in South Africa should consider each of the forms of capital, and attempt to harness not only the economic form, but each of the four: especially reputation and prestige, since they may be "transferrable" for generating economic success and sustainability.

South African companies, for example, should strive to develop reputations based on factors that are respected in biotechnology and business, such as product- or service-quality, product- or service-reliability, foundations that are based on solid science, adding to the global knowledge base, and furthering the fields of science; which could ultimately translate from symbolic capital (SYMC) into economic capital (EC). As noted by Fambrough (2012), in order to change perceptions, companies should place an emphasis on each of the three core aspects of: data, the scientific model, and outside validation. Indeed, as presented in the DNAlysis review in Chapter 3, it could be observed that a scientific model (Jiang et al. 2010), outside validation (Shout Africa 2013), and data (DNAlysis 2014f) were each equally supplementing the company's reputation and symbolic capital; thereby acting as a driver for the creation of economic capital for the company.

These aspects of capital are considered further in relation to the fourth objective of this study, later in the chapter.

6.3.2 Skills shortages

The second most frequently listed weakness in the results of this study was the lack of skills in the country. This included shortages in the expertise and networks required for global market penetration, limited 'scarce skills', and a lack of foreign skilled workers.

This observation was reiterated by the results of Phase 1 of this dissertation; whereby, the category of 'company citizenship' was the highest-rated of South Africa's company processes, at 87.7% of maximum, with points awarded based on a tendency towards South African citizenship. Upon initial consideration, it could be assumed that this high South African citizen representation in companies was a positive result, since it suggests that the initiative as well as the work force for developing the SME-scale HTVs has remained in the hands of South Africans. However, since it has been so frequently noted as a weakness by the respondents in the field, it seems that this characteristic has other facets to it that may render it as a weakness.

An interesting perspective is presented by Al Dosary (2004), which is based on the Saudi Arabia experience. In a country that has had a skills shortage, and the financial resources to “buy in the needed manpower skills” Al Dosary presents various issues that have occurred as a result. Firstly, the prolonged dependence on a foreign workforce in Saudi Arabia over numerous five-year National Development Plans resulted in problems with local young graduates being unable to find jobs in place of the foreigners who were being drawn in instead. As a result, the unemployment rate in Saudi Arabia increased considerably to around 25-to-30 percent. Al Dosary notes that another considerable drawback of the policy was the negative affect on the development of local expertise, which ultimately did not grow. Instead, it resulted in the circumstance of “building a non-national expert system” that could leave the country after obtaining a certain degree of expertise, without much advantage to the country or its national development plans. Ultimately, Al Dosary maintains that buying in foreign skills is “a very attractive option for short-term development plans, but, in the long run, will be very damaging to the national economy.”

Thus, as in the case of Saudi Arabia, solving the problem of the skills shortage in South Africa is not a simple matter of importing foreign skill. Logically, solving this issue with foreign skills shortages would require a balance to be created. For example, the most significant proportion of the skilled and unskilled functions of the companies should be fulfilled by South African citizens; thereby, promoting skills development and reducing unemployment. Concurrently, however, any skills that are lacking in South Africa should be supported in moderation from the foreign community, while these scarce skills are further encouraged and developed locally to boost the local companies over the long term with South African citizens.

Furthermore, it is worth noting that it can be difficult to expect specialists in a field to have experience and skills that are outside of their core focus, while still maintaining world class scientific work. Thus, it may be useful, in many cases, to overcome any skills shortages by surrounding the scientists with suitable teams of individuals who do have the necessary skills. For example, mutually beneficial partnerships between technical and business specialists, or between the individuals who have the particular skills necessary, can be a suitable alternative — or perhaps even a better solution — than expecting select individuals to acquire all the skills necessary to perform all the tasks necessary. In the case of South Africa, DNAlysis (2014a) is one prime example company, as described in Chapter 3, which was created through a partnership between a scientist (Dr Danny Meyersfeld), and a dietician (Ms. Yael Joffe). Each provided the skills necessary to generate a hybrid organisation combining science and dietetics, without requiring either person to acquire all the skills to create the company themselves.

6.3.3 Competition and demand

While there were other weaknesses that were noted on the South African macroenvironment, one weakness that was highlighted repeatedly was the aspect of South Africa’s market. These findings

were supplemented by the results of the Phase 1 competitor and market analysis, whereby the general competition and demand profile suggested that the local demand for new local products appeared to be low throughout all of the categories, but higher when foreign products were being considered.

This result was contrary to findings in the literature, however, which have suggested that South African consumers are usually inclined to favour products that are produced locally (Kamwendo et al. 2014). The Kamwendo et al. study found, though, that 'ethnocentrism' for local products varies between the country's different ethnic groups, with "significantly more ethnocentric tendencies" being exhibited among the Black populations than the other ethnic groups. This would suggest that the target markets for most of the HTVs in Sample 1 were not focused on the Black populations. Although the demographic profiles of the customers were not specifically determined for the HTVs in this study, the Kamwendo et al. study suggests that the ethnic profiles of the target markets of the products should be a factor for consideration for HTVs looking to sell products in South Africa; whereby, the ethnicity of the target market of many products may need to be re-evaluated to improve the overall demand for local versus foreign products in South Africa.

Another point that should be discussed, which pertains to the South African market and its potential demand, is the aspect of inequalities that continue to exist between the income structures of the racial demographics. As noted by van der Berg (2011), racial inequality and inequality in income distribution is still large in South Africa, with the country's Gini being estimated at 0.72 in 2010 (van der Berg 2011). Gradín (2014) argues that in South Africa, "racial inequality goes beyond any imaginable limit", with Blacks earning approximately 9% of the median income of Whites, which translates to an annual income R10 554, compared to R117 249, respectively. This is based on the Income and Expenditure Survey (IES 2005, cited in Gradín 2014) conducted by Statistics South Africa (Stats SA) from September 2005 to August 2006. An example of South Africa's income inequality, relative to the US and Brazil, is shown in Figure 6.2.

This skew in the income levels in South Africa may help to explain why the demand for many HTV products in South Africa is limited, and whereby good products or services are ultimately unable to succeed, since the majority of the population is unable to afford them. Overcoming such demand limitations that are caused by the country's inequalities should be factored into any HTV business model, thereby attempting to provide the products and services to those who need them, while structuring the organisations in a way that they can still be sustainable.

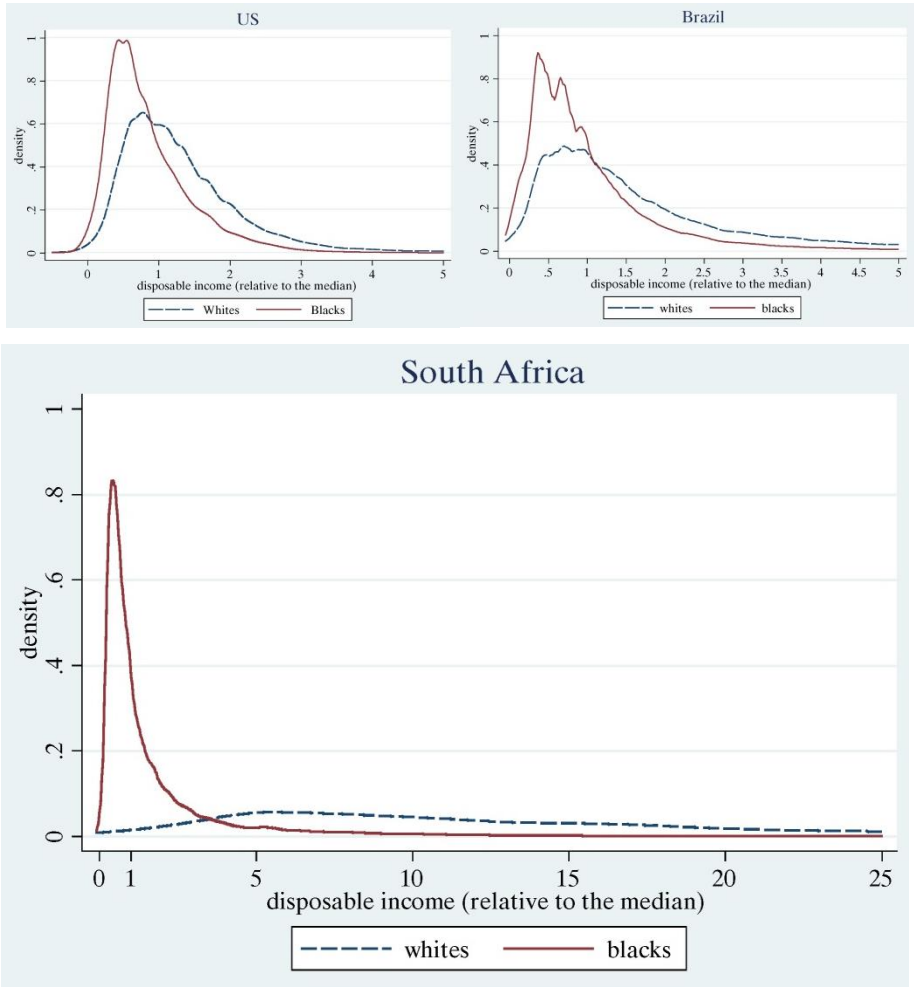


Figure 6.2 Distribution of disposable incomes between White and Black racial demographics in the US (top left), Brazil (top right), and South Africa (bottom)

Source: IES 2005, cited in Gradin 2014

Various issues were referred to relating to the market competition and dynamics, including corporate monopolies, Chinese imports, and overcoming long-standing network alliances between brands. One respondent noted, for example (Sample 1 Anonymous Respondent A 2014):

> *"[The] market is saturated, whereby some of the larger players are directly represented in SA … Those that are not directly represented usually have a long standing relationship with a local company built up over the last 15-20 years … There is a threat from Chinese Distributorships which are ridiculous contracts that most South Africans ignore … The products offered are usually copies of the original thing made in China and selling for a much cheaper price. Someone will bite for the quick buck. Most of the universities and diagnostic sites (pathology labs, etc.) still buy on scientific evidence of performance as published in proven scientific/medical publications, and also from those with whom they have had a long relationship — the trust has been earned".*

Thus, while the majority of South African-based SME-scale HTVs have, to date, been owned and operated by South African citizens, it appears that this local citizenship does not apply throughout the entire HTV market (including large, public HTVs), since many foreign brands and large multinational corporations (with foreign shareholders) are holding a significant share of the country's HTV market. Furthermore, the aspect of Bourdieu's (1986) four forms of capital are already at play in South Africa; whereby, the larger corporations hold the 'social capital' in the form of the well-established network connections and the 'cultural capital' in the form of the trust, reputation and legitimacy with the buyers. Ultimately, entering smaller local HTVs into the South African market requires generating and establishing similar network 'assets' to the corporations, and developing the good will that the buyers respect.

