INDUSTRIAL DEVELOPMENT IN A HIGH TECH SECTOR OF A DEVELOPING COUNTRY: NEW DIRECTIONS AND THE UNFINISHED TECHNOLOGICAL TRANSITION IN THE BRAZILIAN VACCINE INDUSTRY

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A thesis submitted in partial fulfilment of the requirements of the
University of Sussex for the degree of Doctor of Philosophy
in Technology and Innovation Management

September 2010

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I hereby declare that this thesis has not been submitted, either in the same or different form, to this or any other University for a degree.

For my father Eloy (In Memoriam), my mother Hercilia, my daughters Carolina, Daniela and Juliana, my wife Maria Celia and for the coming boy, I dedicate this thesis.

ACKNOWLEDGEMENTS

A DPhil is anything but a lonely endeavour. I am deeply indebted to all those people who have contributed to my efforts in accomplishing this challenging task. It is impossible to name all.

I am grateful to my supervisor Paul Nightingale for all his academic support and constant encouragement throughout the four years of my academic journey at SPRU. I am also grateful to Prof. Mike Hobday for his wise comments and advice on the drafts of my thesis, encouraging me to see what I had not yet seen. Also, I express my gratitude to all those who gave me academic guidance and advice during the SPRU's Research Committees and in informal meetings, and to Janet French for all her support since my application for a place at SPRU and for proofreading the whole draft of my thesis.

My dream would not have been possible without the support of the institution I work for, the Oswaldo Cruz Foundation – Fiocruz/Bio-Manguinhos, who financed my participation in this doctorate, and of FIOTEC, who provided me with the scholarship to live in England during the course. To all my colleagues in both institutions, Artur and Mario in special, who were decisive to the approval of my participation in this doctorate, I extend my sincere thanks. To all those who patiently answered my questions during the interviews in my field work, I express my gratitude.

I am thankful to the Brazilian friends for the camaraderie and friendship that made the adaptation to a new country easier and the distance to our home country appear smaller. I am also thankful to the colleagues at SPRU and CENTRIM for all supportive academic and social relationships that brought me an experience of multicultural learning.

I would like to express my love to my family, always present in the good and bad moments of this academic journey, especially to my wife, who encouraged me since the ideas of attending this doctorate came about, and managed to deal with all my sorts of feelings and moods to accomplish it.

Finally, my sincere thanks to Professor Chris Freeman, who has just passed away, for his visionary wisdom in creating SPRU, this fantastic research Centre where I had the privilege to attend my doctoral studies.

UNIVERSITY OF SUSSEX

Mauricio Zuma Medeiros Doctor of Philosophy

Industrial Development in a High Tech Sector of a Developing Country: new directions and the unfinished technological transition in the Brazilian vaccine industry

SUMMARY

This thesis investigates the development of the Brazilian vaccine industry. This industry has experienced a sharp growth in the last decades supported by public policies and a protected and fast-growing public market. In addition, this development is apparently characterized by continuous processes of technology acquisition, rather than indigenous R&D, as the main source of its technological knowledge, and by other specificities in the vaccine context.

The research draws on studies of the dynamics of technological capability building in catching-up industries of latecomer contexts, especially during the transition period when they are approaching the innovation frontier. It also draws on those studies focusing on new directions/paths as an alternative strategy adopted to overcome barriers and disadvantages to develop. It has been argued that the specificities of the Brazilian context and, of the vaccine sector, may be determining a particular pattern of technological accumulation to this industry, and that interpreting its pattern of development may be useful to understand how and if this industry has overcome its constraints to develop. A framework based on linear approaches of catching-up, and that integrates the innovation transition approach was built as a benchmark model for the search for similarities and differences in the pattern of development of this industry.

The findings show similarities and new directions in the process of technological accumulation of the industry, suggesting that, more recently, it has actually developed through a distinct pattern. They also show the strong role of the government and its public market as one of the drivers of this new path. Distinct roles of the technology acquisition strategy and a high level of technological capabilities currently developed are also revealed. Finally, they show that the technology acquisition strategy has effectively contributed to the development of this industry and that the constraints to the completion of the transition phase is linked less to technical and scientific issues and more to managerial and policy ones.

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ACRONYMS AND ABBREVIATIONS

Abifina	Associação Brasileira das Indústrias de Química Fina (Brazilian Association of the Fine Chemicals Industries)
ANVISA	Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency)
BCG	Bacille Calmette-Guérin (Tuberculosis vaccine's strain)
BCG	Boston Consulting Group
Bio-Manguinhos	Instituto de Tecnologia em Imunobiológicos (Institute of Technology on Immunobiologicals)
BVI	Brazilian Vaccine Industry
CDTS	Centro de Desenvolvimento Tecnológico em Saúde (Centre of Technological Development in Health)
CGIES/CGPNI	Coordenação Geral de Insumos Estratégicos em Saúde/ Coordenação Geral do Programa Nacional de Imunizações
CMO	Contract Manufacturing Organization
COPPE/UFRJ	Instituto Alberto Luiz Coimbra de Pós-Graduação e Pesquisa de Engenharia da Universidade Federal do Rio de Janeiro
CRO	Contract Research Organization
CVI	Children's Vaccine Initiative
DCL	Developing Countries Literature
DCVMN	Developing Countries Vaccine Manufacturers Network
Dt	Adult Double (Diphtheria and Tetanus) vaccine
DT	Infant Double (Diphtheria and Tetanus) vaccine
DTPa	Diphtheria, Tetanus and acellular Pertussis (whooping cough)
DTPw	Diphtheria, Tetanus and whole cell Pertussis (also DTP)
DTPw+Hib	Tetravalent vaccine (Diphtheria, Tetanus and whole cell Pertussis + *Haemophilus influenzae type b*)
EPI	Expanded Programme on Immunization (of WHO)
FDA	Food and Drug Administration
FIOCRUZ	Fundação Oswaldo Cruz (Oswaldo Cruz Foundation)
FUNED	Fundação Ezequiel Dias
GAVI	GAVI Alliance
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GSK	GlaxoSmithKline
HAV	Hepatitis A Vaccine
HBV	Hepatitis B vaccine (also HB)
Hib	*Haemophilus influenzae type b*
HIV	Human Immunodeficiency Virus
IAVI	International AIDS Vaccine Initiative
IBMP	Instituto de Biologia Molecular do Paraná
IH	In-house
INCQS/Fiocruz	Instituto Nacional de Controle de Qualidade em Saúde (National Institute of Quality Control in Health)
INOVACINA	Programa Nacional de Competitividade em Vacinas (National Programme of Competitiveness in Vaccines)
IPR	Intellectual Property Rights

IPV	Inactivated Polio Vaccine
JICA	Japan International Cooperation Agency
LA	Latin America
MCCV	Meningococcus C Conjugate Vaccine
MMR	Measles, Mumps and Rubella
MNC	Multinational Corporation
MOH	Ministry of Health
MVI	Malaria Vaccine Initiative
N/A	Not available
NIAID	National Institute of Allergy and Infectious Diseases (of NIH)
NIC	Newly Industrializing Countries
NIH	National Institutes of Health (USA)
NRA	National Regulatory Authority
OPV	Oral polio vaccine
PAHO	Pan American Health Organization
PASNI	Programa de Auto-suficiência Nacional em Imunobiológicos (Programme of National Self-sufficiency on Immunobiologicals)
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcus Conjugate Vaccine
PMT	Proteína Monomérica Tetânica (Tetanus Monomeric Protein)
PNI	Programa Nacional de Imunizações (National Immunization Programme)
R&D	Research and Development
ST&I	Science, Technology and Innovation
SAGE	Strategic Advisory Group of Experts (of WHO)
SARS	Severe Acute Respiratory Syndrome
SML	Strategic Management Literature
TA	Technological Accumulation
TECPAR	Instituto de Tecnologia do Paraná (Institute of Technology of Paraná)
TRIPS	Trade-Related Aspects of Intellectual Property
TT	Technology Transfer
UN	United Nations
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research
WTO	World Trade Organization
WWII	World War II

Chapter 1 - Introduction

> Development is all about overcoming barriers to catch-up: at the level of the nation, the firm and individuals. Industrial development is at the heart of any national catch-up process, and firms are at the heart of industrial development (Forbes and Wield, 2002:xiii).

1.1 Motivations and Aims

This thesis analyzes the development of the Brazilian vaccine industry (BVI), an industry that has experienced a sharp growth in the last decades. Preliminary data identified some circumstances in both the Brazilian vaccine context and the world vaccine sector that seem to have strongly influenced this development.

On the former, attention is drawn at the national level to a successful immunization programme that coordinates a large and increasing public market, a government policy created to achieve national self-sufficiency on immunobiologicals, and strong government protection for local manufacturers, that has remained steady across the discontinuous industrial policy regimes that have marked the country in the last three decades. At the industry/firm level the two most noticeable issues are the continuous processes of technology acquisition as the main strategy to develop capabilities rapidly and fulfil the public market needs, and public firms dealing with advanced technologies but a level of innovative capabilities developed to date that is not clearly visible.

On the latter, among the most evident factors are the highly specific, sometimes unique, characteristics of the vaccine sector, such as the social impact of and pressures on immunization, strong government regulation, the high technological complexity and costs of the processes of manufacturing and developing vaccines and, in particular, the quick and significant advances in the knowledge frontier, well protected by intellectual property rights (IPR). The vaccine sector has been, indeed, an international business dominated by few oligopolistic firms in the last decades.

The literature on innovation and technological accumulation has inspired this research. More specifically, it draws on studies focusing on the dynamics and diversity of technological capabilities building in catching-up industries/firms of latecomer contexts,

on the characteristics and constraints faced by firms during the innovation transition stage, and on new directions/paths as the strategy to develop. Drawing on them this thesis assumes that a common/linear pattern of development of catching-up firms/industries in latecomer contexts may be represented by the level of importance of two complimentary sources of knowledge – acquisition of foreign technology and local innovative capabilities – along their technological accumulation path, and that this pattern may be influenced by internal and external elements of the context of these firms/industries. It is then being argued that the specificities of the Brazilian context and of the vaccine sector may be determining a particular pattern of technological accumulation within the BVI, and that interpreting its pattern of development may be useful in understanding how and if this industry has overcome its disadvantages to develop.

A scarcity of studies about the vaccine industry, especially in latecomer contexts, and the specific conditions of the context of the BVI seem, together, to constitute an opportunity to extend knowledge about the process of technological accumulation in catching-up firms/industries, particularly during the phase when the firms are approaching the innovation frontier. This thesis seeks to understand, in a broad sense, two main issues on this subject:

1) *how have technological capabilities evolved over time within this industry; and*
2) *how far has the BVI gone to date in the transition phase, how and why.*

In a more specific sense, it investigates:

a) whether or not the BVI has developed through a particular pattern of technological accumulation; the characteristics of the process and importance of the specific circumstances of its context;
b) the extent to which the strategy of technology acquisition has been effective as a source of technological knowledge to the development of local capabilities;
c) the current level of innovative capabilities developed and the main characteristics of the process during the transition phase;
d) possible factors constraining the catch-up process; and,

e) the existence of relationships between the pattern of development and the unfinished technological transition.

In addition to the motivations, aims and objectives described above, this chapter is organized in order to provide an overview of the specificities of the vaccine sector and of the Brazilian vaccine industry, as raised by the preliminary data (Section 1.2), and of the main bodies of knowledge underpinning the conceptual issues of the thesis (Section 1.3). Section 1.4 briefly describes the methodology employed in order that the objectives proposed are achieved, while Section 1.5 describes how the thesis is organized.

1.2 The Empirical Context

Vaccines long have been acknowledged as one of the public health interventions – together with clean water – that has achieved the greatest impact on the improvement in global health (WHO, 2002a; Plotkin and Plotkin, 2004). In addition, immunization is one of the most cost-effective public health interventions (WHO, 2002a; Plotkin and Plotkin, 2004; Blume, 2005; Orenstein et al., 2007).[1] These two remarks highlight the social, political and economic importance of vaccines. However, existing vaccines are still out of reach of most people in poorer countries, and even in poorer regions of wealthier nations, with millions of children dying every year from infectious diseases preventable by vaccines (WHO, 2002b). Moreover, although vaccines for neglected diseases of developing and poorer countries are critically needed, they have not been developed due to economic reasons.

The industry providing vaccines to the world market is full of specificities. It is dominated by only a few oligopolistic firms belonging to some of the largest pharmaceutical companies. These companies own the organizational capabilities and can afford the high investments required to deal with this dynamic business, and with the long and complex process of developing vaccines.[2,3] Altogether the five leading

[1] In this research the terms immunization and vaccination are used interchangeably and with similar meaning, even though some authors argue that the former is more inclusive because it results in the development of adequate immunity (see Stern and Markel, 2005).
[2] Innovation on vaccines and the complex aspects involved in the processes of developing and manufacturing vaccines are stressed throughout Chapter 5.
[3] The terms "organizational capabilities" and "managerial capabilities" are used interchangeably and with similar meaning in this research.

vaccine manufacturers supply around 85% of the global market (Gréco, 2002). The main markets in terms of value are located in developed countries – USA, Canada, Western Europe and Japan – but the biggest demand in terms of volume is located in the rest of world (Boston Consulting Group, 2005).