Furthermore, as was found in the results of both Phase 1 and Phase 2 of this study, the competitor and market profiles of each of the different functional classifications of companies is immensely different in South Africa. For example, medical devices are faced with a very different scenario to the therapeutics companies, public services, or any of the other classifications. Therefore, refining the business model for any new HTV requires observing these differences between the markets; and generating models to best overcome the threats in the environment, and capitalise on any of its strengths.

Finally, it should also be noted that certain business models may act to overcome problems in one HTV sector, with advantages in another; especially if the model were to incorporate various sectors into its model. One possible illustration could, for example, be in the category of medical tourism (Mahomed and Slabbert 2012). These authors, for example, discuss the prospects of "stem cell tourism" in South Africa, along with its ethical considerations and lucrative commercial possibilities. Excluding therapies that have not yet been proven, and focusing only on legitimate, tested treatments (Mahomed and Slabbert 2012), stem cell tourism could present opportunities that span various ancillary sectors and industries, thereby bridging various different sectors of the economy. Miremadi (2014) has suggested that countries, such as Singapore, Israel, China and India, have already "prioritised their national goals to include becoming globally recognised medical tourism destinations". This is because, through bridging the industries of therapeutics, medical surgery, public services, contract services and tourism, companies would stand to annul the weaknesses of any one of these sectors individually, with the strengths of the others.

6.3.4 Strengths in the South African macroenvironment

While there were significant weaknesses discussed in this study, numerous opportunities and strength were also observed, which have aided the country in developing an economic sector employing over 72,800 people, and generating revenues in excess of R767 million, annually (DST 2008); although, much of this income is generated in corporate-sized ventures. HTV entrepreneurs would be encouraged to consider the strengths and opportunities that exist in South Africa's

market to grow the sector further. These include, for example, the large domestic markets for healthcare products, access to the developing markets of Africa, the country's increasing international exposure, and the support that *is* offered by the government.

For example, while the government was criticised by many companies in this study, it was also lauded as the major customer in healthcare through government tenders; as well as for its provision of tax rebates for R&D. South Africa was commended for its openness to biotechnology and health technology advances, compared to Europe; and for assisting in approaching the international community, such as through the DTI's programmes that assist exporters.

South Africa's central geographical location was noted as an opportunity, since its global geographic position has located the country as a potential gateway to the growing African market, along with its abundance of natural resources. The high price of branded imported drugs and the cheaper costs of labour relative to the international countries were also noted as aspects in South Africa's favour; and the country's innovative, entrepreneurial culture; scientific and university quality; academic support; few local competitors; and scope to develop business through relationship building, were each proof of the respondents' ability to see the opportunity in even a potentially difficult situation.

6.3.5 Conclusion of the objective

There appeared to be considerable challenges for the HTVs in this study. The single most commonly noted challenge faced in South Africa was the issue of capital. Methods of overcoming this were proposed, including crowd funding, social entrepreneurship, and generating alternative forms of capital. The second most frequently listed weakness was the lack of skills in the country. Various methods were recommended for overcoming this as well, including surrounding the scientists with suitable teams of individuals who have the necessary skills, or creating mutually beneficial partnerships between technical and business specialists.

Finally, while significant weaknesses were uncovered in this study, numerous opportunities and strength were also observed. These included the high price of branded imported drugs and the cheaper costs of labour relative to the rest of the world; the country's innovative, entrepreneurial culture; the quality and support offered by the universities and academia; few local competitors; and the potential for business development through relationship-building.

6.4 OBJECTIVE III. CORRELATIONS BETWEEN HTV SPENDING, TECHNOLOGY TYPE, SIZE, LOCATION, PRODUCTION METHOD, AND ACTIVITY STATE (SUSTAINABILITY)

This objective hoped to conduct a conclusive inferential statistical analysis of the HTVs in South Africa, and thereby present any correlations between the R&D spending or start-up costs, core functional classification or technology types, employee counts or sizes, HQ locations, production methods, and activity state or sustainabilities of the companies in Sample 2 of the study.

Due to the nature of the data generated in Phase 2, different inferential statistical tests were applied. Tests were performed to observe the correlation or association between categorical data variables, such as the ‘activity state’ of the companies, their ‘HQ locations’, and their core functional ‘classifications’; discrete data variables, such as the ‘size’ of the companies; and continuous data variables, such as the R&D or start-up ‘spending’ of the companies. Where necessary, the discrete and continuous data were grouped into segments as categorical data, while the categorical data of ‘activity state’ was ranked as ordinal data or grouped as dichotomous categorical data to allow the data to be included in each of the tests. Thus, Pearson’s Chi-Square, ANOVA, bivariate correlation, linear regression, logistic regression and multinomial logistic regression were performed on the Sample 2 data, where appropriate.

6.4.1 Chi-Square

Following the Chi-Square tests of Independence of Categorical Variables, it was found that various associations did exist. The most significant was the association between the company’s ‘classification’ and its ‘production type’ ($\chi^2 = 23.525$, df = 12, $p < 0.05$). Therefore, it was observed that, whether a company was a vaccine, biogeneric, therapeutics, nutraceutical or other type of ‘classification’, was related to the different ‘production types’, such as whether the company developed and manufactured internally, was developed by a third party and manufactured internally, or otherwise. With the Chi-Square tests, it was not possible to indicate which classification category was likely to undertake which production type, since the result was simply able to confirm, with high statistical significance, that the null hypothesis could be rejected in favour of the hypothesis. Alternatively, it could be simply stated that the two variables of ‘classification’ and ‘production type’ were not independent.

A second set of categorical variables: the ‘size’ and ‘activity state’ were very closely related due to the principle that closed companies would have had no employees; and companies in a state of ‘general operation’ would have been the largest. The test of these variables formed the control test throughout the inferential statistics portion of the study, as a means of observing the authenticity of the tests, and minimising any possible errors. One shortfall that was observed within the data was the number of values in the data set. During the Chi-Square tests, cells were ‘flagged’ that had expected counts of less than five, violating one of the assumptions of Chi-Square analysis and indicating that the results “may not be meaningful” (Elevers 2014a). Due to the limited number of HTVs in South Africa, this was an unavoidable limitation. Although data could be grouped into fewer, larger categories, grouping the data beyond a certain extent reduced the variability of the data to become meaningless. Furthermore, producing erratic groupings also rendered the results less meaningful. Therefore, the remaining inferential statistical tests were useful in providing additional correlation information. Furthermore, while partial relationships existed between the ‘location’ and ‘activity state’ ($\chi^2 = 10.815$, df = 6, $p < 0.1$); ‘production type’ and ‘activity state’ ($\chi^2 = 14.475$, df = 8, $p < 0.1$), and ‘production type’ and ‘spending’ ($\chi^2 = 13.847$, df = 8, $p < 0.1$), these

were not statistically significant below a 5% significance (they were only below a p-value of 10%), and will therefore not be considered further.

6.4.2 ANOVA

In the ANOVA tests, the control case of the 'size' versus 'activity state' showed an appropriately high F ratio, associated with a p-value that was less than the α level (0.05), whereby $F(3, 77) = 71.451$, $p = 0.000$, as was to be expected for the control test. Two of the variable test cases presented interesting results, though. In the test between 'classification' and 'spending', a high F ratio was observed with an associated p-value less than 0.05 [$F(10, 52) = 20.521$, $p = 0.000$].

In this test, 'classification' was the categorical IV, and 'spending' the continuous DV. Conducting the ANOVA allowed a result to be observed in answering whether the companies' 'classification', had an association with its 'spending'. Thus, the ANOVA test measured the average spending for the 'vaccines' classification, versus the 'biogenerics' classification, and so on, and found that there was a significant difference between the means (Elevers 2014b). Based on the result of the ANOVA, the null hypotheses could therefore be rejected with sufficient evidence to conclude that the means of each of the groupings of the classification variable were not equal. The high F ratio indicated that the variance between the groups was high compared to the variance within the groups.

When considering the graphs of the mean 'spending' in relation to the 'classification' type, as shown in Appendix V, it was apparent that the reason for this high variation was because of a significant spending outlier in the 'vaccines' category; whereby, the average 'spending' for 'vaccines' was a factor higher than the others, at around R200million. The high costs associated with the 'vaccines' category could, therefore, explain the low number of companies in this category, since only two such companies were present in the Sample 2 data set. Spending across the other categories was relatively consistent, except for the medical devices category, which had an average spending of R18million: slightly higher than the total spending average of R13million.

The analysis between 'production type' and 'size', while statistically significant, did not offer a very large F ratio, indicating that, although statistically significant, the means did not vary substantially between groupings, compared to within their groupings. Although it did not present a statistically significant p-value, upon observation of the graph of mean values of 'production type' and 'spending' [$F(5, 57) = 2.282$, $p = 0.058$], a substantial difference between the mean 'spending' relative to the 'production type' category was evident. The 'spending' of those in production type 'one' (who had developed and manufactured their goods and services in-house) was substantially above those in production type 'two' (whose goods and services had been developed by a third party, but manufactured in-house), and production type 'three' (developed and produced by a third party). The average spending between production category one, two and three was R13.4 million, R7.7 million, and R1.6 million respectively.

This was to be expected, since higher costs would have been accrued for R&D and establishing a manufacturing facility, compared to companies that only had a manufacturing facility and had not needed to spend anything on R&D. Similarly, companies that were effectively resellers, and who had neither developed nor produced their goods and services, would have had lower costs than either of the other two categories. The results indicated that when deciding whether to develop and produce in-house or through a third party, the decision should be carefully considered, as it would have significant implications on the overall costs for starting up the venture. This also suggests that outsourcing of manufacturing and functional tasks could be a viable alternative to in-house production for start-ups that are in short supply of funding.

6.4.3 Correlation analysis

Following the correlation analysis using PMCC, an r value of 0.506, which was statistically significant ($r = .506,\ p < .01$) was observed between 'size' and 'spending', indicating that there was a moderate-to-strong positive correlation between the sizes of the companies and the amount that had been spent to date on their R&D or start-up costs. As in the previous ANOVA test observations between 'production type' and 'spending', this was to be expected, since larger companies would have been expected to require more R&D or start-up costs. Since the correlation coefficient 'r' is not unidirectional, this indicates that a larger start-up cost would also have corresponded to the generation of a larger-sized company; whereby, more spending would result in larger operations.

An interesting result from the correlation analysis was the relation between 'spending' and 'activity state', which was shown to have a partial-to-weak negative correlation, evident by each of the values of Kendall's tau ($\tau = -0.209,\ p < 0.05$) and Spearman's rho ($\rho = -0.275,\ p < 0.05$). This suggests that spending more on the organisations did not correspond to a higher rate of sustainability, but in fact the opposite was true. This was supported by the results in Table 5.3, whereby, the percentage of companies in a state of sustainability reduced from 60% down to 33.3% and 33.3% when increasing from R1million to R5million and R10million in spending, respectively. Furthermore, the sustainability reduced from 63.6% down to 54.5%, when increasing from R15million to R20million, respectively, and from 77.8% down to 73.6%, when increasing from R30million to over R30million, respectively. Therefore, it can be stated that investing more money on R&D start-up costs does not necessarily result in a higher chance of reaching sustainability, and in fact the opposite is often true.

Indeed, based on the principles of reaching break-even point and generating a return on investment (Chakma et al. 2010; Masum and Singer 2010), a higher initial investment would require more products or services to be sold, or at a higher price. The average profit margin for companies observed in Phase 1 of the study was 56.9%, which did not alter according to the start-up spending. Thus, the higher initial spending would result in a higher overall risk, without necessarily guaranteeing a higher reward.

6.4.4 Linear regression

The penultimate stage of the inferential statistics involved the linear regression of the data. Due to the nature of the data, linear regression could only be performed on the two numerical variables ('size' and 'spending'), since the remaining variables constituted categorical data. The variables analysed in the linear regression were 'size' as the DV, and 'spending' as the IV. The purpose was to determine whether the nature of the relation between the variables could be specified, and thereby to conclude if the value of one of the variables could be used to predict the value of another of the variables. In this respect, it would determine whether the amount spent for R&D and start-up related to the overall size of the companies.

The r^2 value of the linear regression was 0.256, adjusted to 0.244 ($P < 0.01$) due to the single IV used in the test. The probability of this coefficient occurring by chance alone was also approximately zero, and it could be concluded that 24.4% of the variation in the R&D or start-up spending of the companies could be explained by the number of people who were currently employed at the organisation. Thus, for example, it could be predicted that the spending in a South African HTV would be affected up to 24.4% by its size; and if it had four employees, it would be expected to require an approximate amount of R7 900 788 in start-up spending, calculated as follows:

$$\mathbf{Spending} = \mathbf{271261.9} \times \mathbf{4} + \mathbf{6815726}$$

$$= \mathbf{7900778} \qquad \textbf{[15]}$$

6.4.5 Logistic regression and multinomial logistic regression

Finally, logistic regression and multinomial logistic regression were performed in order to analyse whether any relation could be observed between the categorical variables, and specifically whether the value of any of the variables could be used to predict the 'activity state' or sustainability of the companies. No significant association was observed between any of the variables and their 'activity states', when analysed together as a multivariate analysis or individually as a step-wise regression (except for the control variable 'size'). This suggests that it was not possible to provide an accurate prediction on the overall activity state of the HTVs, based on their attributes, either when considered together as a combined set of variables, or when observed individually. Based on the results of this study, the most significant overall predictor of success or sustainability was drawn from the probability ratios, discussed in the final objective of this study, next.

6.4.6 Conclusion of the objective

Various associations did exist between the start-up spending, technology type, size, location, production method, and activity state (sustainability) of the companies in this study, with the most significant being the association between the companies' classifications and their production types.

The sizes and activity states were also very closely related, due to the principle that closed companies would have had no employees, and companies in a state of general operation would have been the largest. The classifications of the organisations had an association with their start-up spending, where vaccine-based company start-up spendings were far higher than the others, due to an outlier of around R200 million. Medical devices were also relatively higher than other categories, requiring an average of R18 million for start-up. The start-up spending of the other categories, however, was relatively consistent at around R13 million. Statistically significant variations also existed between the production types and sizes of the organisations.

Size and spending showed a moderate-to-strong positive correlation, while interestingly, spending and activity state showed a partial-to-weak negative correlation, suggesting that spending more on organisations did not necessarily correspond to a higher rate of sustainability. Size and spending showed an association that could be predicted though a prediction equation, and this relationship was such that up to 24.4% of the spending in a SME-scale South African HTV, based on the broad spectrum of the companies in Sample 2, would be affected by its size. No specific prediction equation could be made about the activity state (and therefore sustainability) of a company as a result of its start-up spending, technology type, size, location or production method characteristics; although, a probability model based on the statistical occurrences of each of the traits in the Phase 2 of the study has been proposed, and which is discussed in the final objective, next.

6.5 OBJECTIVE IV. THE PERCEPTIONS, RATIOS AND KEYS TO SUCCESS AND SUSTAINABILITY AMONG HTVS

This objective attempted to review the nature of South African HTVs and present a success or failure report. It reviewed the HTVs that had started and were in operation at the time of compiling this data, and considered the definition of their success versus those that were no longer in operation; or that had not yet reached a level of sustainability. Since HTVs are not always measured based on their financial success, and may consider various other factors, such as benefit to society, as their company goal, the ambition was to determine the general nature of the HTVs in South Africa, and statistically observe which organisation types had been most likely to match the needs of South Africa.

6.5.1 Definitions of success

From the study, a spectrum of factors was presented by the respondents to signify their perceptions of success in their organisations. A relatively even distribution was observed between human factors and financial factors, as shown in Section 5.2.9. Human factors included aspects such as humanitarian benefits, skills development, organisational growth, quality of products, and arriving at a scientific and commercial proof-of-concept. While there is an automatic assumption that success in the health technology sector should be based on its humanitarian benefit, it is

unreasonable to assume that HTVs should be exclusively humanitarian, because without a financial success factor, the organisations would fail to exist. It could, therefore, be argued as a positive sign that the proportion of human factors was so comparable to financial factors, because in many other commercial sectors, and especially in the financial providers' perspective, financial factors far outweigh human factors for measuring success (Barba–Sanchez and Atienza-Sahuquillo 2011).

Undeniably, without financial success, companies could not reach a level of sustainability. Thus, it could ultimately be argued that the financial sustainability of the companies should be considered as the fundamental determinant of success, while human factors could be relegated to 'the primary goal'. In a study by Ahmad et al. (2011) the authors argued that business success is a four-factor structure for SMEs, which reflects satisfaction in different aspects of the business, including financial performance by the owner-managers, satisfaction in non-financial performance, the performance of the organisation relative to its competitors, and the business' growth.

It was noted in this study that most companies were in a state of positive annual growth (see Section 5.2.7), in each of the five aspects of their companies involving their numbers of goods and services, numbers of staff employed, numbers of dealers or branches, numbers of products sold or clients and overall company turnovers. This was evidenced by the majority of the graphs of the *percentage growth* being above the X-axis, indicating positive growth in most years, or at the very least, no change; and very few companies observing negative growth. Stated differently, while some years (such as 2012) presented years of slow growth, and some companies observed a negative rate of growth, the majority of companies appeared to be in a state of positive growth. The competitor profile indicated in this dissertation has been discussed in detail previously; and overall, it suggests that while challenges indisputably remain, the majority of companies can be classified in a state of moderate success, as per the four-factor structure of Ahmad et al. (2011). Support of this, in terms of the actual number of HTVs in operation in South Africa is discussed next.

6.5.2 Sustainability ratios

In the first phase of this research, the sustainability of companies in South Africa's health technology market was observed as a measure of whether the companies were able to operate as independent, fully sustainable ventures. Two factors were observed: the number of years that the company had been in operation, and whether the company's operations were self-sustainable. On average, companies in Phase 1 of the study had been in operation for nearly seven years, and just a little over half had reached a level of sustainability.

In the second phase of the study, nearly two thirds of the companies were in a state of general operation, while approximately 20% were either sold, or closed down, and 10% were 'in R&D phase', or 'ready to launch'. According to the dichotomous categorisation of sustainability versus not yet or unsustainable, whereby companies 'in R&D phase' and 'ready to launch' were classified

as having not yet reached a level of sustainability, the overall rate of business sustainability for HTVs could be rated as 66.7% sustainable, and at least 30% were observed to be unsustainable (or not yet in a level of sustainability). The aspects of overcoming survivorship bias have been discussed at length throughout the methodology (Sections 4.3.3.2 and 4.4). These results were, therefore, deemed reliable.

Variations could be observed in the overall rate of sustainability for companies, based on their core functional classification, location, production type, size and start-up or R&D spending. By converting the observed frequencies of activity state, as an indication of sustainability into a probability, it was possible to observe the company type that was most likely, and least likely to succeed in South Africa, based on the broad spectrum of SME-scale HTV companies (both operational and un-operational) approached in this study. As noted in the results, the company type that was found to be most likely to succeed was a ‘vaccines’, ‘biotools’ or ‘public services’ company located in Johannesburg, that had developed its products in-house, but manufactured them externally; that had spent between R20 million and R30 million on its R&D or start-up, and had employed at least 20 employees. Such a company was found to have a 63.7% probability of reaching sustainability, based on the statistical observations of the companies in this study.

Stated alternatively, considering the wide spectrum of companies approached in Sample 2 (relative to the entire available South African SME-scale HTV market), it could be argued that a company with a core functional classification of ‘vaccines’, ‘biotools’ or ‘public services’; located in Johannesburg; that has developed its products in-house, and manufactures externally; that has spent between R20 million and R30 million on its R&D or start-up; and has at least 20 employees, could be expected to have a 63.7% probability of reaching sustainability, based on the statistical observations of the companies in this study.

Conversely, the company type that was found to be least likely to succeed, based on the participants in this study, was a nutraceuticals company based in Cape Town, that had developed and manufactured its products in-house; spent between R1 million and R10 million on its R&D or start-up; and employed between six and 20 employees. Such a company would be expected to have a 3.2% chance of reaching sustainability. Note that the company size of zero was not used, since based on this calculation it would have not had any possibility of success, therefore the next lowest company ‘size’ was used.

Interestingly, from the results of the samples in this study, no companies were observed that fitted the profile of the company most likely to succeed in South Africa, indicating that this profile may yet be of value to a new HTV start-up. Conversely, one company existed in this study’s data set that fitted the profile that was least likely to succeed. It had closed, and was no longer in operation.

Once again, the model proposed is a probability model, based on the statistical occurrences of each of the traits in the Phase 2 of the study. It does not assume that there were specifically any relationships between the traits, but only what the chances of success or failure would have been

for a company with a specific set of traits, based on actual observations of the Sample 2 companies. In deliberating the significances of this in relation to future HTV success in the South African environment, this equation should be regarded with caution for predicting future trends. Just as in the case of a coin toss, whereby past trends cannot guarantee future trends, here too, past probabilities cannot necessarily guarantee future company performances. This is not to say, based on this study's observations of the market circumstances of South Africa that these trends are not the outcomes of inherent market characteristics in South Africa. However, assessing whether these are outcomes of inherent dynamics in the country or random fluctuations would only be determined by similar future studies on similarly wide samples of the South African HTV market, to observe whether the trends of success and failure across the business traits persist.