Although being only a fraction of the pharma market, the global vaccine market has presented an impressive growth in the last two decades, with an average growth of 10% in the 1990s (Mercer Management Consulting, 2002), and an estimated average growth of 14% in the 2000s, the latter based on WHO projections (2009a). This makes this market one of the fastest growing sectors of the industry (Asian Development Bank, 2001). In terms of volume, however, the average growth was only 1% in the 1990s.[4] This contrast is explained by the introduction of new enhanced paediatric vaccines and proprietary products in the market by the "Big Pharma" (Mercer Management Consulting, 2002), and is suggestive of the importance of new-to-the-world product innovation as well as of the technological dimension to this industry.

However, biotech firms and local manufacturers have also been important actors in this industry.[5] The former are mainly located in developed countries and have been characterized by their highly skilled people, high investments in R&D and strong capabilities to perform the first stages of the process of vaccine development. The most successful biotech firms have then been acquired by, or formed alliances with, the "Big Pharma". Local manufacturers have recently been re-emerging in the vaccine industry and have performed an important role in developing countries' markets by providing the low cost/margin old technologies usually required by their public programmes that are no longer produced by "Big Pharma" firms.[6] However, they have struggled to acquire the capabilities needed to govern the process of technical change and develop the vaccines for the neglected diseases of developing and poorer countries. These are not of interest to the "Big Pharma" firms due to the high investment needed and their lower economic returns.

[4] Further details of the global and Brazilian vaccine markets are stressed in Section 6.3 of Chapter 6 (pg. 144-151).
[5] The term "local manufacturers" is frequently employed in the literature on vaccines, and encompasses the smaller manufacturers, which mainly address their country's public and/or private markets.
[6] Local manufacturers have also been important in some developed countries in providing the low cost/margin vaccines.

The focus of this study is the development of the Brazilian vaccine industry (BVI), an industry currently constituted of four old public manufacturers who have addressed the Brazilian public market almost exclusively.[7,8] The two main firms of this industry have re-emerged in the last three decades after a national crisis in the supply of immunobiologicals. This crisis, generated by the tighter quality requirements imposed by the Brazilian regulatory authority in the early 1980s and the high investments needed to comply with these new requirements, culminated in the withdrawal of the then biggest Brazilian vaccine manufacturer, a private company receiving foreign capital. The situation left the then recently created National Immunization Programme (PNI) faced with an insufficient local vaccine supply from the existing smaller public producers, who also ran their production under precarious conditions at that time (Gadelha and Azevedo, 2003; Ponte, 2007).

To tackle the problem the Brazilian government set the vaccine sector as an issue of "national security" (Benchimol, 2001:359) and put forward a new and ambitious programme of national self-sufficiency in immunobiologicals (PASNI), in order to end the high dependence on external products. As a consequence, around US$158 million were invested in the modernization of the public manufacturers' facilities between 1985 and 1998. In addition, the development of the main firms of the BVI has benefited from a huge, protected and fast-growing public market coordinated by the PNI, who has successively introduced new technological products in the immunization routine of the country, especially in the last decade. To serve this public market these local firms do not compete with each other.

However, the needs involved in the technological dimension of this industry go far beyond the simple building of production capacity. As a result of the unidirectional policy of the government to this sector, innovation in the technological frontier has posed huge challenges for the firms of the BVI. Consequently, the acquisition of foreign technology has apparently been an increasingly important source of knowledge and a strategy to develop local capabilities, in order to supply the growing needs of the PNI

[7] This research approaches the business of human vaccines only. Therefore, other segments explored by the main firms of the BVI (e.g. serum, diagnostic reagents, biopharmaceuticals and blood products) are not approached here.

[8] The smallest of the manufacturers is not public but a non-profit private organization. However it has benefited from the same incentives provided by the government.

for more advanced vaccines in good time, as well as to keep the benefit of market protection provided by the government.

Within the Brazilian context, therefore, it is noticeable that the main firms of the BVI have developed important capabilities and, under very specific circumstances, have grown rapidly in the last decades. They have reversed the government's high dependence on imported vaccines, and, although they have been unable to finish the technological transition to date, have been able to imitate and improve some existing non-patented technologies. Although being a fast-follower may appear a natural alternative strategy in a business dominated by few oligopolistic firms, reaching the technological frontier seems to be the main aim of the firms in a country that seeks self-sufficiency in a sector where the new technologies continuously required by the National Immunization Programme are well protected by IPR, and innovation seems to be a result of high investments in R&D.

1.3 The Theoretical Context

Innovation has long been recognized as a central phenomenon to the development of firms, industries and nations. Understanding some key concepts such as uncertainty, diversity and interactivity and networking, as stressed in Sub-section 2.2.2 of Chapter 2 (pg. 13-16), is critical to interpreting the process of innovation. However, rather than innovation itself, what really matters for the development of firms and industries in the long run are the capabilities needed to generate innovation (Dahlman et al., 1987; Rush et al., 2007). To understand how innovation has been generated, therefore, an increasing number of scholars have used the technological capability framework in the last 30 years or so, not only in latecomer contexts, where technological accumulation is more easily observable in its basic forms, but also in advanced contexts, where more distinctive capabilities are more commonly found.[9]

If one considers the level of importance of two sources of knowledge (the acquisition of foreign technologies and the development of local innovative capabilities) literature on technological accumulation in latecomer contexts shows that the catching-up process of firms and industries develops through a common/linear pattern. It starts from a high

[9] This research uses the terms technological accumulation, technological capabilities building and technological capabilities development interchangeably.

dependence on the acquisition of foreign mature technologies due to the lack of significant local innovative capabilities and technological infrastructure (e.g. Dahlman and Fonseca, 1987; Bell and Pavitt, 1993, 1995; Hobday, 1995; Kim, 1997).

During this phase minimal local innovative capabilities are normally required to absorb and adapt the acquired technologies (Freeman and Soete, 1997). As firms need to innovate to be successful, over time they gradually develop more advanced innovative capabilities to adapt and improve existing technologies and, eventually, to generate new technologies (Mytelka, 1978). In doing so they become less dependent on knowledge from technologies imported from developed countries. As shown by Hobday (1994, 1995) the whole process is long and painstaking. In addition, this body of literature stresses that internal and external factors, such as markets, government and institutions, culture, prior experience, national capabilities among others, heavily influence the development of technological capabilities inside firms.

Although the broad view provided by the catching-up approach is useful in generating understanding of the importance and directions of these two sources of knowledge for technological accumulation in latecomer countries, it does not provide all the elements needed to interpret the relationships between them and how the process unfolds over time, especially in specific contexts and stages. Other elements found in more in-depth studies within the same body of literature should then be integrated to this approach.

In this regard, some studies have stressed the role of foreign technology acquisition in the development of technological capabilities in catching-up firms/industries in more detail (e.g. Dahlman and Fonseca, 1987; Hobday, 1995; Radosevic, 1999). In other studies the interrelationships between the acquisition of foreign technologies and the development of innovative capabilities have been approached and a variety of different results have emerged. Mytelka (1978), for instance, found a strong correlation between the licensing of imported technologies and low engagement in in-house R&D, especially in state-owned firms, when analysing 90 firms in three South-American countries. Kim (1997) found that a passive attitude toward the learning process in some Korean firms could be related to the acquisition of foreign technologies through licensing from single sources. However, Hobday et al. (2004) have shown that both strategies are adopted by firms approaching the innovation frontier in Korea.

The development of innovative capabilities has been the main focus of other studies and has been approached from different directions. Bell (2007), for example, emphasizes design and engineering as a type of important innovative capability for the industry and infrastructure sectors, but frequently neglected in the literature. The pioneering works of Dutrénit (2000, 2007) and Hobday et al. (2004) are concerned with the specific challenges faced by firms approaching the innovation frontier. The innovation transition approach, first employed by the former and further stressed by the latter authors, has revealed important aspects and characteristics of, as well as constraints to, the transition process of firms of Asia and Latin America trying to catch-up and reach the technological frontier. Although it is an important approach to interpret the specificities of technological accumulation in firms/industries that have already developed advanced technological capabilities, the authors argue that further research is still needed to strengthen the knowledge about this issue in other firms/industries and contexts.

The process of innovative capability building has also been approached inspired by Gerschenkron's ideas (1962), emphasizing new directions/paths as an alternative strategy of latecomers to get around their disadvantages and catch-up with the leaders. The works of Forbes and Wield (2002, 2008) focus on the processes of growing value-added through manufacturing and innovative capabilities by follower firms in order to move from process to product innovation and then to proprietary process and product innovation. They use cases in East and South Asia, Africa and regions in Latin America to illustrate their arguments about new strategies to develop. Hobday (2003) shows that the development of the Asian newly industrializing economies has been characterized by significant deviations from experiences of earlier industrialization, and encompasses a mix of strategic innovation and careful imitation He suggests that catch-up is unlikely to happen from imitation alone. Figueiredo (2009) investigates the aspects of a specific pattern of innovative capability accumulation taken by firms involved in forestry, pulp and paper industries in Brazil that evolved in the technological catch-up process across distinct policy regimes, and macro-economic disruptions faced by that country.

This research draws on these bodies of knowledge to build a broader and simple framework in order to interpret the specific characteristics of development of the BVI, hopefully applicable to a wider variety of latecomer contexts.

1.4 Research Strategy, Design and Methods

To achieve the objectives proposed, this research integrates the catching-up and innovation transition approaches, to combine the broad perspective of the former with the deeper focus of the latter. It builds a simple framework based on linear approaches of catch-up to look for differences and similarities in the pattern of development of the BVI. This strategy constitutes an attempt to interpret the general characteristics of development of the Brazilian vaccine industry over a long period of time, while throwing light on the micro dynamics of the critical phases of development of innovative capabilities.

The focus on contemporary events, and the "how" and "why" type of questions, set the stage for an explanatory case study (Yin, 2003). Although the study analyzes events happening inside the firms, the focus of the research and its results are intended to represent the industry as a whole, constituting what the same author calls a single and embedded-case study – a single case-study with multiple units of analysis. Moreover, as technological capabilities usually develop over long periods of time, the research takes a retrospective account and investigates the development of the BVI during the last four decades.

On empirical grounds multiple forms of data collection were used. In this sense, the Brazilian context was covered by interviews with senior actors of the firms and with other senior actors linked to the industry and to the policy level. Secondary sources such as government publications, firms' institutional folders, annual reports, specialized magazines and firms' and other institutions' web pages were also used. This research also benefited from some few informal conversations and from a survey carried out in the main firm of the BVI to assess levels of technological capability. The international context was mainly covered by publications, papers and institutional web pages.

1.5 Organization of the Thesis

This thesis is constituted of three main parts. The first part encompasses the theoretical issues and is formed by Chapters 2, 3 and 4. Chapter 2 stresses the bodies of knowledge about innovation and technological capabilities that underpin the conceptual constructs and the analysis carried out in this study. Chapter 3 describes the research problem, stresses the main arguments of the research, presents the research questions and

propositions, and explains the conceptual and analytical frameworks developed to link the theory to the phenomenon being investigated. Chapter 4 is about the research methodology: it details the research strategy and design, and explains how data was defined, collected, processed and analyzed within the research.

The second part relates to the empirical issues of the thesis and encompasses Chapters 5, 6 and 7. The first two chapters address both the Brazilian and international contexts, while Chapter 7 is entirely dedicated to the Brazilian vaccine industry. In Chapter 5 the specificities and main aspects about vaccine and innovation on vaccine are presented. It stresses the main facts, the history, some important technological breakthroughs, the actors and the complexities involved in the processes of developing and manufacturing vaccines. Chapter 6 is about the vaccine industry, markets and institutions in Brazil and in the world. It provides detailed aspects and data of the dynamics of the vaccine business of the "Big Pharma" firms, the biotech firms and the local manufacturers. It also presents introductory descriptions of the Brazilian vaccine firms. Data about the international and Brazilian vaccine markets, and the complex role of the institutions giving support to the vaccine industry in the international and Brazilian context, are also presented in this chapter. Chapter 7 stresses the development of technological capabilities inside the Brazilian vaccine industry during the last four decades, with emphasis on the two main firms of this industry and on the processes of technology acquisition and the development of innovative capabilities. The characteristics of development of technological capabilities during the transition phase are approached in this chapter. Finally, the chapter presents the results of the survey carried out in the main firm of the BVI to strengthen the analysis of the previous findings.

The third part refers to the analysis and conclusions of the research. It is constituted by the last two chapters of the thesis. In Chapter 8 the findings are analyzed and discussed by addressing the research questions and propositions. Chapter 9 summarizes the main findings of the research and draws some implications for policy, management and for the future of this industry. In addition, it points out contributions and limitations of the study as well as issues and questions for further research.