6.5.3 Academic improvements for success

One aspect that was included in this study was the recommendations that respondents presented, based on their experiences in the South African macroenvironment, for changes and improvements that could be made at the country's academic institutions to better prepare students for the South African HTV job market. The results of Phase 1 of the study suggested that three primary adjustments should be made in South African academic institutions: 'inter-disciplinary training', 'practical or industry experience', and 'academic institution changes'. Aspects of each of these were presented in detail in Chapter 5, though the vast majority of recommendations were within the category of inter-disciplinary training, and specifically to provide science students with business cross-disciplinary training. This, for example was suggested to include training in commerce, entrepreneurship, finance, business management, law, marketing, and sales. Recommendations to reinforce these, practically, included mentorships between academic institutions and industry, business training for students, and internships for scientists with business mentors.

Indeed, these results reflected the sentiments of Collet and Wyatt (2005), described in Chapter 2, who argued that success in HTVs requires "champions" with a sound knowledge of the respective scientific principles, and the business principles that relate to market development, product innovation and venture capital. The authors' emphasis on "entrepreneurial culture" was frequently reiterated by the respondents in this study, suggesting that a significant requirement is for scientists to view not only the scientific side of research, but also the "commercial exploitation of their results."

6.5.4 The keys for success

One final aspect that was sought from this study was to generate a possible roadmap for success among the HTVs in South Africa. While a fool-proof system can never be devised, and a business in any sector should always be open to adapting and changing to its dynamic environment, as well

as capitalising on opportunities and strategising for threats, many mistakes and lessons that have been learned by the experts who have already travelled those roads, need not be relearned by each new HTV entrepreneur. Instead, by building on the experiences of these experts with the information that they have, a more solid HTV infrastructure can be generated, and the entire industry can grow and develop in unison; whereby, the new challenges that arise and face each organisation equally, can be confronted as a body of combined intellectuals.

According to the communications with the various experts in the field, the following key points were observed:

1. Official recognition and conformity rating, in the form of CE, SABS and research publications, is essential. For some companies approached in this study, this has caused a major hindrance. For example, as noted by Sample 2 Anonymous Respondent D (2014):

"Though we have been very successful in our development of a [medical device] Instrument we have, unfortunately, "hit a brick wall' with the European Patenting Office and this has negatively affected an existing funding option as well as all future possible funding strategies. Until we are able to finalise a US patent application or reach an alternative deal with a large manufacturer, the project must be placed on hold as any further development cannot be justified out of the limited funds still available.

2. Intellectual property rights and ownership is fundamental, especially since the large multinational corporations are able to outpace the smaller companies against any head-to-head activity. For example, as noted by one respondent (Sample 2 Anonymous Respondent A 2014):

"This is very important: From the outset I negotiated with a University for exclusivity on their [intellectual property] for commercial use. They may use it for academic purposes, but they may not sell it to any other commercial manufacturer. Without this protection the big multinational companies will destroy you within weeks after you have done all the initial research and publication on the test."

3. Capital is a fundamental requirement for the success of HTVs. Capital, as described earlier in the chapter, covers not only the financial resources, but the social resources, networks, legitimacy and trust. These are described further here, but as a central component, the financial capital must be secured, because as noted by Sample 2 Anonymous Respondent D (2014), the company will fail to exist without it:

"We have limited finances still available and we intend to apply this to the patent application for the product in RSA and US. It is, therefore, likely that the facility … will have to be closed. Though we would have loved to continue the product we have run out of external funding options and the prospect of finding further funding until we have secured a US patent is very

small. We are not in a position to fund the organisation out of personal funds beyond the minimum to maintain it as a going concern and guardian of its IP rights."

4. The demand in the market is essential, and specifically if it is to be sold in Africa or South Africa, it must be customised for this environment. As with any industry, the goal is to find the products to satisfy the market rather than find a market for the products. As explained by one respondent (Sample 2 Anonymous Respondent A 2014):

"True. Your product is useless without a market, no matter how WOW it is. In Africa as a whole the situation is far more complex. If you have identified a market and you have a potential technology to fill this gap, you still need to sell it to get momentum. In general, the public health sector in Africa is years behind developed nations and we do not spend any money on diseases that are classified as 'first world diseases'. Let's say you manage to produce a new pre-natal genetic screen predicting most Immune deficiencies in babies, there is no way that our public healthcare would even think of buying the test. If you develop the same test in a developed economy, it will probably be implemented as a routine diagnostic test for all pregnant mothers and you will sell millions."

5. 'Selling' in Africa is a complex undertaking, since the public who needs the products, often does not have the money to pay for them. It is, therefore, essential to factor the subsidisation of the products into the business model, and where necessary collaborate with the ideal partners to make the venture sustainable. As noted by Sample 2 Anonymous Respondent A (2014):

"even if the market is massive and you have got the product, you will probably not get any sales into Africa. The situation will force you to team up with other large multinational companies and that will probably be the end of you. My market is over 300 million infected people in Africa but >98% of my orders come from foundations, NGO's, researchers and private entities, all sponsored by the developed world. Even if I half the price of my test they still won't buy it – and I focus on a neglected tropical disease listed on the WHO website (mainly an African disease). I now sell <3% of my product in SA and I can honestly say that the private sector in SA is just too small to sustain a company like mine. You can use it as part of your initial research and commercialisation but you have to sell elsewhere."

6. Although it was not a popular method of production for the HTVs in South Africa, outsourcing many of the company's menial functions appears to have merit. Rather than wasting capital and resources on recreating facilities that others are able to provide, it may prove better to award the task to those who are already set up to perform those functions efficiently; and thereby, free up one's own resources to focus on the core functions of the company. Sample 2 Anonymous Respondent A (2014) explained:

"Yes, some … companies also struggle with volumes and appreciate this arrangement. It also makes sense because [the contractors have] already made the costly mistakes that you are going to make. Those mistakes might end up destroying your market and even your company. If you are greedy and want to get rich quick it might just end up the other way. Example: For international sales our product has to be produced in a facility that complies with strict international ISO accreditation. Who would loan a few million to a start-up operation?"

7. Networking and goodwill is a big factor. This includes the use of human resources, and in many cases it requires the power of connections, such as relying on resources from contacts wherever possible. It helps in saving considerable time and money. Sample 2 Anonymous Respondent A (2014), for example noted:

   "Networking, but lots and lots of goodwill as well (both ways). I have donated thousands of tests at huge cost without interfering with their research and publications, even at times when the company didn't have the cash."

8. Perseverance is another trend that was apparent among the HTVs. While this is not a factor exclusive to the health technology sector, it seems to be a major factor, especially when funds are limited (Ahmad et al. 2011). Irrespective of the apparent demand for a product or service in South Africa, it still requires a concerted drive to get it off the ground, with hope for a 'big break' to help the process whenever possible.

While this presents a concise list of the keys for success, two more elaborate communication excerpts are included in Appendix VI. One is based on a company that has reached sustainability, and the other is from a company that has not. While they could not be entered into the dissertation in their entirety, it was useful to include them as supplementary material.

6.5.5 Conclusion of the objective

From the study, a relatively even distribution of human and financial factors was noted to determine what constitutes success, with the human factors including aspects such as humanitarian benefits, skills development, organisational growth, quality of products, and arriving at a scientific and commercial proof-of-concept. The financial factors for defining success included return on investment (ROI), profit, international business and the trade sale at EXIT.

Most companies were in a state of positive annual growth, and nearly two thirds of the companies were in a state of general operation (66.7% sustainable), with at least 30% unsustainable or not yet in a level of sustainability. The maximum probability of reaching sustainability for a company that matched the most successful traits of start-up spending, classification, size, location, and production type, based on the participants in this study, was found to be 63.7%. Matching a

company with the least successful of the above traits, however, would render the company with only a 3.2% chance of reaching sustainability, based on the participants in this study.

The three primary adjustments that should be made in South African academic institutions to better prepare students for the South African HTV job market are inter-disciplinary training, practical or industry experience, and academic institution changes.

Keys to success, in no particular order, include acquiring official recognition and conformity rating, in the form of CE, SABS and research publications; acquiring intellectual property rights and ownership; acquiring capital; defining the demand in the market; factoring the limitations and complexities of selling in Africa; collaborating with the ideal partners; outsourcing the companies' menial functions, where possible; networking with communities of people, institutions, organisation and associations; developing goodwill; and persevering.

6.6 RECOMMENDATIONS

This study was carried out as thoroughly as possible, in order to generate a complete overview of the South African HTV environment. Future research may be conducted, though, to supplement any gaps in this research or to present additional material that may enhance the knowledge base.

Firstly, during the correlation analysis between the technology, venture, size and location, the size of the company was calculated using the number of employees as the determinant of size. Another, potentially more economically accurate determinant could have been annual turnover, and for various reasons described previously, this parameter was not included in this study. It may be informative in a future study, though, to include annual turnover (or balance sheet total in the case of companies in R&D) in conjunction with the number of employees as the determinant of the companies' sizes. Secondly, the activity level of the companies was considered as a 'snapshot' at the current moment in time, and did not consider past of future trends. To improve the ability of forecasting potential trends, a future study could consider a more in-depth analysis of the growth trends in the companies to observe the categories of the HTV sector that are in a state of high growth and those that are in a state of decline.

In a future study, biotechnology companies or venture types that exist outside of the field of the remediation of human disease may be analysed. This could include, for example, agricultural, plant-based, environmental and industrial biotechnologies; producers and suppliers of health technology for non-human recipients; producers and suppliers of products for general health and wellness, such as vitamins and dietary supplements; and producers and suppliers of general medical equipment. It may also be interesting in a future study to observe whether the interaction of officials in government posts within or among the internal operations of HTVs, for example as staff at the HTVs or vice versa, would in any way associate with the attitudes and outcomes of the government departments towards HTV support and development. Moreover, while it is possible

that ‘government goodwill’ may play a significant role in overall success or failure of HTVs, this was not specifically interrogated here, and may present a factor for consideration in future studies.

Finally, as a comparison of similar data sets to another comparative county, a repeat study can be performed on a similar country’s HTVs to observe whether there may be any correlations or inferences that can be generated, based on a comparison between the two countries.

6.7 CONCLUSION

This concludes the final chapter of the dissertation. The correlations or patterns between the majority of HTVs and the types of core functional techniques that they are using has been observed, while examining the detailed theoretical elements of some of the scientific techniques that are being used at one of these ventures. The challenges that advanced HTVs face in South Africa as compared to other developing and developed countries have also been examined.

The types of costs involved with advanced HTVs in South Africa have been identified, and deliberations have been presented on the correlations that exist between the start-up spending, technology type, size, location, production method, and activity state (sustainability) of the HTVs. In the final section of the study, what constitutes success in the South African HTVs, the proportion of HTVs that are successful or sustainable, and the keys to their success or sustainability have each been determined and discussed.

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APPENDICES

APPENDIX I: LETTER OF INFORMED CONSENT AND ETHICAL CLEARANCE CERTIFICATE

Mr. JEREMY. R. SAYER (BSc(Med)(Hons)), PGDipMan
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10th January 2013

Dear Sir or Madam

I am currently conducting a study as part of my Master of Science degree at the University of South Africa (UNISA), with the aim of determining the key factors and characteristics that SME-scale commercial biomedical ventures require to succeed in the South African environment, compared to other developed countries. Information from the study will be presented as a dissertation, and the valuable data that is gathered from the study will have potentially far-reaching implications. The data will be incorporated into the design of the newly upcoming biotechnology and biomedical courses at the UNISA Campus, to enable the degrees to be more industry related, and current; thereby preparing students better for the South African market.

We believe that by analysing biomedical ventures, such as yours, we will be able to identify key areas of success in the South African environment, and thereby have the opportunity to structure new and existing business prospects to better capitalise on these macroeconomic strengths. Conversely, by identifying areas of lower success in the country, your company will help towards devising strategies that assist new start-ups to better prepare for, or otherwise overcome such barriers.

While I understand that there are potential risks to participating in the study, due to the release of company information, as well as any other data of a confidential nature, I and all involved with the study assure that all information gathered is strictly anonymous, and no company names will be divulged in the data set. Participation in the study is also completely voluntary, and while comprehensive data is a key objective of the study, you may withdraw from the survey(s) and data record, or decline to release any information at any time. The questionnaire is also carried out anonymously via an email portal, without interaction with the researcher.

Thank you for taking the time to complete the survey. By accepting to partake in this anonymous study, it is presumed that you approve that the information provided may be used for this academic research project.

Sincerely

Jeremy Sayer

UNISA university of south africa

2013-09-11

Ref. Nr.: 2013/CAES/071

To:
Student: JR Sayer **Student nr: 50662546**
Supervisor: Prof J Dewar
Department of Life and Consumer Sciences
College of Agriculture and Environmental Sciences

Dear Prof Dewar and Mr Sayer

Request for Ethical approval for the following research project:

A determination of the key factors and characteristics that SME-scale commercial biomedical ventures require to succeed in the South African environment, as compared to other developing nations

The application for ethical clearance in respect of the above mentioned research has been reviewed by the Research Ethics Review Committee of the College of Agriculture and Environmental Sciences, Unisa. The Ethics committee can at this point not provide you with full Ethical clearance as data has already been gathered for this particular study which is considered a retrospective application for which clearance cannot be given. The Ethics committee reviewed the documentation provided on 4 September 2013. The committee did consider the Ethical complexity of the information provided but did not find any major Ethical concerns related to the various aspects of the study. However, this only applies if Ethical practices were followed during collection of the data and any resulting analysis. It is hoped that Ethical procedures were followed during the collection of data from companies and that a consultative process was followed through which permission was received to gather data from the respective companies. Although the standard college consent form was not used it is hoped that this procedures was implemented during data gathering. Ethics clearance for the above mentioned project (Ref. Nr.: 2013/CAES/071) is not given based on the retrospective nature of the submission.

The Ethics Committee wishes you all the best with this research undertaking.

Kind regards,

Prof E Kempen,
CAES Ethics Review Committee Chair

University of South Africa
Preller Street, Muckleneuk Ridge, City of Tshwane
PO Box 392 UNISA 0003 South Africa
Telephone: +27 12 429 3111 Facsmile: +27 429 12 429 4150
www.unisa.ac.za

APPENDIX II: QUESTIONS FROM INTERVIEW AND QUESTIONNAIRE OF THE STUDY

Table 8.1 Questions from the online questionnaire of study Phase 1

What is your job title / role at your company? Please select one.
Do you offer a product or service? Please select one.
Which products or services do your company offer? Please fill out wherever possible.
Are your products or services produced or manufactured locally (in SA)? Please indicate on a sliding scale between 0% and 100%, where 0% means they are all manufactured internationally and 100% means your products are all manufactured locally.
Are any raw materials sourced locally (in SA)? Please indicate on a sliding scale between 0% and 100%, where 0% means they are all sourced internationally and 100% means your raw materials are all sourced locally.
Are/were your products or services researched and developed locally (in SA)? Please indicate on a sliding scale between 0% and 100%, where 0% means they are/were all developed internationally and 100% means your products are/were developed locally.
Are your products or services sold locally (in SA)? Please indicate on a sliding scale between 0% and 100%, where 0% means they are exclusively exported and 100% means your products or services are exclusively sold within SA.
In which field of medical / biotechnology infrastructure is the company situated? Please select one that best applies.
Is the company owned by South African citizens? Please indicate between 0% and 100% where 100% = all RSA citizens, 50% = mix and 0% = no RSA citizens.
Was the company started by South African citizens? Please indicate between 0% and 100% where 100% = all RSA citizens, 50% = mix and 0% = no RSA citizens.
What portion of the technical or skilled workforce comprises South African citizens? Please indicate between 0% and 100% where 100% = all RSA citizens, 50% = mix and 0% = no RSA citizens.
What portion of the general or unskilled workforce comprises South African citizens? Please indicate between 0% and 100% where 100% = all RSA citizens, 50% = mix and 0% = no RSA citizens.
In your opinion, what additional training should South African academic institutions offer to better prepare graduands for the South African job market? Please specify.
Where are the company headquarters based? Please specify.
Does the company have branches internationally? Please specify where.
How was the company start-up funded? Please rate one for each drop down menu
In terms of the sustainability of the company: Please answer each
What percent of the selling price of your goods or services are spent on costs for these goods or services? Please suggest a percentage.
Please provide some feedback on the relative growth of the company. Yearly figures / data should be placed in each box.
To identify where your company fits into the South African market, please complete the matrix below. Please select one choice from each box.
What do you see as the greatest risks or threats for the South African biomedical / biotechnology industry? Please indicate in order of priority (greatest to least risk).
What do you see as the greatest opportunities or dynamics of the South African biomedical / biotech industry? Please indicate in order of priority (highest to lowest).
If there are any pieces of valuable information that you can offer, such as what has made your company a success, or details you think we have not covered, please be so kind as to highlight them here.

Table 8.2 Questions from the online email survey of study Phase 2

QUESTION	Response
What Industry sector or category does your company fall into? Vaccines, Biogenerics, Therapeutics, Nutraceuticals, Reagents and Biotools, Diagnostics, Medical devices, Contract services, Other (Please Specify)	(e.g. A)
What is your company's stage of business operation/activity? In R& D phase Ready to launch In general operation Sold, EXIT or globalised out of SA Closed, or no longer in operation Closed before operation began Other (Please Specify)	(e.g. C)
Were your primary products/services developed by you or another company (i.e. is your company a reseller or a direct producer)? Developed and produced by your company 3rd party developed, but produced by your company 3rd party developed and produced, your company resells	(e.g. B)
Where are your headquarters based?	(e.g. Cape Town)
How many staff members currently work at your organisation (more than 20 hrs/week, paid or unpaid)?	(e.g. 10)
How much capital has been/was used for your R&D to date/or company start-up?	(e.g. R1m)

APPENDIX III: DATA CONSIDERATIONS FOR THE STUDY PHASE 2

Table 8.3 Numerical coding of the inferential statistics during the Study Phase 2

	Core Function (Classif.)	HQ Location	Production Type	Start-up Costs	Size	Activity State (Sustainability)			
Data Type	Nominal (categ.)	Nominal (categ.)	Nominal (categ.)	Interval (Contin.)	Discrete		Nominal (categ.)	Ordinal (Ranked)	Dichotomous (Binary)
No. code						Variable	Numerical Code		
1	Vaccines	JHB and surround	Developed and manufactured in-house	Actual Figures of ZAR, corrected for Inflation to Dec. 2014	Actual Figures of employees, paid or unpaid who work more than 20 hours per week – As at December 2014	Closed before operation began	6	1	0
2	Biogenerics	Bloem.	3rd party developed; manufactured in-house			Closed, or no longer in operation	5	2	
3	Therapeutics	Cape Town	3rd party developed and manufactured			Sold, EXIT or globalised out of SA	4	3	
4	Nutraceuticals	Durban	Developed in-house; 3rd party manufactured			In R&D phase	1	4	
5	Reagents	Port Eliz.	Multiple categories			Ready to launch	2	5	
6	Diagnostics	Pretoria				In general operation	3	6	1
7	Medical devices	Stellen.							
8	Biotools	KZN (excl.							

		Dbn)							
9	Contract services	Eastern Cape (excl. PE)							
10	Public services								
11	Multiple categories								

Table 8.4 Pearson Chi-Square tests performed during Study Phase 2

Correlation	Variable 1	Data Type	Variable 2	Data Type
Does the classification have a correlation or association with the activity state?	Classification	Categorical Data	Activity State	Categorical Data
Does the classification have a correlation or association with the production type?	Classification	Categorical Data	Production Type	Categorical Data
Does the location have a correlation or association with the classification?	Location	Categorical Data	Classification	Categorical Data
Does the location have a correlation or association with the activity state?	Location	Categorical Data	Activity State	Categorical Data
Does the production type have a correlation or association with the activity state?	Production Type	Categorical Data	Activity State	Categorical Data
Does the production type have a correlation or association with the spending?	Production Type	Categorical Data	Spending	Categorical Data
Does the spending have a correlation or association with the activity state?	Spending	Categorical Data	Activity State	Categorical Data
Does the size have a correlation or association with the activity state?	Size	Categorical Data	Activity State	Categorical Data

Table 8.5 One-way ANOVA tests performed during Study Phase 2

Correlation	Independent Variable (IV)	Data Type	Dependent Variable (DV)	Data Type
Does the classification have a correlation or association with activity state?	Classification	Categorical Data	Activity State	Ordinal Data
Does the location have a correlation or association with activity state?	Location	Categorical Data	Activity State	Ordinal Data
Does the production type have a correlation or association with activity state?	Production Type	Categorical Data	Activity State	Ordinal Data
Does the spending have a correlation or association with activity state?	Spending	Categorical Data	Activity State	Ordinal Data
Does the size have a correlation or association with activity state?	Size	Categorical Data	Activity State	Ordinal Data
Does the classification have a correlation or association with Spending?	Classification	Categorical Data	Spending	Continuous Data
Does the classification have a correlation or association with the size?	Classification	Categorical Data	Size	Discrete Data
Does the location have a correlation or association with spending?	Location	Categorical Data	Spending	Continuous Data
Does the production type have a correlation or association with spending?	Production Type	Categorical Data	Spending	Continuous Data
Does the production type have a correlation or association with size?	Production Type	Categorical Data	Size	Discrete Data