Chapter 2 – Innovation, Technology, Capabilities and Industry Development – Literature and Links

2.1 Introduction

The literature on innovation has grown at a high rate in recent decades, and its size and diversity reflects the importance of innovation to social and economic development. As noted by Fagerberg (2005), it is not possible to have a comprehensive overview of the entire scholarly work on innovation without years of study. On the other hand it is difficult to resist the temptation of going beyond the boundaries of a research topic when analyzing the subject. For academic methodological reasons this paradox is put aside. This chapter introduces the bodies of knowledge – theoretical and empirical constructs on the subject of innovation and technological development – that underpin the building up of the conceptual approaches and the analysis of the arguments in this research.

The Chapter is organized in four main parts. Section 2.2 presents a quick overview of the antecedents and features of innovation as an important phenomenon to economic and industrial development. Section 2.3 introduces the literature on the concept of technological capability as one of the most successful ways of analyzing and understanding how innovation has been generated inside industries and firms. Section 2.4 attempts to present an alternative and/or complementary approach to interpret the development of latecomer industries. Section 2.5 summarizes the ideas approached in the previous sections.

2.2 Innovation and Development

Understanding the key concepts of innovation is an obligatory step for anyone exploring the field of industry development. Firstly, this section reviews in brief the precursory attempts to link innovation and economic development (Sub-section 2.2.1). The main features of the innovation process that became the core foundation for any subsequent study on this field are then outlined (Sub-section 2.2.2). The approach of National Systems of Innovation (Sub-section 2.2.3) and indicators for measuring innovation (Sub-section 2.2.4) end the literature review in this section.

2.2.1 Antecedents – an overview

Innovation, as an important phenomenon to the development of firms, industries and nations, has been historically recognized, especially in the most general sense, since the times of Adams, Marx and List. Neo-Classical economists of the first half of 20th century, however, were mainly interested in short term economic analysis, and tended to treat the innovative activities as exogenous variables (Freeman and Soete, 1997).

In the first decades of the 20th century, Schumpeter first stressed the importance of innovation as central to the dynamism of firms (Pavitt, 1990). Besides placing technical change at the heart of capitalism development, Schumpeter's works also pioneered recognition of the vital importance and relationship of the organizational, social and technical dimensions involved in innovation (Freeman, 1988). The impact of his propositions to the neo-classical theory at this time was "devastating and radical", in the words of Rosenberg (1994:47). His work, however, was essentially theoretical and not based on statistics. Furthermore, as indicated by Freeman (1988:6), the work of Schumpeter concentrated its analysis on the developed world and did not pay attention to international trade or international diffusion of technology. Therefore, it needed to be complemented.

During the following decades, and within an evolutionary perspective later stressed by Nelson and Winter (1974, 1982), attention was directed to the attempts to understand the relationship between technical change and economic growth. This generated two linear and opposite theories – the "technology push" and "demand pull" mode of innovation. In the former, economic growth was seen as resulting from technology produced by continuous investments in science. The latter was based on the idea that technology was produced from market signals and changes in demand. From the 1970s onwards, the availability of new statistical data and empirical and theoretical studies have provided a deeper and more diverse understanding of the process of innovation inside organizations, and of the complexity and relationship of science, technology and economic development, putting an end to the idea of linearity in the innovation process (Martin and Nightingale, 2000).

2.2.2 Key Features of Innovation

As noted by Freeman (1991), most research on innovation were simply "anecdotal and biographical" before the 1970s. Nelson and Winter (1977) criticized the presumptuous assumption that knowledge about innovation was already strong enough to provide guidance to policies toward innovation at that time. Extensive and detailed research on innovation since then started unveiling its mysteries, strengthening knowledge and bringing to light some key features that constituted the core foundations of the theory on innovation. These key features became the starting point for most of the subsequent empirical and theoretical studies on the subject, influencing a great range of scholars who looked for new explanations and theoretical knowledge for new policy and management directions. To date, they remain essential. The two most important features or characteristics – uncertainty and diversity – are summarized below:

a) *uncertainty* – this key feature of the innovation process has been described as encompassing two intertwined dimensions. The first is inherent to the process of research and development inside organizations, and deals with the inability to foresee and plan the most efficient path and outcome of the search process (Rosenberg, 1994:93).[10] The second is related to the important implications to the institutional innovation strategies posed by the uncertainties present in the external environment (Nelson and Winter, 1977; Tidd et al., 2001). In some works both dimensions are approached (e.g. Dosi, 1988).

The problem of uncertainty was also raised in some empirical studies. Pavitt (1990, 1991) highlighted the fact that the high uncertainty of innovative activities among the key properties of large innovative firms had been identified in previous empirical studies. According to these studies a very low proportion of R&D projects – about 10% – become a commercial success, and about 50% of R&D industrial firms find no profitable application. In a more elaborated approach, Freeman and Soete (1997:243) attributed innovation failure to three types of uncertainty – technical, market and general political and economic. They also linked technical uncertainty to cost and risk, and differentiated the degree of uncertainty by a range of categories of innovation (*ibid.*

[10] Rosenberg also emphasizes that knowing the content of a patent is very useful in dealing with uncertainty in this sense. Even though patents do not disclose details to permit imitation, the simple fact of knowing that something is feasible can contribute in the reduction of uncertainty during the research process.

p.244). From empirical evidence they suggested that the degree of uncertainty drives decision on industrial R&D since less than 5% of all R&D expenditures in most OECD countries is concentrated in basic research, whilst the majority of these expenditures are concentrated in less uncertain categories of projects such as minor technical improvements and quicker payback projects (*ibid.* p.255).

b) *diversity* – this feature of the innovation process has been explored in several different contexts within the literature.[11] Central, however, is the idea that innovation processes vary in many different respects, and are dependent upon external and internal conditions such as economic sector, field of knowledge, type of innovation, size of the firm, corporate strategy, prior experience, and so on (Pavitt, 2005:87), with evident important implications for policy and management. One seminal work characterizing the diverse and contingent nature of the innovation process was carried out by Pavitt (1984).[12] In this work economic sectors are classified in four categories according to their technological trajectories – "supplier dominated", "production intensive" (this subdivided into "scale intensive" and "specialized suppliers") and "science based" – and regular differences and similarities among the sectors are identified, characterizing what he called "sectoral patterns of technical change".[13] This work also confirmed that the knowledge applied in innovation is largely firm specific, which strengthens its cumulativeness property and the importance of the knowledge built up through experience – the tacit knowledge.[14] In another direction, diversity inside firms, emphasized in literature on strategic management, has been analyzed to the understanding of differences in competitiveness (e.g. Cohen and Levinthal, 1990; Prahalad and Hamel, 1990; Nelson, 1991; Leonard-Barton, 1992).[15]

[11] Diversity is inherent to the complexity of the process of innovation. Therefore it has been analyzed from many different perspectives, be they economic, organizational, managerial, social or psychological (see Pavitt, 2005).

[12] This empiric work was based on the analysis of data on about 2,000 significant British innovations since 1945 (Pavitt, 1984:15).

[13] Later on a new technological trajectory was identified – "information intensive" – from the emergence of the field of information technology – IT (see Pavitt, 1990; Tidd et al., 2001).

[14] Cumulativeness is also an important feature of the process of innovation. The central idea behind this concept lies in the notion that past experience strongly conditions what firms can expect to do in the future. This concept is further approached in other sections of this chapter.

[15] These works deal with internal aspects of firms such as learning, capabilities and organizational characteristics. Some of them are discussed in more detail in Sub-section 2.3.3.

Later on a third very important characteristic emerged from the need of firms to deal with the growing complexity and shorter life-cycles of the technologies. The speed of development then became a crucial factor for the competitiveness of firms, as noted by Rothwell (1994). The interactions and search for external knowledge then became an increasing part of the strategies of firms. Some aspects of this feature of the innovation process are discussed below.

c) *interactivity and networking* – There is a common belief in the more recent literature that innovation does not take place in isolation, but rather firms depend upon a large range of interactions and relationships with their environment to innovate (Cohen and Levinthal, 1990; Freeman, 1995; Fagerberg, 2005). Two features seem to underpin the importance of interactivity: 1) the increasingly specialized and interdisciplinary nature of the innovation process, as pointed out by Rosenberg (1994:148) and Pavitt (2005:88), especially in a sector such as pharmaceuticals; and,[16] 2) the learning as an interacting and central element for the innovation process, as described by Lundvall (1992a:1) and Johnson (1992:23). These features result in internal and external interactions and have been explored in several works. Pavitt (1991) stresses the sources of learning and its interactions inside large innovative firms. The partly tacit nature of knowledge and the collective nature of the learning activity require frequent personal interaction for effective learning, according to some of his findings. Also, strong linkages between R&D laboratories, and other technical functions, and the marketing function are of central importance in the dimensions of learning inside firms (*ibid.* p.47). Increasing external linkages such as acquisitions, alliances, licensing, for obtaining new technologies are one of the major features of contemporary business, according to Granstrand et al (1997:87). In the project SAPPHO, the existence or lack of external linkages and networks were emphasized among the most important characteristics of the success and failure of innovations.[17] Two of these conclusions are quoted below.

> (1) *User needs and networks.* Successful innovators were characterised by determined attempts to develop an understanding of the special needs and circumstances of potential future users of the new process or product. Failures

[16] Rosenberg points out the remarkable advances in fields such as biochemistry, molecular and cell biology, immunology, etc, to emphasize a newly emerging pattern of innovation and recognize that success in pharmaceuticals requires close cooperation among a growing number of specialists.

[17] Project SAPPHO analyzed several pairs of successful and unsuccessful innovations competing in the same markets to identify the differences between them (Rothwell et al., 1974).

> were characterised by neglect or ignorance of these needs. … (3) *Linkage with external sources of scientific and technical information and advice.* Successful innovators, although typically having their own in-house R&D, also made considerable use of other sources of technology. Failures were characterised by the lack of communication with external technology networks, whether national or international (Freeman, 1991:500).

Lundvall (1988) analyzes the interactions in the process of innovation from two dimensions. Within a microeconomics framework he approaches the specific aspects involved in the interactions between users and producers. In this work the focus of his analysis is on the process of learning since successful innovation must be based upon knowledge about the needs of potential users (*ibid.* p.350). In the second part of his paper Lundvall outlines some of the implications of his approach to the national and international contexts in an attempt to develop introductory ideas on a model of national systems of innovation. Interaction in this broader sense has been the object of intense attention by scholars, as well as, more recently, generating a vast range of concepts and frameworks. Given its repercussion the National Systems of Innovation framework is discussed in the next Sub-section.

One very relevant empirical work on networks was written by Galambos and Sewell (1995). They describe in historical perspective the rich and diverse networks of innovation that contributed to the development of Merck Sharp & Dohme, one of the four current global leading vaccine firms. One of the most prominent merits of this work is revealing the special features of the networks in this sector.[18]

2.2.3 National Systems of Innovation

The first attempt to link the interactions among institutions within the borders of a nation and their influence on economic growth is attributed to List in 1841 (Lundvall, 1992a; Freeman, 1995).[19] It was in the late 1980s and early 1990s, however, that this approach was first extensively used in order to investigate the relationship among national elements contributing to economic growth and innovative performance within the context of countries, and to stress similarities and differences across countries (e.g.

[18] One important finding highlighted by Galambos and Sewell was the tendency of long cycle networking originated by the specificities of the process of vaccine development.

[19] The work of Freeman (1987) was the first to explicitly employ the concept of "National Systems of Innovation" (Lundvall, 1992a:16; Edquist, 2005:183). Freeman (1995:5), however, attributes to Lundvall the first use of this terminology.

Freeman, 1987; Dosi et al., 1988; Lundvall, 1992b; Nelson, 1993). Notwithstanding, the use of this terminology does not mean that the interactions that permeate the process of innovation are restricted to, or take place only in, a national dimension. There was already a common awareness in these works, that systems of innovation transcend national geographical borders or clusters into regions, sectors, industries or other economic and social spaces. However, this diversity was not explored in these works, except in Freeman (1987).[20] Another common view and point of departure of these studies was related to the systemic nature of innovation – R&D as not only part of the innovation process but rather of a system where several elements interact and influence the process (Nelson and Rosenberg, 1993). On the other hand, these works adopted different perspectives and distinguished different elements or determinants that influence the innovation process, generating, therefore, different concepts and a lack of a generally accepted definition for this approach (Edquist, 2005:183).[21]

Rapidly increasing bodies of research on this topic have attempted to conceptualize and understand in depth the characteristics of the systems of innovation since then. Nevertheless, it has not been a simple task. Edquist defines systems of innovation as all important economic, social, political, organizational, institutional and other factors that influence the development, diffusion and use of innovations (2005:182), and indicates a problem in his own definition: if there are some potential factors missing in this definition, because they are still not known, there is a danger of excluding what might prove to be an important determinant from the analysis (*ibid.* p.183). Hence the implications of applying a system perspective to the study of innovation, as Fagerberg (2005) observes.