APPENDIX IV: RESULTS OF PHASE 1 NOT INCLUDED IN THE WRITE UP

Results pertaining to Section 5.2.2 Company citizenship

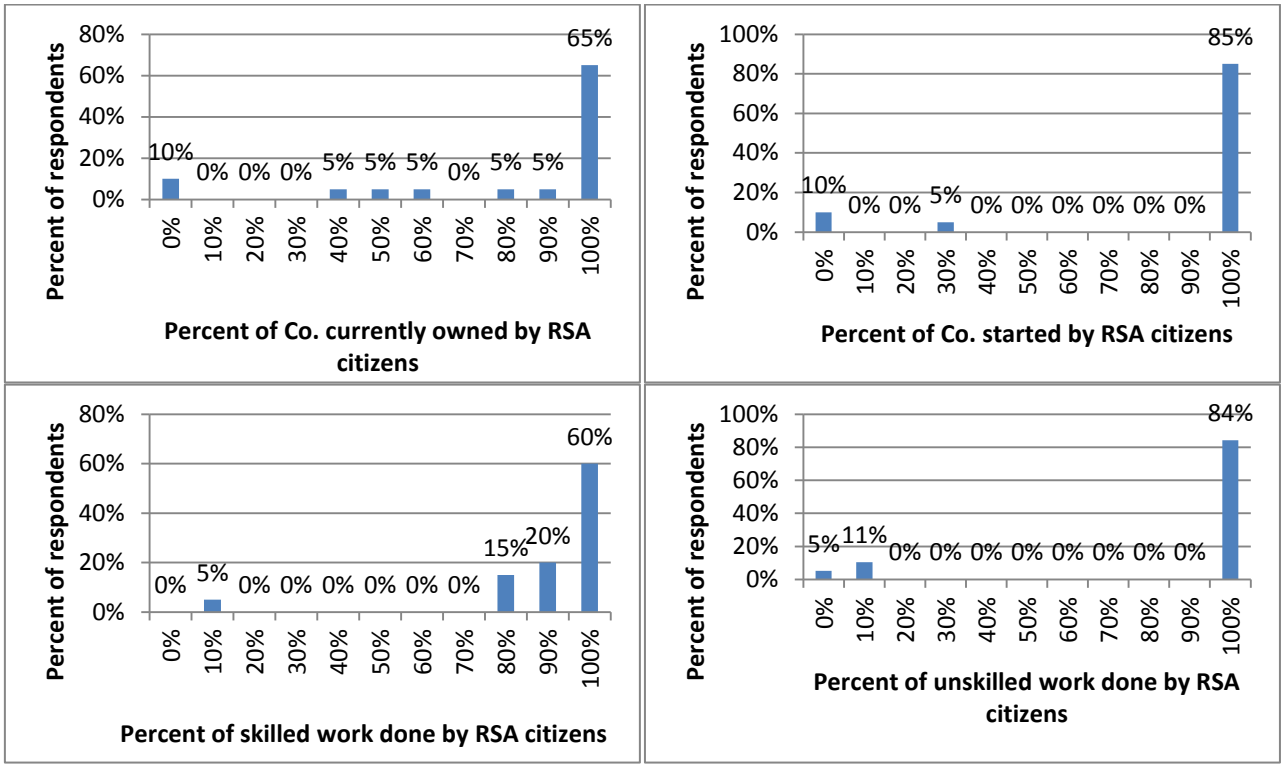


Table 8.6 Factors noted by respondents in each of the categories of strengths

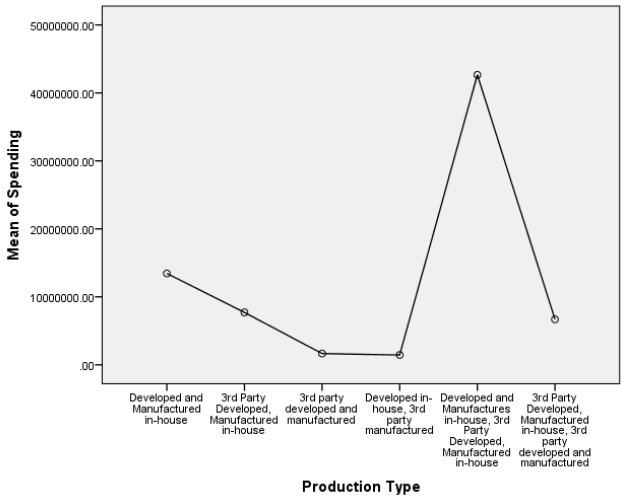
Strength	No. Repeats	Individual aspects noted
MKT OPPRTY	7	MKT OPPRTY; DEVL MKTS; INTL. EXPSR
GOVT.	5	GOVT HLTHCR; GOVT. TNDR; TAX REB; LIBRL; EXPRT ASST.
GEOG	4	GEOG; NATRL RSRC.
CMPTV DYN	4	CMPTV PRICE;CMPTV R&D COSTS; HIGH IMP COSTS/CMPTV PRICE; LABR COST
INNOV. CULTURE	3	ENTR. CLTR; INNOV. CLTR; TAKE RISKS;
TALENT	3	TALENT; GOOD SCI; GOOD UNIV
LOW CMPTN	2	LOW CMPTN
ACAD SUPP	1	ACAD SUPP
RELATN DEVT	1	RELATN DEVL

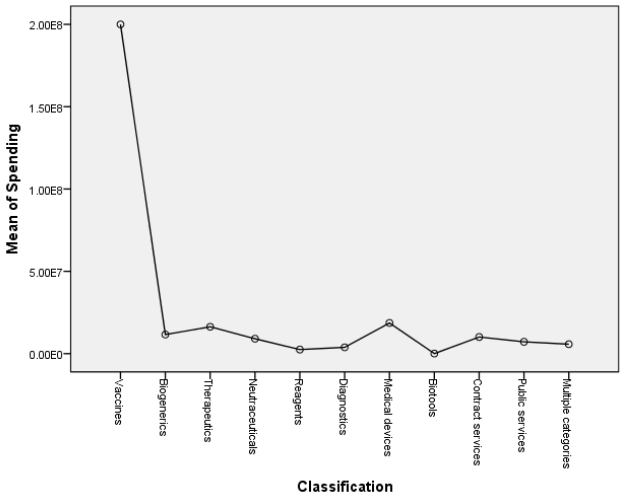
Table 8.7 Categories noted as weaknesses

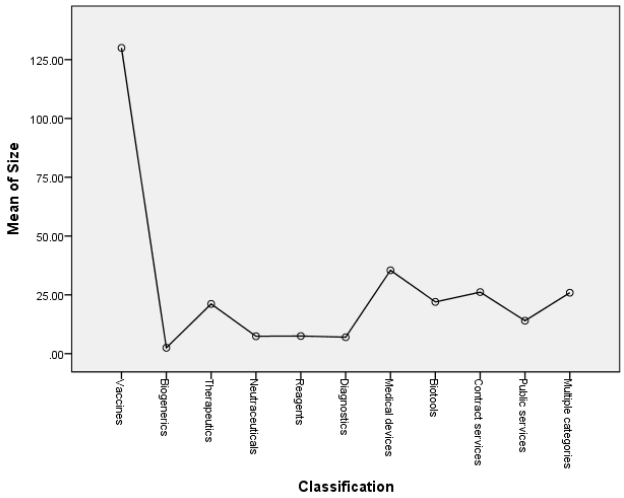
Weakness	No. Repeats	Individual aspects noted
FUNDS	12	FUNDS; EARLY/VC FUNDS; FRGN INV; LW VC RSK.
SKILL	8	SKILL; FRGN SKILL
MKT	6	SML MKT; CORPS; CHINA IMP; EST ALLNC.
FOREX	5	ZAR VOLAT; FOREX
CLIENTS	4	LOCAL FAITH; NAÏVE MKT
SUPPORT	3	GOVT. SUPP; R&D SUPP;
REGULN	3	CLINC REGLN; LEGIS; PR REGLN.
COSTS	3	R&D COST; REGNL COSTS; TARIFFS
ATTITUDE	2	CORRUP; DRIVE
GEOG	2	GEOG; HUB DISTR
INTL. DYN	2	INTL. DUMPING; INTL. NETW
NON-UNI JOBS	1	NON-UNI JOBS
TTO	1	UNIV TTOs

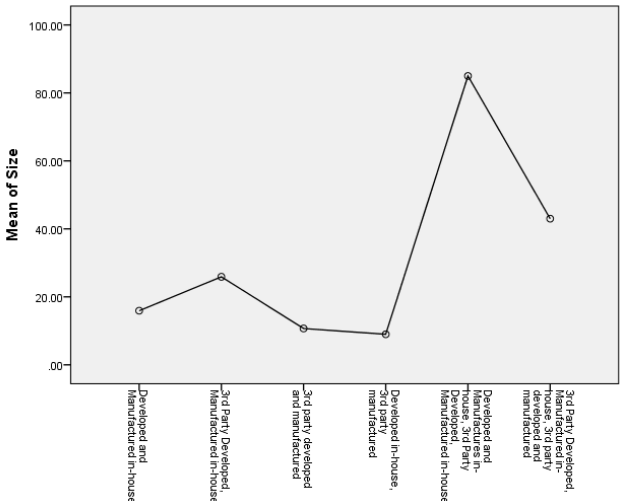
APPENDIX V: RESULTS OF PHASE 2 INFERENTIAL STATISTICS NOT INCLUDED IN TEXT

Results of the ANOVA tests not in text









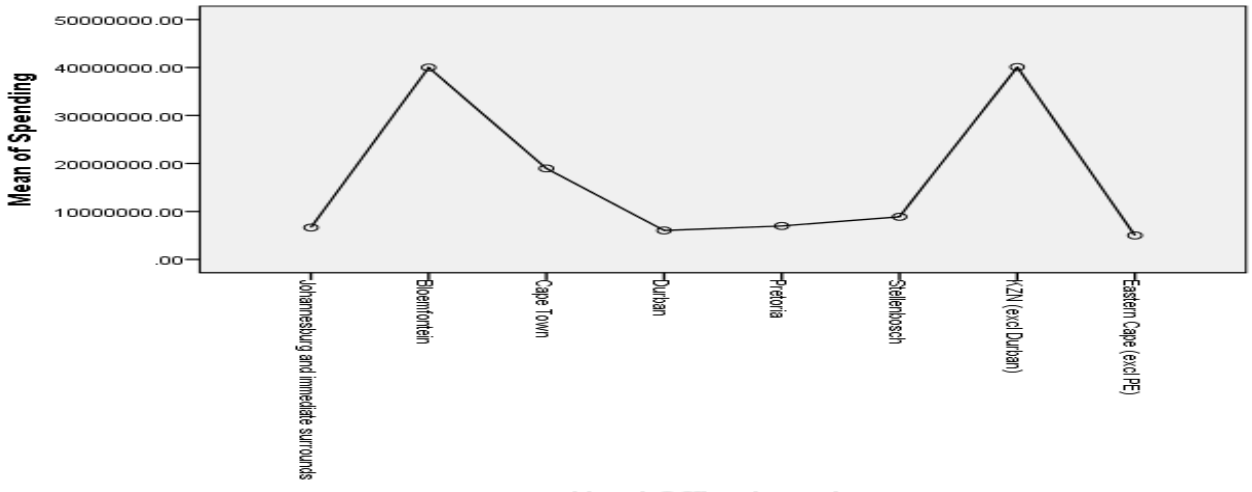


Table 8.8 Results of the logistic regression

Variables in the Equation		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Classific11CATwMULTI			.000	10	1.000	
	Classific11CATwMULTI(1)	3.963	59963.729	.000	1	1.000	52.603
	Classific11CATwMULTI(2)	.264	32697.782	.000	1	1.000	1.302
	Classific11CATwMULTI(3)	-.415	38540.879	.000	1	1.000	.661
	Classific11CATwMULTI(4)	-40.906	33853.067	.000	1	.999	.000
	Classific11CATwMULTI(5)	-2.554	41725.276	.000	1	1.000	.078
	Classific11CATwMULTI(6)	-.767	22227.460	.000	1	1.000	.464
	Classific11CATwMULTI(7)	1.531	30591.112	.000	1	1.000	4.622
	Classific11CATwMULTI(8)	1.952	46623.564	.000	1	1.000	7.040
	Classific11CATwMULTI(9)	1.524	50133.391	.000	1	1.000	4.590
	Classific11CATwMULTI(10)	1.192	35175.822	.000	1	1.000	3.295
	Location5mainCAT			.000	4	1.000	
	Location5mainCAT(1)	-33.953	38604.782	.000	1	.999	.000
	Location5mainCAT(2)	-33.125	44470.718	.000	1	.999	.000
	Location5mainCAT(3)	4.701	56841.476	.000	1	1.000	110.097
	Location5mainCAT(4)	-34.411	41435.503	.000	1	.999	.000
	Production6CAT			.000	5	1.000	
	Production6CAT(1)	-2.093	46668.995	.000	1	1.000	.123
	Production6CAT(2)	-3.195	54849.545	.000	1	1.000	.041
	Production6CAT(3)	-4.900	59522.896	.000	1	1.000	.007
	Production6CAT(4)	-3.334	63247.254	.000	1	1.000	.036
	Production6CAT(5)	-3.614	52957.359	.000	1	1.000	.027
	Spending7CAT			.000	6	1.000	
	Spending7CAT(1)	3.297	42753.724	.000	1	1.000	27.035
	Spending7CAT(2)	3.204	44196.154	.000	1	1.000	24.643
	Spending7CAT(3)	1.634	39689.115	.000	1	1.000	5.124
	Spending7CAT(4)	.248	42415.494	.000	1	1.000	1.281
	Spending7CAT(5)	-35.470	51825.765	.000	1	.999	.000
	Spending7CAT(6)	.526	46031.666	.000	1	1.000	1.692
	Size4CAT			.000	3	1.000	
	Size4CAT(1)	-38.215	25829.728	.000	1	.999	.000
	Size4CAT(2)	1.735	27696.757	.000	1	1.000	5.667
	Size4CAT(3)	1.603	27714.501	.000	1	1.000	4.970
	Constant	53.979	81764.762	.000	1	.999	27732078268523374000000 0.000

a. Variable(s) entered on step 1: Classific11CATwMULTI, Location5mainCAT, Production6CAT, Spending7CAT, Size4CAT.

Table 8.9 Results of the multinomial logistic regression

Parameter Estimates

Current Activity State[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Closed before operation began	Intercept	-2.717	1.052	6.666	1	.010			
	[Classific11CATwMULTI=1.00]	-1.947	7.551	.067	1	.796	.143	5.330E-008	381811.895
	[Classific11CATwMULTI=2.00]	.864	2.319	.139	1	.710	2.371	.025	223.157
	[Classific11CATwMULTI=3.00]	.975	1.509	.417	1	.518	2.650	.138	51.047
	[Classific11CATwMULTI=4.00]	-1.847	7.824	.056	1	.813	.158	3.454E-008	720129.173
	[Classific11CATwMULTI=5.00]	-1.883	7.815	.058	1	.810	.152	3.392E-008	682524.365
	[Classific11CATwMULTI=6.00]	.413	1.499	.076	1	.783	1.512	.080	28.557
	[Classific11CATwMULTI=7.00]	.887	1.227	.523	1	.470	2.428	.219	26.913
	[Classific11CATwMULTI=8.00]	-1.947	6.195	.099	1	.753	.143	7.600E-007	26778.612
	[Classific11CATwMULTI=9.00]	-1.704	4.318	.156	1	.693	.182	3.840E-005	862.705
	[Classific11CATwMULTI=10.00]	-1.947	4.444	.192	1	.661	.143	2.355E-005	864.216
	[Classific11CATwMULTI=11.00]	0[b]	.	.	0	.	.	.	.

Closed, or no longer in operation	Intercept	-4.111	2.063	3.972	1	.046			
	[Classific11CATwMULTI=1.00]	-.197	6.599	.001	1	.976	.821	1.983E-006	340240.759
	[Classific11CATwMULTI=2.00]	-13.811	5924.744	.000	1	.998	1.005E-006	.000	.[c]
	[Classific11CATwMULTI=3.00]	.277	3.534	.006	1	.937	1.320	.001	1345.427
	[Classific11CATwMULTI=4.00]	4.559	2.296	3.944	1	.047	95.494	1.061	8591.606
	[Classific11CATwMULTI=5.00]	3.833	2.375	2.606	1	.106	46.207	.440	4853.186
	[Classific11CATwMULTI=6.00]	2.945	2.166	1.849	1	.174	19.011	.273	1325.798
	[Classific11CATwMULTI=7.00]	2.262	2.159	1.098	1	.295	9.602	.140	660.438
	[Classific11CATwMULTI=8.00]	-.197	5.518	.001	1	.972	.821	1.649E-005	40895.356
	[Classific11CATwMULTI=9.00]	2.557	2.334	1.199	1	.273	12.891	.133	1251.031
	[Classific11CATwMULTI=10.00]	-.197	4.166	.002	1	.962	.821	.000	2886.286
	[Classific11CATwMULTI=11.00]	0[b]	.	.	0	.	.	.	.
Sold, EXIT or Globalised out of SA	Intercept	-2.713	1.050	6.671	1	.010			
	[Classific11CATwMULTI=1.00]	-2.288	8.898	.066	1	.797	.101	2.707E-009	3803882.087
	[Classific11CATwMULTI=2.00]	-15.902	8378.853	.000	1	.998	1.241E-007	.000	.[c]
	[Classific11CATwMULTI=3.00]	1.107	1.465	.571	1	.450	3.025	.171	53.439
	[Classific11CATwMULTI=4.00]	-2.188	9.220	.056	1	.812	.112	1.593E-009	7899261.747
	[Classific11CATwMULTI=5.00]	-2.224	9.209	.058	1	.809	.108	1.568E-009	7469130.991
	[Classific11CATwMULTI=6.00]	1.247	1.287	.939	1	.332	3.480	.280	43.320
	[Classific11CATwMULTI=7.00]	-.209	1.477	.020	1	.887	.811	.045	14.680
	[Classific11CATwMULTI=8.00]	-2.288	7.290	.098	1	.754	.101	6.322E-008	162891.094
	[Classific11CATwMULTI=9.00]	-2.044	5.057	.163	1	.686	.129	6.418E-006	2611.927
	[Classific11CATwMULTI=10.00]	-2.288	5.208	.193	1	.660	.101	3.742E-006	2751.912
	[Classific11CATwMULTI=11.00]	0[b]	.	.	0	.	.	.	.
In R&D phase	Intercept	-4.216	2.172	3.766	1	.052			
	[Classific11CATwMULTI=1.00]	-.197	6.951	.001	1	.977	.821	9.940E-007	678611.155
	[Classific11CATwMULTI=2.00]	-13.811	6245.229	.000	1	.998	1.005E-006	.000	.[c]
	[Classific11CATwMULTI=3.00]	2.435	2.435	1.000	1	.317	11.411	.097	1349.357
	[Classific11CATwMULTI=4.00]	3.548	2.559	1.923	1	.166	34.758	.231	5238.261
	[Classific11CATwMULTI=5.00]	-.132	7.176	.000	1	.985	.876	6.833E-007	1122905.583
	[Classific11CATwMULTI=6.00]	3.079	2.268	1.842	1	.175	21.737	.255	1854.117
	[Classific11CATwMULTI=7.00]	2.679	2.243	1.427	1	.232	14.571	.180	1182.357
	[Classific11CATwMULTI=8.00]	-.197	5.813	.001	1	.973	.821	9.261E-006	72839.337
	[Classific11CATwMULTI=9.00]	.047	4.291	.000	1	.991	1.048	.000	4703.297
	[Classific11CATwMULTI=10.00]	-.197	4.388	.002	1	.964	.821	.000	4461.977
	[Classific11CATwMULTI=11.00]	0[b]	.	.	0	.	.	.	.
Ready to Launch	Intercept	-5.720	4.582	1.558	1	.212			
	[Classific11CATwMULTI=1.00]	-.197	14.676	.000	1	.989	.821	3.644E-013	2551338166919.156
	[Classific11CATwMULTI=2.00]	-13.811	.000	.	1	.	1.005E-006	1.005E-006	1.005E-006
	[Classific11CATwMULTI=3.00]	.277	7.841	.001	1	.972	1.320	2.793E-007	6235381.711
	[Classific11CATwMULTI=4.00]	-.097	15.159	.000	1	.995	.908	2.133E-013	7274551696653.622
	[Classific11CATwMULTI=5.00]	-.132	15.145	.000	1	.993	.876	2.125E-013	6822058507338.110
	[Classific11CATwMULTI=6.00]	.499	6.347	.006	1	.937	1.646	6.509E-006	416420.395
	[Classific11CATwMULTI=7.00]	3.996	4.622	.747	1	.387	54.368	.006	467182.587
	[Classific11CATwMULTI=8.00]	-.197	12.271	.000	1	.987	.821	2.954E-011	22910022023.187
	[Classific11CATwMULTI=9.00]	.047	9.048	.000	1	.996	1.048	2.082E-008	52731537.278
	[Classific11CATwMULTI=10.00]	-.197	9.262	.000	1	.983	.821	1.072E-008	62912889.631
	[Classific11CATwMULTI=11.00]	0[b]	.	.	0	.	.	.	.

a. The reference category is: In general operation.

b. This parameter is set to zero because it is redundant.

c. Floating point overflow occurred while computing this statistic. Its value is therefore set to system missing.

APPENDIX VI: LETTERS FROM HTV EXPERTS ON SUSTAINABILITY AND SUCCESS

From Sample 2 Anonymous Respondent A (2014):

This is an excerpt from an email interview with Sample 2 Anonymous Respondent A (2014). It presented a very insightful and detailed overview of his experiences with the South African HTV environment, in getting their product to market. While it could not be entered into the dissertation in its entirety, it was useful to include it as a supplementary item, here. Names have been removed for anonymity.