One common feature of systems is that their components have strong complementarities and the lack of one critical component may affect the entire system (*ibid.* p.13). Complementarity is also found across systems of different levels, e.g. continental, national or sub-national (Freeman, 2002), and the question to be asked will determine the most appropriate context to be focused, as noted by Edquist (2005). In fact, analysis of sub-systems has been proved quite useful, either because technologies differ across

[20] In this work Freeman analyzes the organization and interactions between sub-systems of innovation in Japan.

[21] Fragmentation of empirical works on innovation preventing the building up of specific theoretical approaches had been previously noticed by Nelson and Winter (1977).

sectors (Pavitt, 1984; Malerba, 2005) or because innovation is a learning process and therefore tends to be highly influenced by local and specific contexts (Fagerberg, 2005).[22,23] One relevant example is the work of Albuquerque and Cassiolato (2000), which focuses on the specificities of the innovation system of the health sector in Brazil. Besides the interactions between the components of this highly specific system, they analyze interactions of the health sector system with other national systems.

2.2.4 Measuring and Assessing Innovation

Quantitative methods have also been extensively used as a foundation for the analysis of innovation, both in the national and industrial contexts. Initiatives of measuring scientific and technological activities were a result of the increasing interest in understanding the role of technological change in economic growth, and, some decades ago, this ability made economists increasingly more confident in dealing with technological issues in economics (Rosenberg, 1974). Despite eventual criticism on their limitations, quantitative techniques of measurement have been largely used to assess innovation since then.

The most common indicators used in science, technology and innovation analysis are R&D data, patent data and bibliometric data (Smith, 2005), although they are complemented by several other families of statistics (OECD, 2005). However, R&D has been by far the most used indicator of innovative activities (Smith, 2005).[24] The rapid and wide propagation of studies using measurement techniques in the assessment of innovation activities, led to the development of standards or guidelines as a reference for surveys attempting to examine the characteristics of the innovation process (e.g. Arundel et al., 1998; OECD, 2002, 2005).[25]

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[22] Malerba (2005:386) argues that sectoral systems coexist in three different dimensions – local, national or global.

[23] Arundel *et al*. (1998) point out that the specificities and complexity of some sectors make the boundaries of systems of innovation unclear and problematic to define. They show the example of the pharmaceutical sector: this sector is supposedly highly globalized, with firm strategies depending little on where they are located, at the same time they are closely tied to national infrastructure, such as regulatory systems and public research.

[24] R&D intensity – the ratio of R&D expenditures to some measure of output – is the most used R&D indicator. Patents are considered more as an invention indicator whilst bibliometrics are considered more related to scientific activities (Smith, 2005).

[25] The Frascati Manual (OECD, 2002) was first edited in 1963. Now in its 6th edition, it is a standard for R&D surveys; the Oslo Manual (OECD, 2005) is a general guideline for surveys in innovation. In its first edition in 1992 the focus was on technological innovation in manufacturing but it has been updated and expanded since then. Now, in its 3rd edition, it encompasses service sectors as well as other types and

Innovation is very complex and, however sophisticated the indicators are, there are many innovative activities that are not directly measurable. Arundel et al. (1998:8) illustrate this assertion with two examples: the first is related to tacit knowledge and its relation to the ability to innovate; the second concerns why firms adopt particular strategies.[26] The growing concern of the importance of knowledge and learning to the innovative process has generated a tradition since the early 1980s of assessing the process of building up technological capabilities inside firms, especially in developing countries, to strengthen the understanding about innovation. This is the object of the next section.

2.3 Linking Innovation and Development of Technological Capabilities

In this section the review of the literature seeks to present the concepts of technological capability accumulation as one of the most diffused frameworks to analyzing and understanding the process of innovation inside firms and industries (Sub-section 2.3.1). It presents the basic concepts (Sub-section 2.3.2) and some approaches of the strategic management literature (Sub-section 2.3.3). Emphasis is put on the approaches applied in the analysis of latecomer firms, and on the key characteristics of the process of building up technological capabilities (Sub-section 2.3.4). Some models for assessing technological capabilities are also discussed in this section (Sub-section 2.3.5).

2.3.1 Knowledge, Learning and Development of Technological Capabilities

As discussed in Sub-section 2.2.1, innovation has long been recognized as vital for the development of firms, industries and nations. In the last thirty years or so, an increasing number of scholars have studied the process of technological capability accumulation as a way of understanding how innovation has been generated (e.g. Bell et al., 1984; Fransman and King, 1984; Katz, 1987; Lall, 1992; Bell and Pavitt, 1992, 1993, 1995; Hobday, 1995; Ernst et al., 1998a; Dutrénit, 2000, 2007; Figueiredo, 2001, amongst others). Rather than innovation itself, what matters for firms and industries in the long run is the capability to generate innovation (Dahlman et al., 1987; Rush et al., 2007), and the accumulation of the capabilities needed to generate continuous technical change

areas of innovation such as organizational, marketing, incremental innovations and innovation linkages, so it accompanies the changing and newly understanding of the innovation process. The IDEA 3 report (Arundel et al., 1998) focuses on survey questions aiming to provide more suitable indicators to the innovative process.

[26] According to the authors these types of limitation point out to the need of focused case studies and semi-structured interviews as complementary to innovation indicators.

is, therefore, essential for competitiveness (Bell and Pavitt, 1995). The complexity and nature of technology, however, as stressed by Pavitt (1987), means that the development of technological capabilities at the level of the firm is essentially based on learning processes. In general, although differences across industrial sectors should be considered, even for the borrowers of technology, the accumulation of technological capabilities is not always automatic but requires substantial and, quite frequently, explicit effort in undertaking different types of learning activities.[27] In the sense employed by Bell (1984:188), learning refers to the "acquisition of increased technological capacity – e.g. technical skills and knowledge – by individuals and organizations". Fransman (1984) points out the high specificity of the process of knowledge accumulation so that one cannot expect the same forms of knowledge to emerge from two identical industrial plants. Hence the emphasis on the learning mechanisms to understand how the process of technological accumulation takes place inside firms and thus generates innovation. The importance of learning at the management dimension to technological accumulation is barely approached in these two latter works.

2.3.2 Technological Capabilities – Basic Concepts, Definitions and Levels

Literature on technological capability is also broad and diverse and frequently disconnected. It is a difficult task to capture all the dimensions approached in the literature on technological capabilities in a single definition. Bell (2007) has identified two levels of technological capabilities analysis within the literature: the macro or country level, and the micro or enterprise level. More recently micro analysis has also addressed the capabilities interacting beyond the boundaries of the firms (*ibid.* p.98). Within the micro level some approaches suggest different elements or categories of technological capability – e.g. production, investment and innovation, as in Dahlman et al (1987) and Kim (1997), or production, investment, minor change, strategic marketing, linkage and major change, as in Ernst et al (1998b). Others distinguish the types of technological capability in a matrix that categorizes the capabilities by functions and degrees of complexity (Lall, 1992; Bell and Pavitt, 1995; Figueiredo, 2001). The use of stages as a reference is also a common approach in the analysis of the sequences by

[27] The idea of explicit effort for learning is used here in the way stressed by Bell (1984) to refer to the other mechanisms not based on experience or "doing-based" learning. In this latter form technological capabilities are acquired as a by-product of the production activities.

which technological capabilities develop in latecomer firms, and this model has been represented by several different forms, as in Kim (1980, 1997), Dahlman and Fonseca (1987) and Hobday (1995), to cite only a few works.

For the reasons above mentioned we can find several different definitions for the technological capabilities approach. In addition, in the literature the term capability is also interchanged with the terms mastery, competence and capacity. The broader and more common sense captured from most of these works is that capability means the ability to do things, and technological capability refers to the stock of different skills, knowledge and organizational resources that enables a firm or industry to absorb, adapt and generate new technologies as well as to change the technology it uses.[28,29]

Technological accumulation can mean, therefore, the process of building up technological capabilities or, according to Bell and Pavitt (1993, 1995), the process of learning inside firms. The problem with this broader definition is that one should consider technological capabilities encompassing the different dimensions that involve the activities inside firms, be they operating, innovative or organizational. Hence the usual need to delimitate the scope of each work. The building up of technological capabilities in the micro or enterprise level will be addressed in more detail in Sub-section 2.3.4 within the most recent perspective, that is, encompassing its interactions with the boundaries of the firm.

2.3.3 Capabilities at Technological Frontier Level: the Strategic Management Literature

Recent reviews of the literature on technological capability (e.g. Dutrénit, 2000, 2004; Figueiredo, 2001) have highlighted the two main streams that have characterized the studies on this subject in the last decades: the strategic management literature (SML), which draws attention to the existing capabilities of technological frontier companies, and the developing countries literature (DCL), which focuses on the processes of building-up technological capabilities in latecomer companies.[30] Both bodies of

[28] The term absorb employed here includes the acquisition, assimilation and use of a given technology.
[29] The definition was condensed from the micro or enterprise level of literature and it does not fit the macro or national level.
[30] This distinction implies that firms in more technologically advanced countries have already developed the capabilities needed to innovate, whilst latecomer firms enter into a business acquiring technology

literature have, therefore, distinguishing objectives. Whilst the former is interested in the kinds of distinctive capabilities that have enabled technological frontier firms to deal successfully with the fast changing environment and achieve and/or sustain their technological competitive advantage, the latter focuses on the range of capabilities – frequently from the most basic ones – still being developed in latecomer firms that are normally struggling to become innovative and to catch-up.

These distinctive capabilities have been stressed within the SML through several approaches. The "Core Competences" (Prahalad and Hamel, 1990), the "Dynamic Capabilities" (Teece and Pisano, 1994; Teece et al., 1997) and the "Core Capabilities" (Leonard-Barton, 1992) are among the most influential ones. However, as pointed out by Dodgson (1993) and Dutrénit (2000), these approaches share some similar ideas such as the uniqueness of the firm's core competencies, due to the tacit characteristic of the learning process inside firms, as well as the importance of the organizational dimension along with the technological dimension in the building up of these competencies.

Although sharing similar ideas, these works put emphasis on different aspects of the organizational dimension to describe the characteristics of these distinctive capabilities. For Prahalad and Hamel (1990) the need for developing core competencies is a management issue rather than a lack of technological capabilities.[31] It is a collective learning and the harmonization of the diversity in production skills, of multiple streams of technology and of the understanding of key personnel about customer needs and technological possibilities.

The approach developed by Leonard-Barton (1992) explores the paradox of dealing with core capabilities. On the one side core capabilities may enhance the development of new products and processes. On the other they may hamper these innovation processes – what she then denotes as core rigidities. Moreover, she describes four dimensions to the sets of knowledge that constitute the core capabilities, with emphasis on the fourth – values and norms – as frequently neglected by managerial literature but

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from other firms in developed countries and need to develop their capabilities from basic stages (Figueiredo, 2001).

[31] The authors' argument is based on comparisons between some Japanese corporations and their American and European market competitors that were outperformed by the former.

crucial to managing both the innovation processes and the core capabilities.[32] For the author, the same dimensions that may be appropriate for the development of core capabilities in some contexts may result in core rigidities or inappropriate sets of knowledge in others.

In the Dynamics Capabilities approach the strategic dimensions of the firm (Teece and Pisano, 1994:541-548) are represented by:

1) its ability to coordinate and integrate activities, to learn and to reconfigure and transform its asset structure (managerial and organizational processes);
2) its business – technological, complementary, financial and locational – assets (present position); and,
3) its prior history and technological opportunities available (paths).

One major problem of these approaches, as indicated by Teece and Pisano (1994:538) and highlighted by Dutrénit (2000:27) and Figueiredo (2001:19), relates to the scarcity of works focusing on the first development of these core capabilities. Another visible problem is that these works focus almost exclusively on the largest companies, and pay little or no attention to small and medium sized enterprises. This brings about some limitations to the use of these approaches in the analysis of latecomer firms.

Other approaches within the same stream of literature, however, introduce some concepts which seem to be more easily adaptable to the context of latecomer firms. Pavitt (1991) links the building up of firm-specific competencies to the firm's size and its accumulated competence.[33] In addition, he links the improvement of these competencies to the continuous, collective and diverse processes of learning experienced by the firms. The organizational forms, and the methods of allocating resources required to create the firm-specific competencies, complete what Pavitt identifies as the four central characteristics of large innovating firms.

[32] According to the author the three first dimensions of knowledge are embodied in employee knowledge and skills, and embedded in technical and managerial systems.
[33] The accumulated competencies are represented in this work by the technological trajectories of the firms – e.g. science-based, scale intensive, information intensive and specialized suppliers.