Date of communication: 11th and 15th December 2014.

"We are selling [XXXX] diagnostic … based test. The tests detects [XXXX] antigen… Up to date it took me about 9 years to develop, research, publish and build the company. The initial research into the antigens was done at [XXXX] University in the Netherlands. After about 30 years they are still busy with … related research. I am a medical doctor consulting for [XXXX] on a full time bases. I must say, from the outset there was a lot of goodwill from all parties involved. I initially met the senior researcher from [XXXX] University 9 years ago at [XXXX] laboratories in Pretoria. They tried to commercialise one of their diagnostic tests which ended up in failure and decided to discontinue the test all together. There was a need in South-Africa for a qualitative urine based … test and I decided to engage with them.

This is very important: From the outset I negotiated with the University for exclusivity on the use of their monoclonal for commercial use. They may use it for academic purposes, but they may not sell it to any other commercial manufacturer. Without this protection the big multinational companies will destroy you within weeks after you have done all the initial research and publication on the test. Since my company has helped [XXXX University] with their research over many years there was enough goodwill that they agreed to sign. At this point I tried to engage with an incubator called Egoli-Bio to see if I could arrange some funding for the project. Although they were very helpful, I soon realised that I will be completely swamped with paperwork to obtain and maintain funding. On top of this the funding would be insufficient, short lived and the incubator would also obtain a relative [sic] large share in the company which I was not willing to just give away. I met a number of biotech entrepreneurs during that time and somehow I met a diagnostic manufacturer in Cape Town.

From this point onwards there were a lot of interaction between myself, the university and the manufacturer. With the help from the university (Netherlands) we provided the initial methodology of the test for the manufacturer to produce a number of sample tests. We kept on optimizing the test until we were happy to send it out for evaluation. I completely relied on my European connection to convince some of his research colleagues to evaluate and publish on the test. This cycle kept on going for many years and we are still improving and publishing on the test.

I will now try to explain the financials:

Development:

If you plan to outsource the initial test development to a third party producer you will have to fork out anything from R300 000 to R800 000 depending on how desperate they are for business. To avoid this expense we decided to partner up - I will keep my future production with them as long as they do the development for free. This required goodwill from both sides since there are serious risks involved. Although we provided the initial production methodology they ended up refining it and I will have to re-develop should the relationship sour. On the other hand nothing stops me from moving my production elsewhere. We are still working with this understanding.

Please note that we did not develop the monoclonal antibodies. These monoclonals are very unique and nobody else produced them up to this point. It will probably cost a few million to do the research and then produce these monoclonals.

Publication

In medicine any good product requires lots and lots of publication (evidence based studies). We were very fortunate to have direct access to the scientific community via my friend at [XXXX University]. Although his work was well published at the time he managed to convince some of his research fellows to try out the test. Quite soon word spread and they also published some of their research data. As the test quality and penetration improved more and more researchers evaluated the test (field studies). Our big break came when some of the bigger consortiums decided to investigate the use of our test on large scale. In one of these projects the Bill Gates Foundation allocated over $20milion US to evaluate different tests for diagnosis, mapping and eradication of … in Africa. At that stage, we had a proper commercial product and several field studies were done that resulted in wide publication on the test.

These studies normally involve sponsorship of a number of researchers into an African country for weeks if not months. We are talking several million dollars if you take it over a period of 6 years. We did not have to fund this and the studies were completely independent. What people don't always understand is that most first world researchers have to engage in these activities to justify their salaries. Once the researcher, university or research institute decided what they want to do they apply for funding from their national governments or other foundations. If you can provide them with something novel that they can sell to their sponsors they will gladly engage in research. Once they proved the link between HIV and … they had more than enough reason to ask for funding.

Since this is a new technology It took us 7 years to get major market acceptance.

Production:

Production is currently outsourced to a third party also based in South Africa, Cape Town

I have the luxury of using our own laboratory in … to evaluate the tests and store the monoclonals at -80degrees. This would be a huge expense if not for goodwill.

Distribution:

I initially did my own distribution but due to my full-time employment as medical doctor I decided to outsource this function to a third party also based in Cape Town.

Summary:

Although we managed to build the company over 9 years it is very difficult to guess what it would have cost if you had to get funding. We developed the test with goodwill from The Netherlands, Cape Town (manufacturing) and [XXXX] laboratories.

Everybody involved had their own income and allocated their time for free, in my case a few thousand hours by now. Due to my full-time consulting at [XXXX] I have outsourced all labour to 3rd parties and my company has basically become a holding company. Since we are all employed elsewhere and withdraw payment as and when the need arise you can basically say we are 2 unpaid employees. Indirectly we probably support 10 permanent jobs at 3rd party locations."

From Sample 2 Anonymous Respondent D (2014):

This is an excerpt from an email interview with Sample 2 Anonymous Respondent A (2014). It presented a very insightful and detailed overview of his experiences with the South African HTV environment, in failing to get their product to market to date. While it could not be entered into the dissertation in its entirety, it was useful to include it as a supplementary item, here. Names have been removed for anonymity.

Date of communication: 12th November 2014.

Though we have been very successful in our development of a [medical device] Instrument we have, unfortunately, "hit a brick wall' with the European Patenting Office and this has negatively affected an existing funding option as well as all future possible funding strategies. Until we are able to finalise a US patent application or reach an alternative deal with a large manufacturer the project must be placed on hold as any further development cannot be justified out of the limited funds still available.

Trials performed during 2012 showed positive results but require a modification which, although already designed, cannot be implemented until further funding or a partnership is established to justify the investment.

We will complete our South Africa Patent application and apply for a US patent in 2013. Both applications will take 12-18 months to complete and extra defence costs are expected in the US due to the negative EPO report. Both our patent attorneys and Spoor & Fisher agree that we have a solid application though despite the EPO's opinion. We, therefore, justify the cost as our last

realistic chance of securing IP which will enable future development or investment prospects and an increased value for a possible divestment.

Application will be made to the IDC and TIA to allow for the possibility of selling or licencing the IP to a non-RSA based organisation.

Patenting

Our PCT application received a negative response from the European Patent Office (EPO) regarding novelty and inventiveness. Though we believe this opinion to be incorrect due to the fact that the EPO is not correctly interpreting our most innovative design feature, which is the particular way in which … [it] … is knitted from a fibre, while they are comparing our design to other … apparatus which consist of woven or meshed strands, the EPO have maintained their opinion even after a costly appeal was launched.

In the first instance this is a devastating blow to our chances of receiving any European patent and will certainly increase the cost of any attempt to obtain a European patent as every application will have to go through a process of appealing against this opinion.

In the second instance a positive opinion from the EPO was the requirement laid down by a new group of investors who were willing to invest R4 million into our project. On receiving the negative opinion on our appeal this group has decided not to invest which now leaves us without any further funding options and a mountain to climb before we are likely to convince anyone else to invest in our, now beleaguered, design.

We have obtained a second opinion from a leading South African Patent firm (Spoor & Fisher) and they are also of the opinion that our design is indeed novel and inventive and that the EPO ruling is unnecessarily biased against us, however, everybody agrees that any application would now be 'on the back foot' and costs could spiral out of control.

However, we have been advised and intend to complete our RSA patent application and file for a US patent. Both of these will be easier to achieve notwithstanding the EPO ruling and securing a US patent will give us a major selling point to manage to get some return out of this project. We do not expect to hear from either of these patent offices within 12-18 months. During this time it is not sensible to invest further in the development of the product as a negative US patent application would surely mean the end of the viability of the product.

Design

During our trials we confirmed that the design of the --- Instrument would have to be modified --- Though we have completed revised designs for this type of device we are unable to produce these new devices without further funding and access to further manufacturing technology which is not readily available in South Africa.

Facility

Our Facility in --- passed inspection and verification for an ISO 7 clean air room according to ISO 14644 standards. This was a major milestone in our productive capacity. It is unfortunate that we can now not utilise this room as the manufacturing is currently halted and the future of the facility is in jeopardy.

Finances

We have limited finances still available and we intend to apply this to the patent application for the product in RSA and US. --- it is, therefore, likely that the facility in --- will have to be closed.

Though we would have loved to continue the product we have run out of external funding options and the prospect of finding further funding until we have secured a US patent is very small. We are not in a position to fund the organisation out of personal funds beyond the minimum to maintain it as a going concern and guardian of its IP rights until such time as we have a final opinion on a US patent.

Future prospects

During the time that we launch a US application we have the opportunity to attempt to broker a deal with a larger manufacturing company in the Medical devices industry to manufacture or take over the product. We are limited in the ability to do this only by the conditions of our funding from the IDC and the TIA and will appeal to both to allow us to consider finding a solution which may include having to sell or licence the technology to a non RSA company. We feel that this is the best chance everyone (shareholders, directors and IDC / TIA) have of ever seeing a return on the investment which has already been made and that there is no realistic chance of finding a South African company with the necessary technology, materials and funding to keep this within our borders.

South African Context

During this project we have identified several issues which make it particularly hard to manufacture medical devices in South Africa. These are the opinion of our directors and are based on personal experience rather than research and should be read as such.

1. *It is almost impossible to find* ***suitable raw material*** *in South Africa for the manufacturing of CE mark medical devices. Medical devices must be manufactured from ISO 10993 raw materials to comply with the CE Mark. This grade of material is only available from Europe and the US and the suppliers of this grade of material are very cautious to supply to anyone as they need to protect themselves from liability. This leads to them wishing to set in place elaborate legal contracts before supplying material and they are unwilling to go to this expense for a small company. A small company in SA is thus in a catch-22 situation where you are unable to get the material until you are a big company and unable to become a big company until you can get the material. Consequently*

we are forced to out-source manufacturing of components to large manufacturers or manufacturers located in the EU, US or China. In all cases it is hard to control quality (for which you are responsible) and import and shipping costs are often more expensive than the part cost making it economically infeasible. This may not be the case for an established SA manufacturer and there is a case for small companies to work together on sourcing material, however requirements differ significantly and the varieties available are numerous. Supply of 8 tons of material is possible, but sourcing 25kg for a trial run during prototyping and before trials is almost impossible.

2. ***Certification*** *– All manufacturers of CE Marked devices need to be certified to ISO 13485. This certification needs to be performed by an auditor from a certified body from the EU. Although an equivalent SA standard exists (SANS 13485) it is of no use to be certified according to this standard as it is not accepted by the EU authorities (and reportedly never will be due to a host of other issues).*

3. ***Size –*** *The South African Medical Device manufacturing industry is small and unable to invest in products such as our device as they are mostly focussed on their own internally generated product groups or contract manufacturing of International product designs, often for export. Until we have proven efficacy and a final design we are unlikely to find a local partner for our endeavour."*

END