The "Absorptive Capacity" concept of Cohen and Levinthal (1990) departs from the assumption that the innovation process is critically dependent upon outside sources of knowledge, and that prior related knowledge is essential to the assimilation and use of new knowledge[34]. In their own words they argue:

> Outside sources of knowledge are often critical to the innovation process. … The ability to exploit external knowledge is thus a critical component of innovative capabilities. We argue that the ability to evaluate and utilize outside knowledge is largely a function of prior related knowledge. … Thus, prior related knowledge confers an ability to recognize the value of new information, assimilate it, and apply it to commercial ends. These abilities collectively constitute what we call a firm's "absorptive capacity" (*ibid.* p.128).

The authors also emphasize that R&D has two functions inside the firm: to generate innovation and facilitate learning[35]. Prior related knowledge and learning, therefore, underpins the development of absorptive capacity and have important implications on the innovative performance of the firms[36]. Notwithstanding the importance of technical knowledge, the awareness of the useful sources of complementary expertise inside and outside the firm is also critical in enhancing organizational absorptive capacity. This awareness, in turn, is strengthened with a broad and active network of internal and external relationships developed by the firm (*ibid.* p.133-134).

2.3.4 Building up Technological Capabilities in Latecomer Catching-up Firms: common approaches and key characteristics

The emergence of latecomer economies in the international economic scenario in the post war era, especially in Asia and Latin America, has led to the development of several approaches to address issues on how these countries have technologically grown, and how some of their industries have caught-up or are in the process of catching-up. One common idea in these approaches takes into account the fact that the development of technological capabilities inside industries and firms of latecomer countries usually begins from the experience on simple production activities and takes a progressive move – frequently over long periods of time – towards more complex technological

[34] An R&D unit is considered by the authors to be the formal innovative unit. Therefore, even other units inside the firm, such as manufacturing or marketing, are considered as outside sources of knowledge and information.
[35] This idea is stressed in more detail in a previous work of the authors (Cohen and Levinthal, 1989).
[36] The prior related knowledge is typified by the authors. It must be both close and fairly diverse to the new knowledge to permit its assimilation and exploitation.

activities (Hobday, 2003). This happens because these industries draw frequently on the acquisition of imported technologies that already exist, reversing the usual sequence – innovation/investment/production – of developing new capabilities in developed countries (Dahlman et al., 1987). The importance of production capabilities and of this reversed sequence is then emphasized by these authors:

> Experience in production is generally needed to know what makes sense in expansions and new plants. Experience in production and investment is generally needed to know what is wanted and what is possible in the way of new products and processes. Acquiring this experience is not automatic, however. Nor it is rapid and effortless. It takes conscious effort over a long period of time (*ibid.* p.764).

Research exploring this reversed sequence is not rare. The sequences are usually represented in stages and this way of interpreting the technological development of industries and firms in latecomer countries has proved an useful tool (Hobday, 2003). The stages model has then been applied to a range of different sectors. One important work stressing this idea was developed by Kim (1980) who later further developed his idea in another work (Kim, 1997). In his works Kim identified three main sequential stages in the process of technological development within the electronics industry in Korea: Implementation, Assimilation and Improvement.[37] During the first stage a complete lack of local capabilities to establish production operations was observed and the firms opted to acquire "packaged" technologies overseas.[38,39] Afterwards, other production units benefited from capabilities developed previously and were established from local technological transfers. This evolution, along with increasing market competition and the mobility of experienced technical personnel, allowed firms to move to the second stage.[40] The technical emphasis during this assimilation stage was basically concentrated upon engineering and development. Greater emphasis in local research, development and engineering was a characteristic of the third stage when

[37] In his second work Kim used the term "Acquisition" instead of "Implementation". The idea behind this first stage of his model, however, remained the same.
[38] By "packaged" technology the author means complete technical assistance from the seller of the technology, including specifications and know-how for the product and assembly processes, technical personnel and components parts (Kim, 1980:258-259).
[39] Kim highlights the fact that government protection and import substitution policies were key to open market opportunities and therefore for the initial establishment of the electronics industry in Korea, in a similar pattern to other developing countries (Kim, 1980:257-258).
[40] The importance of the movement of people is also stressed by other authors, such as Dahlman and Fonseca (1987), Bell and Pavitt (1993) among others.

firms gradually began improvements in foreign technologies and gained access to export markets.[41]

The stage model was also successfully used by Hobday (1995) to interpret the development of the newly industrializing economies (NIEs) of East Asia and its economic and technological significance to Japan.[42] In this broader research the author identified five technological stages during the learning process of the industries and firms. Although in greater number, the stages encompass the usual sequence of developing technological capabilities from the basic to the most advanced level. In his research, however, the author links the technological stages to a range of marketing stages, suggesting a tendency of latecomer firms in improving both capabilities simultaneously in order to develop (*ibid.* p.40).[43] Formal and informal mechanisms of technology acquisition by the firms are also presented and linked to the stages of learning and improving both capabilities.[44] Moreover, the research revealed that some later entrants did not necessarily pass through all the technological stages to develop or exactly follow the usual sequence, as in some cases they had already begun carrying out more complex activities.[45]

Other later entrants may benefit from an improved infrastructure to advance more quickly through the stages. However, the common pattern observed is related to a long and hard cumulative process of technological learning rather than leapfrogging (*ibid.*

[41] For more about the importance of design and engineering as innovative capabilities see footnote 56.
[42] The NIEs in this study comprehend the four dragons of East Asia: South Korea, Taiwan, Hong Kong and Singapore.
[43] In his research Hobday used a five stage marketing model developed by Wortzel and Wortzel who analyzed the export market strategies of three of the four NIEs plus Thailand and Philippines. For reference and more detail see Hobday (1995:39).
[44] The most important mechanism used by the firms in East Asia was the OEM/ODM system. The Original Equipment Manufacture strategy is frequently linked to the earlier stages of development since it implies complete technical dependence on the seller. The Own-Design and Manufacture implicates the need of intermediate level of technological capabilities already developed by the buyer. When the firm reaches the highest stage of technological and marketing development (and catches-up) it is able to carry out its Own-Brand Manufacture (OBM). The technological and marketing stages are then also represented by the author as a sequence from OEM to ODM to OBM (for this issue see also Hobday (2003:298)). Other formal mechanisms of foreign technology acquisition involve foreign direct investment (FDI), joint ventures, licensing, sub-contracting, overseas acquisitions and strategic partnerships. Among the informal mechanisms, overseas training, hiring and returnees were listed. For details about how each of these mechanisms fits the stages of development of the firms see Hobday (1995:35-39).
[45] This finding is in line with Lall's work described in the following paragraph, and is also noted by Bell and Pavitt (1995).

p.200).[46] In another dimension, the Hobday's work also explores the diversity of policy models in the region to induce and sustain the development of the electronics industry, and shows the different results achieved by this industry in each country.

The framework developed by Lall (1992) contemplates a matrix where the main technological capabilities at the firm level are categorized by function and by degree of complexity or difficulty. According to the author, the investment and production functions detailed in his approach are merely illustrative as they can vary from industry to industry. Nor do the three levels of complexity – simple/routine (experience based), adaptive/duplicative (search based), and innovative/risky (research based) – necessarily indicate a sequence of learning. Notwithstanding, the author suggests that firms must be able to identify the basic core of functions needed to ensure the success of the enterprise, and that the capabilities must grow over time as more complex activities are undertaken. In addition, the author also points out the importance of the elements of the external environment in stimulating the development of capabilities within firms. One advantage of this approach is its flexibility in adapting to the analysis of different industries. In fact, this approach was later adapted by other scholars and applied in different contexts and case studies.[47]

In another case study the stage model is not explicitly applied but it is clearly linked to the technological development of a firm. The research carried out by Dahlman and Fonseca (1987) shows that USIMINAS, a Brazilian steel company, developed its technological capability using the acquisition of foreign technology as the starting point of a continuous and progressive learning process, which led it to a stage of creating new techniques, processes and products and to its technological independence. The authors conclude the study stating:

> The evolution of USIMINAS shows that rather than seeking to resist foreign technology, as is currently advocated by many, this firm has sought to pull itself up by it. USIMINAS started by being completely dependent on foreign technology and using that as a base from which to selectively absorb more advanced technology through which it has progressively developed its potential. From a technological dependent firm it has evolved to the point where it is

[46] The author had reached the same conclusion in a previous work. See Hobday (1994:853).
[47] E.g. Bell and Pavitt (1993, 1995) and Figueiredo (2001, 2007).

> developing technology of its own and selling technical assistance both nationally and internationally (*ibid.* p.172).

Therefore, studies focusing on stages since the development of the most basic capabilities are related to the capture of the entire dimension of the dynamic process of building up technological capabilities inside latecomer firms. The importance of this dynamic perspective has been acknowledged in later studies (Figueiredo, 2001, 2007; Bell, 2006). Bell (2006) argues, however, that even empirical studies focusing on sequential learning stages, with few exceptions, have been unable to provide useful information on how long it takes firms to move through these stages, and how and why these periods vary under specific circumstances. He then suggests the need for changes in the way research is currently organised and funded to enable more longitudinal studies. Figueiredo (2007) is keen to identify some common features of firm's capabilities building rates from some few empirical studies based on similar frameworks. His analysis, however, reveals variations in the capability development rates among firms, and suggests that there is still no substantial evidence to treat these findings as conclusive.[48]

Other works focus on certain specificities of the process of technological accumulation with a diversity of results. The process of acquiring foreign technology and its relationship to the development of local capabilities is one of them. The work of Dahlman and Fonseca (1987), cited above, emphasizes the importance of this channel of knowledge acquisition for the development of the steel industry in Brazil, and suggests that this strategy is seen with reluctance by many. Mytelka (1978), for example, explores the means by which this process occurs with an emphasis on licensing, and analyzes the relationships between licensing and technology dependence in 90 firms of the metalworking and chemical industries in Peru, Ecuador and Colombia. Among the results she points out that licensing did not promote what she calls technological self-reliance, i.e. to foster local R&D, but, in fact, causes a kind of technological dependence syndrome, especially in state-controlled firms (*ibid.* p.456).

In the Korean context of several industries, Kim (1997) identified that the acquisition of foreign technologies could lead to a passive attitude in terms of learning when licensed

[48] Yet the author's findings show no significant variation in the rate of capability development in the lower levels (level 1 – basic, and level 2 – renewed).

from single sources. In the same context, Hobday et al. (2004) showed that acquisition of foreign technology and development of local innovative capabilities are complementary strategies of firms approaching the innovation frontier.

Historically the process of technological capability accumulation has changed, as noted by Bell and Pavitt (1995). Increasing specialization and professionalization have become the accumulation of technological capabilities required to generate change that is progressively more distant from the production activities, as opposed to the early stages of industrialization when these capabilities were generated along with the expansion of production capacity and output (*ibid.* p.77).[49] For this reason the framework proposed in the approach of Bell and Pavitt (1992, 1993, 1995) to analyse technological accumulation, makes a distinction between production capacity and technological capability.[50]

This distinction is also emphasized by Fransman (1984) with some few differences.[51] The latter adds that the ability of firms to make the qualitative jump from the capabilities involved in the "know-how" to those involved in the "know-why" is a necessary condition to long-run progress.[52] The purpose of the distinction in the approach of Bell and Pavitt is to concentrate the analysis of technological accumulation in the capabilities needed to generate and manage technical change.

In fact, some studies concentrate the focus on innovative capabilities due to some specific purpose. In an original fashion Dutrénit (2000, 2004, 2007) identified a missing issue between the SML and DCL, and proposed a framework to analyze the "transition process", a phase where firms are in the process of developing the kind of strategic innovative capabilities needed to catch-up. The author argues that, due to its peculiarity, both bodies of literature neglect this transition process, which she named the process of

[49] One important implication of this change, also noted by the authors, is that capabilities accumulated only from cumulative operational experience – the learning-by-doing – will not keep firms that import technology competitive.
[50] According to the authors this distinction is important because the resources to generate and manage technical change differ substantially from those needed to produce industrial goods (Bell and Pavitt, 1995:78).
[51] Fransman refers to the paper of Lall (1984) as also making the same distinction.
[52] The "know-how" capabilities are described by Fransman as those involved in four kinds of activities: search and selection of technologies; mastering of technology; adaptation of technology; and, further development of technology. The "know-why" capabilities are recognized as usually the most complex and costly, and are represented by R&D and basic research activities.

building up "embryonic strategic capabilities". According to Dutrénit, SML concentrates the analysis on the strategic innovative capabilities already built by firms with a complex knowledge base. The focus of research is then on organizational aspects rather than on technological ones. On the other hand, DCL has primarily focused on the technological aspects of firms still building intermediate innovative capabilities of a simple knowledge base.

To build up embryonic strategic capabilities, latecomer firms need to develop deeper and broader stocks of knowledge in both technological and organizational dimensions (Dutrénit, 2004:231). By applying her framework on case studies, and investigating the process of building up technological capabilities in three large Mexican firms, Dutrénit has identified four factors influencing the transition process: a) the unevenness in the knowledge bases;[53] b) the profile of R&D activities and the technology strategy options of latecomer firms; c) the impact of the context on the stability of the technology strategy and the knowledge creation process; and, d) national science, technology and innovation capabilities. According to the author, it is important to highlight the fact that these factors lie in the micro, meso and macro levels, and that the first three factors should be managed by the firms whilst the fourth is beyond their decision power (Dutrénit, 2007:145). Dutrénit has the merit of being the first to explore this dimension of the process of technological accumulation. However, as she also stated, further research should be conducted to strengthen the knowledge about this issue.

In a similar direction Hobday et al. (2004) analyzed a sample of 25 leading Korean firms approaching the world frontier, from different industrial sectors and different sizes, and focused on their transition phase to leadership. The study sought to identify the key aspects and challenges involved during the transition process, and the strategies followed by the firms to deal with the higher R&D costs, uncertainties and threats of competing as leaders on the international scenario – the innovation dilemma.

[53] By unevenness in the knowledge base the author means an imbalance in the levels of knowledge both between technological fields and between organizational units.

To determine whether or not the firms had reached the transition phase, a framework for assessing the firm-level innovation capability was applied.[54] The findings of this study revealed interesting technological and non-technological aspects of this transition phase.[55] Among them the study showed that technological strategies vary according to the size of the firms. Large firms, even when already competing in the innovation frontier, pursue different strategies according to the stage of development of each of their products. Therefore, they may adopt a mix of leadership, followership and latecomer technological strategy at the same time. In addition, the in-house R&D route is not the only option, and technological partnerships are also among the strategies used to develop the capabilities needed to go through this transition stage. On the other hand, small and medium size firms generally deliberately pursue a niche strategy that does not involve reaching leadership positions.

On the non-technological side the study points out that the transition phase implies the need to develop stronger marketing capabilities, a new strategic mindset and new organizational structures. In a similar way to Dutrénit's conclusion, the authors point out the need for further and deeper research. If the mix of industries and firm's size analyzed provided important contrasting aspects of the transition phase on the one hand, it prevented the exploration of some key points in more depth on the other.

Other aspects of innovative capabilities are emphasized in some studies. With the objective of providing an overview of possible activities to be officially supported in order to strengthen the development of productive capacities and technological learning in Least Development Countries, Bell (2007) proposes a simple framework that distinguishes two types of capability: a) operating capabilities – those capabilities involved in the use and operation of given forms of technology; and, b) innovative capabilities – those capabilities to create new knowledge and to transform it into new specifications and production systems. For the purpose of the paper, and due to the characteristics of the least developed countries, the author directs focus to the second capability. More specifically, he subdivides innovative capabilities into two types: b1)

[54] The framework for assessing technological capability developed by Bessant et al. (2001) measures the degree of awareness of firms on the need to change and on what and how to change. This framework is discussed in Sub-section 2.3.5.

[55] The authors have pointed out that the results are indicative rather than conclusive due to the small size of the sample.

R&D capabilities – those for creating new knowledge; and, b2) design and engineering capabilities – those for transforming knowledge. The purpose of this distinction is to throw light on the importance and features of design and engineering, the kind of innovative capability that plays a central role in innovation but is frequently neglected. This issue is also highlighted in other previous works (e.g. Dahlman et al., 1987; Lall, 1992; Bell and Pavitt, 1995).[56] Therefore, by stressing the importance of design and engineering capabilities, Bell places it at an intermediate level between the operating and R&D capabilities. Rather than emphasize its importance as a link between the two types of capability, however, he recognizes this type of capability as a basis for the development of R&D capabilities. The simple framework proposed by the author does not contemplate any kind of stage or movement through degrees of complexity nor functional distinctions for the analysis of the development of capabilities.[57] At the end, what Bell implies with this emphasis is that innovative capability is more than simply R&D capability and more attention should be directed to it. The general industrial and infrastructure context approached in that paper favours the emphasis on design and engineering capabilities argument. Yet, in other specific contexts, such as case studies on industries in the pharmaceutical sector, where the knowledge base is basically originated from biomedical, biological and chemical sciences, design and engineering may have a different importance or a different role from that approached by the author.

One singular model for analyzing the development of catching-up firms was developed and stressed by Forbes and Wield (2002, 2008). The authors argue that firms develop indigenous technological capability and catch-up by innovating and continuously growing value-added. A learning hierarchy of process to product innovation is then identified in firms of some newly industrializing countries (NIC). It consists of a progressive move throughout several stages represented by learning to produce, learning to produce efficiently, learning to improve production, learning to improve products and learning to develop new products. The model consists of mapping the moving up of the firms within a process-product/non-proprietary-proprietary grid.[58] To move to the

[56] Bell argues that part of the underemphasis of the importance of design and engineering as generating innovation comes from the narrow concepts and boundaries for the research and development activities adopted by the OECD Frascati Manual. A thorough discussion about this problem is carried out by the author in Annex 2 of his paper.

[57] They are introduced when needed by the qualitative analysis throughout the paper.

[58] The process-product-proprietary grid is presented in Forbes and Wield (2002:87 - Figure 5.1; 2008:74 - Figure 1).

proprietary quadrants the firms need to develop distinctive capabilities in either or both process and product innovation. The position of the firms is defined by the sum total of their assets and capabilities. The trajectory within the quadrants is dependent upon their strategies, choices, culture and policy environment.

As outlined above, the development of technological capabilities in latecomer catching-up industries/firms has been approached in different ways, and new areas have been identified and explored within the contemporaneous literature on this issue. One common belief in most of the studies is that the development of technological capabilities is significantly constrained by the conditions present in the technological, organizational, local and national contexts of the firms, and the findings of each firm, industry, sector or country may vary considerably.

This raises some concerns. First, it suggests attention when trying to draw lessons from the experience of other countries (Hobday, 2003), and opens space for further research. Second, the use of the above approaches and frameworks should be carefully considered. As shown they are frequently adapted to the specific circumstances of the studies, even in studies within the same technological sector. For instance, as indicated by Malerba and Orsenigo (2002), the factors and dynamics of the evolution of both computer and pharmaceutical industries are radically different, even though they belong to the so-called science-based sector. In this particular sense, no specific work analyzing the technological capabilities development of the pharmaceutical/vaccine industry in a latecomer context was identified during the literature review. This makes the use of a ready-made framework for such a context more difficult.

However difficult it is to find a ready-made approach suitable for every specific purpose, it is helpful to identify some common characteristics/elements of the process of technological capabilities development in these studies, either in DCL or in SML, or in both. Within the literature these characteristics/elements are frequently acknowledged as decisive and closely linked to the incentives and/or constraints of the process. Careful attention should be given to these when approaching the development of technological capabilities whatever the approach used. Some of them were then selected from the literature and are being named here as key characteristics/elements. They are presented

below arranged in two groups: the sources of technological knowledge, and the other influencing elements.

In the first group – sources of technological knowledge – five key characteristics/elements were identified:

- The first is discussed in most of the literature and refers to ***the acquisition of foreign technology***, the common way latecomer firms usually start their business and complement the development of their local capabilities, as highlighted by several authors (e.g. Dahlman et al., 1987; Bell and Pavitt, 1993; Hobday, 1995; Kim, 1997; Forbes and Wield, 2002).[59,60]
- The second relates to the role of ***R&D as the main source of new knowledge***, especially in science-based sectors. ***However it is not the only one***, suggesting the need to investigate other forms of knowledge creation inside firms (e.g. Cohen and Levinthal, 1989, 1990; Bell and Pavitt, 1993, 1995; Forbes and Wield, 2004; Hobday et al., 2004; Bell, 2007).
- A firm's ability to identify and establish ***internal and external technological linkages*** as increasingly important new sources of knowledge, and a significant part of the process of technological accumulation, is the third key characteristic raised by many authors (e.g. Dahlman and Fonseca, 1987; Lundvall, 1988; Cohen and Levinthal, 1990; Freeman, 1991; Bell and Pavitt, 1993; Hobday, 1995; Hobday et al., 2004; Kim, 1997; Ernst et al., 1998b).[61]
- The fourth key characteristic concerns the importance of the existence of ***prior knowledge***, or accumulated competence, as a prerequisite to enhance the capability to assimilate and exploit outside sources of knowledge and to develop new knowledge, as stated in several works (e.g. Cohen and Levinthal, 1989, 1990; Pavitt, 1991; Bell and Pavitt, 1993; Kim, 1997).[62]

[59] The citations for each key characteristic are not exhaustive. They mostly reflect the works where the issue is more clearly and emphatically addressed.
[60] As noted by some authors, although critical for latecomer countries, the acquisition of imported technology is also a strategy adopted by firms in developed countries (Lall, 1992; Bell and Pavitt, 1993, 1995; Hobday et al., 2004).
[61] The increasing complexity and specialization of the technological knowledge impels firms to search for different types of collaboration to develop the technological capabilities they need to innovate. This also includes interactions with users.
[62] The importance of prior knowledge is determined by the complexity of technology and the specific, cumulative and partly tacit nature of the technological learning (Pavitt, 1987; Bell and Pavitt, 1993).

- Technological accumulation is a learning process and the main elements of this process are regarded to be inside business firms. As technological learning is only partly tacit and technology has become increasingly more complex, the fifth key characteristic implies that firms should be aware of the need for initiatives and explicit investments in ***learning*** to develop technological capabilities, especially innovative ones (Bell, 1984; Bell et al., 1984; Bell and Pavitt, 1993; Hobday et al., 2004).

In the second group – other influencing elements – three further characteristics/elements were identified. One is the role of the ***markets*** – domestic and export – in promoting competition and inducing innovation, as stressed by Lall (1992), Hobday (1995), Ernst et al. (1998b), Mytelka et al. (1998), Kim (1998) and Forbes and Wield (2002, 2008), among others. The second key characteristic of this group is found in both bodies of literature and refers to the significance of the ***organizational dimension of technological capabilities***, but frequently neglected especially in DCL (Prahalad and Hamel, 1990; Bell and Pavitt, 1995; Dutrénit, 2000; Figueiredo, 2001; Tidd et al., 2001; Hobday et al., 2004). The last key characteristic selected is the importance of ***government and institutions*** in promoting national basic conditions such as general education, incentives, regulation, market creation, protection and stimulation and so on, as they directly affect the development of capabilities. This point is widely emphasized in several studies (e.g. Lall, 1984, 1992; Bell et al., 1984; Dahlman and Fonseca, 1987; Dahlman et al., 1987; Hobday, 1995; Kim, 1997, 1998; Mytelka et al., 1998; Figueiredo, 2001).

Identifying the above characteristics may constitute a starting point for the development of an alternative approach that is more suitable for a specific context. However, some implications of doing this should be considered. Although emphasized in a great range of works these characteristics/elements cannot be considered exhaustive as there is always a risk of excluding potential important elements for a specific situation. Moreover, notwithstanding each of them can be considered of great importance in isolation, it is clear that their importance increases and really matters as they are seen as integrated parts of a system. In a broader perspective, as the business corporations are regarded to operate, these elements have strong complementarities and interactions, as

noted by Fargerberg (2005) and Bell (2007), and stressed in Sub-sections 2.2.3 and 2.3.2 respectively.

2.3.5 Assessing Technological Capabilities

The approaches and frameworks described in the two previous sub-sections can be viewed as useful and classical ways of analyzing the development of technological capabilities. However, literature has presented recent attempts to develop models to directly measure and assess technological capabilities in both national and firm levels. Ultimately these models seek to appraise the performance of countries and firms as a basis for qualitative analysis on how these capabilities develop, and on how they are influenced by internal and external elements. The spread of these new models reflects today's existing relative consensus shared by some disciplines such as economics, social sciences and management on the nature of technology (Archibugi and Coco, 2005).[63]

At the national level the models have been applied to contrast differences among countries and, not surprisingly, countries have been increasingly ranked according to their performance in science and technology activities (*ibid.* p.176).[64] At this level quantitative indicators are mostly used, including the two most common indicators used for measuring innovation: R&D intensity and patents. As an illustrative example, two influential works are mentioned here. Lall (1992) applies his framework to measure national technological capabilities of eight countries through a set of data in two main categories: education, and science and technology.[65] Patel and Pavitt (1984) do not present any specific framework, but use an elaborated set of indicators based on patent data across many different sectors of OECD countries as a basis to conclude that technological development is uneven even among developed countries; this is different from what was supposed at that time.[66] Although the importance of measuring national technological capabilities for policy and management is argued by many, Archibugi and Coco (2005) note that they should be interpreted with caution as they can obscure some

[63] The authors refer to national technological capabilities but this notion can be perfectly applied to the firm context.
[64] On occasion, similarities are also identified and highlighted, as the work of Lall (1992) shows.
[65] This work concentrates on latecomer countries. The sample contemplates South Korea, Taiwan, Hong Kong, Singapore, India, Brazil and Mexico.
[66] Indicators based on R&D and on qualification of the workforce are also used in this study.

aspects of the economic and social development, such as, for example, health and well being.

At the firm level, models for the assessment of technological capabilities are less diffused. They are used for management purposes as well as by policy-makers and researchers and data should be gathered directly from the firms. One common characteristic in some models is the use of benchmarks and its importance is stressed by Tidd et al. (2001:375). One of the first methodologies for assessing technological capabilities was developed by Panda and Ramanathan (1997). The model is intended to provide information for strategic planning decisions. The authors identify three main categories of technological capabilities to be addressed – strategic, tactical and supplementary – each of them with some sub-categories. The framework still contemplates a range of steering capabilities, which are not technological. The methodology is flexible and the technological activities to be assessed are defined after the identification of the value added stages performed by the firm. The application of the model will determine the technological capabilities gap between the firm assessed and a benchmarking firm. The model was then applied by the authors in a case study comparing the capabilities of two companies in the electric sector.[67] Even though the methodology is complex and long it seems to be easily adaptable to other sectors. The problem with this model is the huge amount of data to be gathered from the firms and therefore some analysis may be precluded.[68]

One more simple framework was developed by Bessant et al. (2001). The "Audit Tool" is based on a model where firms are categorized into four types – A, B, C and D – representing progressive stages of technological competency and maturity.[69] Two dimensions determine the location of the firms within this framework, where the awareness of the need to change and the awareness of what and how to change are assessed. Underpinned by SML and DCL, nine components of technological capabilities are then identified and generate a series of questions that enables the

[67] The companies assessed were the Electricity Generating Authority of Thailand and the Electricité de France. The latter was used as the benchmark firm.
[68] Problems with data gathering were reported by the authors for these case studies (see pg. 386 and tables).
[69] The four types are: Unaware/Passive (Type A), Reactive (Type B), Strategic (Type C) and Creative (Type D). For a graphic representation of this classification see Bessant et al. (2001:2).

assessment of the technological capabilities of the firm (Rush et al., 2007).[70] The average score in each of the components can be compared to the total possible score that represents the best practice. The authors also developed three different tools to enable the assessment process.[71]

Although the purpose of this model is broader it seems very useful as a support tool for studies focusing on transition stages. One good example can be found in Hobday et al. (2004). In this work the authors used the above tool to identify firms approaching the technological frontier in Korea in order to analyze the transition phase to leadership. The sample of firms was mainly composed of those who fell into Type C – Strategic category.[72] The use of this model in isolation for policy purposes, however, remains unclear.

2.4 Older Concepts, New Applications – Gerschenkron and the Backwardness Approach

In this section an alternative approach is presented and reviewed in an attempt to open space for different perspectives on the analysis of the technological development of industry/firms in the context of latecomer countries.

The economic historian Alexander Gerschenkron is the author of a singular theory about economic and industrial development in the early 1960s, concerned with the development of Europe during the industrial revolution. His ideas have matured remarkably and have influenced many scholars in recent years (Fishlow, 2003). Gerschenkron's theory departs from his half-disagreement with the Marxian generalization about the history of industrialized countries as a determinant to the future of more backward ones. [73] In Gerschenkron's own words:

[70] The nine components of technological capabilities identified are: awareness; search; building core competence; technology strategy; assessing and selecting; acquiring technology; implementing; learning, and; linking to external sources. They are stressed in Rush et al. (2007:227-228).
[71] A "simple survey tool" was designed for a quicker assessment and may be conducted by mail or e-mail. An "interview tool" is a more detailed assessment and requires access to key personnel of the firms. A "case study" is a very detailed assessment and requires multiple interviews with managers across the organization. For details see Bessant et al. (2001:9).
[72] For methodological reasons the authors also included in the sample some firms that fell in Types B and D.
[73] Marx's generalization referred to by Gerschenkron came from Marx's famous work "Das Kapital".

> For the half-truth it contains is likely to conceal the existence of the other half – that is to say, in several very important respects the development of a backward country may, by the very virtue of its backwardness, tend to differ fundamentally from that of an advanced country (Gerschenkron, 1962:7).

Although accepting that historical events change the course of subsequent events, and that industrial development cannot be understood if considered in isolation, the emphasis of his work is therefore in the deviations from earlier industrialization. The differences to which Gerschenkron refer are related to both the speed of development and the productive and organizational structures of industries. They were developed in the more backward countries by state intervention, application of institutional instruments, ideology and other local and external circumstances, to remove existing obstacles and substitute "missing prerequisites" of earlier industrialization.[74] Therefore, his model assumes the idea that the patterns of development of backward countries embedded imitation in combination with indigenous elements. This is closely connected to his other important argument, which rejects the generalization of Rostow, to whom there is a necessary existence of preconditions or prerequisites for industrial growth.[75] The concept of "Substitution for Missing Prerequisites" suggests, on the contrary, that the development of more backward countries presented significant innovative initiatives, relying on the "substitution" rather than on the "dependence" of prerequisites. This idea is clearly explicit in his statement below:

> … the very concept of substitution is premised upon creative innovating activity, that is to say, upon something that is inherently unpredictable with the help of our normal apparatus of research (*ibid.* p.359-360).

What is interesting to notice is that, whilst contemporaneous literature on innovation and technological accumulation puts more emphasis on the key characteristics for the success of developed countries that have enabled the technological development of latecomer economies and industries, Gerschenkron's approach makes evident the differences or deviations. According to Hobday (2008), in a broader sense Gerschenkron's model rejects the "follow the leader" dominant thinking in the last

[74] The idea of "substitution for missing prerequisites" can be represented for the government and banks, in the lack of capital from entrepreneurs to invest in the industry, or the import of skilled people, to substitute illiteracy or low standards of education, among others.
[75] The work of Rostow may be found in Rostow, W.W. (1960) *The Stages of Economic Growth: A Non-Communist Manifesto*. Cambridge, Cambridge University Press.

decades since the "Washington Consensus", and suggests the search for new innovative paths as a strategy more backward countries should adopt in order to develop.

On the other hand, one should argue that his model is not proper for microanalyses on technological development in the 21st Century. In fact Gerschenkron focuses on national contexts and events that took place in a remarkably different era, especially in contrast to the current particular characteristics of economic and technological development. Furthermore, most of his arguments were built on statistical evidence. Some authors argue that the application of his approach requires a quantitative emphasis (e.g. Fishlow, 2003).

Despite these apparent hindrances, some of Gerschenkron's arguments are rich and seem to be very present in the current development context of economies and industries. As an example, recent works have approached the development of firms and industries drawing on the theory of Gerschenkron. They emphasize new directions/paths as alternative strategies adopted by some firms/industries to get around their disadvantages as latecomers, overcome barriers and take advantage of opportunities to develop and catch-up. In line with Gerschenkron's ideas, these works go beyond the common linear approach of the catching-up approach, and assume that these firm/industries embody at least some innovative characteristics in their directions/paths in order to deal with unfavourable circumstances of their environment and develop.

One successful attempt to interpret the electronic industrialization in East and South East Asian by using the Gerschenkron approach was carried out by Hobday (2003). In this work the author observed that the development of the Asian newly industrializing economies has been characterized by significant deviations from experiences of earlier industrialization, and encompasses a mix of strategic innovation and careful imitation.[76] These findings suggest a pattern where the stages of latecomers' industries development are distinctive due to their own characteristics and governed by the substitution for missing prerequisites. As a consequence Hobday suggests that catch-up is unlikely to happen from imitation alone, and that there is no ready-made model of development to

[76] For strategic innovation the author refers to a broader concept of innovation including the introduction and implementation of new ideas, new institutions, new governmental policies and experimental business strategies (ibid. p.311 - note1).

be automatically transferred to other developing countries (*ibid.* p.310). Figueiredo analyzed the nature of catching-up of 13 firms from the forestry, pulp and paper industries in Brazil, and found a kind of path-creating capability accumulation that these firms followed across discontinuities in the policy regimes to catch-up and even overtake world leaders.

Other works are equally relevant in approaching the development of firms/industries under this Gerschenkronian perspective, among them Perez and Soete (1988), Lee and Lim (2001), Forbes and Wield (2002, 2008) and Mathews (2006). These works show that the notion of substitution for missing prerequisites may be adapted for different contexts and constitutes a useful alternative and a complementary device to help the interpretation of the development of technological capabilities in latecomer industries.

2.5 Summary

This chapter has reviewed the bodies of literature on innovation and technological capabilities that can underpin the construction of the frameworks for the analysis of the arguments and assumptions raised in this research.

Within the literature on innovation section this review has presented some of the key features of the process of innovation that became the starting point for any research in this field. National Systems of Innovation, one of the most extensively used frameworks to investigate the process of innovation in the last two decades, was also presented and discussed. As shown, this framework puts the emphasis on the analysis of the determinants of the innovation process. Finally this section has briefly discussed the use of quantitative indicators as an alternative method to analyze innovation across countries and industries.

Given its extent and importance within the literature on innovation, the technological capability framework was presented and discussed in a separate section. It has also been largely and successfully used in the last three decades as a way of understanding how innovation has been generated, especially in latecomer contexts. The review in this section has shown at least two main streams in the literature on this approach – SML and DCL – and that there are a great variety of types, levels, definitions and frameworks developed and adapted for the analysis of different contexts.

The focus of this review was directed at the literature on micro-analysis. However it also highlighted the importance of the interaction of capabilities with other elements in the meso and macro levels. As discussed, the emphasis of this approach is on the learning processes and on the dynamics of building up the capabilities needed to develop. It was emphasized that the accumulation of technological capabilities in industries of latecomer catching-up countries follows a well-known pattern, usually beginning from simple production capabilities and progressively moving to more complex ones. At least eight common key characteristics linked to the process of development of technological capabilities were also identified and selected within the literature. Furthermore, the literature has also shown that the transition phase to the development of advanced/competitive innovative capabilities is a critical one inside firms. This is a recent and still not fully explored area. The section has also presented and discussed more recent attempts to develop and use models for assessing technological capabilities.

The subsequent section presented and discussed Gerschenkron's theory and the notion of substitution for missing prerequisites as an alternative approach that might be adapted and used as a complementary device for the analysis of technological capabilities development in latecomer industries. Empirical works carried out under the Gerschenkronian perspective suggests that patterns of technological development are distinctive and shaped by the specific characteristics of each industry/country and the specificities of their environment. As shown, no ready-made model of development can be automatically transferred from the experience of more developed countries, and missing prerequisites should eventually be substituted as a conditional path for the development of today's developing countries.

All in all, some final remarks can be drawn from the literature reviewed. The process of innovation is quite complex and its analysis requires the domain of some key concepts and the awareness of its key features. On the one hand, literature has provided a great number of useful frameworks, approaches and indicators for analyzing, interpreting and assessing this important phenomenon of the development of firms, industries and nations. On the other, it has shown that these approaches and indicators should be applied with caution in order not to lead to misleading interpretations and conclusions, given the great diversity in the technological, industrial, social and economic contexts

of the firms. Therefore, although a rich variety and diversity of works have been carried out on this issue, there are specific contexts, such as the vaccine sector, and other areas, such as the innovation transition approach, still not fully explored and therefore potential subjects for new research. These gaps are some of the aspects underpinning the development of the conceptual and analytical frameworks in the following chapter.

Chapter 3 – Motivations, Research Questions, Propositions and Frameworks

3.1 Introduction

This chapter has multiple theoretical purposes. It presents the research problem, arguments and objectives of this research, and it also sets forth the research questions and propositions. It describes the building of the conceptual and analytical frameworks that link the theory to the phenomenon to be researched in order to identify its elements and relationships. These frameworks also orient and support the choices about research design and operational strategies for the investigation of the problem, and the search for the answers to the research questions.

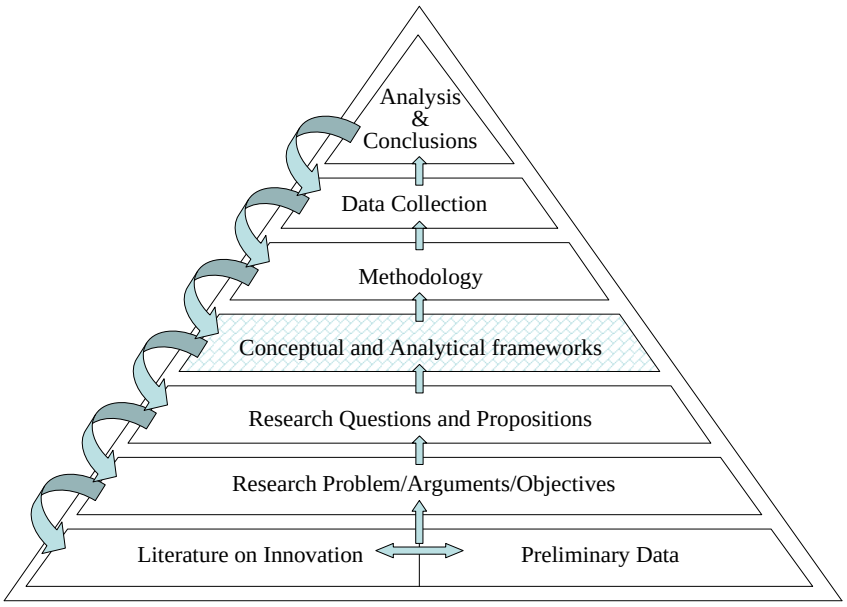
As stated in Chapter 1, literature on innovation and technological capabilities, and preliminary data of the vaccine industry, underpinned both the identification of the research problem and the formulation of the research questions. It is argued that specific characteristics both inside and outside of the context of the Brazilian vaccine industry (BVI) may be determining a particular pattern of technological accumulation within this industry, and that interpreting this pattern of development may be useful in understanding how and if the BVI has overcome its disadvantages to develop.

The chapter is organized as follows: Section 3.2 briefly describes some methodological aspects of the process of building the frameworks, for academic clarification only. In Section 3.3 the research problem and objectives, and the research questions and propositions are restated and explained. Section 3.4 introduces the broad concept of the research, the conceptual framework, describes the two conceptual issues embedded in the model, and sets out an explanation of its elements and relationships. Section 3.5 introduces the analytical framework and describes the analytical aspects of the elements of the model. Section 3.6 summarizes the whole chapter.

3.2 Introductory Notes on the Rationale of Building the Frameworks

Similar to other research in social sciences, the first ideas devised in this research benefited from a trade-off between literature on innovation and technological capabilities and preliminary data previously gathered about the vaccine industry. From

this trade-off specific assumptions about the development of this industry in Brazil arose, and, in turn, made possible a clearer identification of some research problems amongst the wide variety of those possible. The main arguments and objectives were then set up and the research questions and propositions posed. This construction, however, was not as linear as it appears since feedback during the process of the research gradually helped to improve its stages and tighten the conceptual and analytical structures. The simple sequence and feedback embedding the present research construction is represented in Figure 3.1.



Source: Own elaboration

Figure 3.1: Logical Sequence and Feedbacks of the Research Construction

Literature on research methods recognizes different forms of organizing these events. Huberman and Miles (2002), for example, support straighter and tighter initial designs arguing that key constructs emerging from the case may take a long time. Moreover they suggest that formulating research questions is a direct step from the conceptual framework and the beginning of its operationalization – a deductive model.

Other authors support more iterative models (e.g. Eisenhardt, 1989; Alford, 1998; Van de Ven, 2007).[77] In the Engaged Scholarship Research Model of Van de Ven (2007),

[77] Huberman and Miles also admit the use of less tight designs and the formulation of research questions preceding the development of conceptual frameworks depending on certain circumstances of the research, although they emphasize their preference for the opposite (*ibid.* p.17 and 23).

although a sequence of four research activities is suggested, they can be performed in any sequence. According to the author, this is "because they are highly interdependent and are seldom completed in one pass" (*ibid.* p.11).[78] Furthermore, in the model of Van de Ven the research questions often represent the end of the process of formulating the research problem, and the development of the conceptual model requires close familiarity to the problem domain. The rationale and sequence employed in the present research is closer to the latter, as we shall see in the next sections.

3.3 Research Problem and Research Questions

In this section the research problem, arguments and objectives of the research are restated (Sub-section 3.3.1), and the research questions and propositions are presented and explained (Sub-section 3.3.2).

3.3.1 Motivations, Research Problem, Arguments and Objectives

The previous chapter showed that the technological capability framework has been one used most by scholars to understand the process of innovation and development of firms, industries and nations, both in developed and in latecomer contexts. In the review of this body of knowledge it was emphasized that the development of technological capabilities in catching-up industries of latecomer countries follows a well-known pattern, usually beginning from simple operating capabilities and progressively moving to more complex innovative ones. Within a great diversity of concepts and empirical findings, some common key characteristics linked to the process of development of technological capabilities were identified. The previous chapter also highlighted recent works addressing the innovation transition issue, which showed that the transition phase to the development of advanced/competitive innovative capabilities is a critical one inside firms approaching the innovation frontier, but this is still a not fully explored area. Other works, inspired in an alternative approach that analyzes the technological development of latecomer economies from a different perspective of the linear catch-up approach, were also identified within the literature.

[78] The engaged scholarship diamond model of Van de Ven encompasses four activities: problem formulation, theory building, research design and problem solving. The engaged scholarship method proposed by the author is based on the participation of key stakeholders in the research process in order to produce more penetrating and insightful knowledge.

On the other hand, some special circumstances of the context of development of the BVI and of the vaccine sector, a sector barely approached in the literature, were brought to light by preliminary data. These special circumstances were identified as strongly influencing the sharp growth of this industry in the last decades. They were found at both the national and industry/firm level. They were also found in the general context of the vaccine sector, including the international context.

At the national level three initiatives of the Ministry of Health (MOH) draw attention. The first refers to the National Immunization Programme (PNI), created in 1973. This internationally acknowledged programme coordinates a large and rapidly increasing public market that has continuously introduced recently developed technologies in the immunization routine. The second relates to another programme created by the government: The Programme of National Self-sufficiency on Immunobiologicals (PASNI). This was created in 1985 after a national supply crisis, in order to support the modernization of the facilities of local public firms, allow import substitution and cope with vaccine shortages in the international scenario.[79] The third relates to the market protection granted by the government to these public firms to complement the support of the PASNI. This policy has remained steady across both the discontinuities in the industrial policy regimes in Brazil since then and the macro-instability of the country in the 1980s and 1990s.

At the industry/firm level attention is drawn to persistent and successfully implemented processes of foreign technology acquisition as the main strategy of this industry to quickly develop capabilities and address the public market needs. Attention is also drawn to the existence of public firms that have developed important technological capabilities, but do not present a clearly visible level of innovative capabilities developed to date.

In the general context of the vaccine sector it draws attention to its specificities: the high impact of vaccines on society and how susceptible this sector is to social pressures, the strong regulation, the high complexity of manufacturing and developing vaccines and, most dramatically, the significant advances in the knowledge frontier that are well

[79] In the case of serum the objective of PASNI was to cope with the non-existence of products manufactured abroad for the specific venoms of the Brazilian species.

protected by intellectual property rights (IPR) and dominated in the last decades by few oligopolistic firms.

The above issues seem to give ground to a singular opportunity to extend knowledge about the process of technological accumulation in catching-up firms/industries, particularly during the transition phase to the development of advanced/competitive capabilities. In addition, they motivate the following assumptions:

1) although embedded in the so called science-based sector, with a century-old tradition in vaccines and with the more recent development of significant technological capabilities, the recent impressive growth of the BVI relies, and has relied, predominantly on foreign technology acquisition rather than on indigenous R&D as a strategy to develop and catch-up;[80]
2) the BVI has been forced to adopt and maintain this strategy to fulfil the growing needs of the Brazilian public market. This is due to the complexities of the vaccine industry and the extent of major breakthroughs in the knowledge frontier currently dominated by few oligopolistic firms. In turn, the BVI might be neglecting the development of innovative capabilities; and,
3) this might be determining an endless technological transition phase in which the BVI has developed some important technological capabilities but has been unable, so far, to catch-up and reach the technological frontier.

Some points, therefore, remain unclear: a) whether or not the BVI has developed through a particular pattern of technological accumulation, the characteristics of the process and the importance of the specific circumstances of its context; b) the extent to which foreign technology acquisition has been effective as a source of technological knowledge to the development of local capabilities; c) the level of innovative capabilities developed so far and the main characteristics of the process during the transition phase; d) possible hindrances to the development of advanced/competitive innovative capabilities that could enable this industry to catch-up and compete globally at the leading edge; and, e) the existence of relationships between the pattern of

[80] The impressive growth of BVI stands for an increase in sales of more than 5 fold from 1996 to 2006. Moreover, it took place at the same time that almost all of the vaccine producers in Latin American countries have simply vanished (details and figures about these issues are presented in Chapter 6).

development/strategy of technology acquisition and the unfinished technological transition.

This research draws on the literature reviewed, on the above assumptions, and on the unclear issues. It argues that the specificities of the context of the Brazilian vaccine industry (BVI) may be determining a particular pattern of technological accumulation within this industry, and that interpreting this pattern of development may be useful in understanding how and if the BVI has overcome its disadvantages to develop.

The aim of this research is, therefore, to investigate these unclear circumstances of the development of the Brazilian vaccine industry in order to understand how technological capabilities have evolved over time within this industry, and how far the BVI has gone to date in the transition phase, how and why.

3.3.2 Research Questions and Propositions

Van de Ven (2007) states that the research questions are often the solution to the research problem in research, just to show the interactions between both. Research questions also help to focus on specific aspects of interest (Alford, 1998; Huberman and Miles, 2002). Yin (2003) goes further by emphasizing the importance of stating some propositions in order to direct attention to the relevant points that need to be examined and challenged within each research question. To investigate the research problem identified and address points raised that are unclear, the following research questions and propositions are being posed:

RQ1 How have technological capabilities in the Brazilian vaccine industry evolved over time?

> *P1* Technological capabilities have been developed in the BVI in a distinct pattern of that represented by the traditional catch-up mode identified in the literature on technological accumulation in latecomer firm/industries, influenced by specific circumstances of the context of this industry;
>
> *P2* The strategy of continuous foreign technology acquisition adopted by the BVI has not contributed effectively to the development of local capabilities that could help to narrow the gap to the technological frontier.

RQ2 How far has the Brazilian vaccine industry gone to date in the transition phase, how and why?

P3 The BVI has been unable to develop significant innovative capabilities so far within the transition phase;

P4 The speed of change in the scientific/technological frontier is the most important factor hindering the transition to competitive innovative capabilities;

P5 The unfinished transition is a by-product of the strategy of continuous foreign technology acquisition adopted by the BVI.

3.4 The Conceptual Framework

In this section the conceptual framework is presented and explained. The three conceptual issues underpinning the building of the conceptual framework are introduced in Sub-section 3.4.1. Sub-section 3.4.2 addresses the first of these concepts – technological capabilities development in catching-up industries, whilst the second concept – transition within innovative capabilities development, is addressed in Sub-section 3.4.3. The third conceptual issue – new directions/paths as an alternative strategy to develop – is addressed in Sub-section 3.4.4.

3.4.1 Building a Conceptual Framework as a Benchmark Model

The first two conceptual issues addressed in this research are technological capabilities development in catching-up industries of latecomer countries, and transition within innovative capabilities development. This research integrates these two conceptual dimensions looking to benefit from their complementarities. It then builds a simple framework to be used as a benchmark model, in order to unveil the main characteristics of the pattern of development of the BVI and address the third conceptual issue: new directions/paths as an alternative strategy of latecomers to develop.

As shown in Chapter 2, the common/linear pattern of developing technological capabilities in catching-up industries of latecomer countries is the reverse sequence – e.g. from production to investment to innovation; this is because existing technologies are acquired as the main source of initial technological knowledge, usually from

developed countries (Dahlman et al., 1987).[81] At this time, minimal innovative capabilities are required for the successful absorption of the foreign technology (Pavitt, 1987; Freeman and Soete, 1997). As time passes these industries gradually develop new capabilities for adapting existing and introducing new technologies, inverting the importance of the sources of knowledge. Intermediate and advanced levels of technological capabilities development are mainly based on increasing internal innovative capabilities and on exploiting other new sources of technological knowledge, internal and external, and are increasingly influenced by other internal and external elements, as noted by several authors (e.g. Lall, 1992; Hobday, 1995; Kim, 1997; Bell and Pavitt, 1993, 1995; Ernst et al., 1998a).

As also shown in Chapter 2, recent literature has approached the transition phase from intermediate and advanced levels to competitive levels of innovative capabilities, and has highlighted it as a critical phase in the catching-up process of firms and industries, though not fully explored so far (Dutrénit, 2000, 2007; Hobday et al., 2004). Although not explicit in this body of literature, this could suggest that the level of importance of the sources of knowledge for the development of technological capabilities of catching-up firms/industries changes more dramatically during this transition phase. Initial findings from these few existing studies has started to unveil some challenges, specificities and factors influencing the completion of this transition process in some industries, but there is still a large number of issues to be understood on this subject.

In Sub-section 3.3.1 it was suggested that the Brazilian vaccine industry (BVI) has possibly been developing through a distinct pattern of technological accumulation. This possible different pattern is supposedly the result of persistent high levels of technology acquisition and slow increasing levels of innovative capabilities. Both seem to be greatly conditioned by specificities of the context of this industry and especially constrained by major breakthroughs in the development of new vaccines in the knowledge frontier. In turn the transition phase to a competitive level of innovative capabilities seems to be endless as the technological frontier moves quicker than the ability of the BVI to build up this type of technological capability and catch-up.

[81] The nomenclature of the stages of this reverse sequence varies across the wide literature on this subject but the logic remains the same.

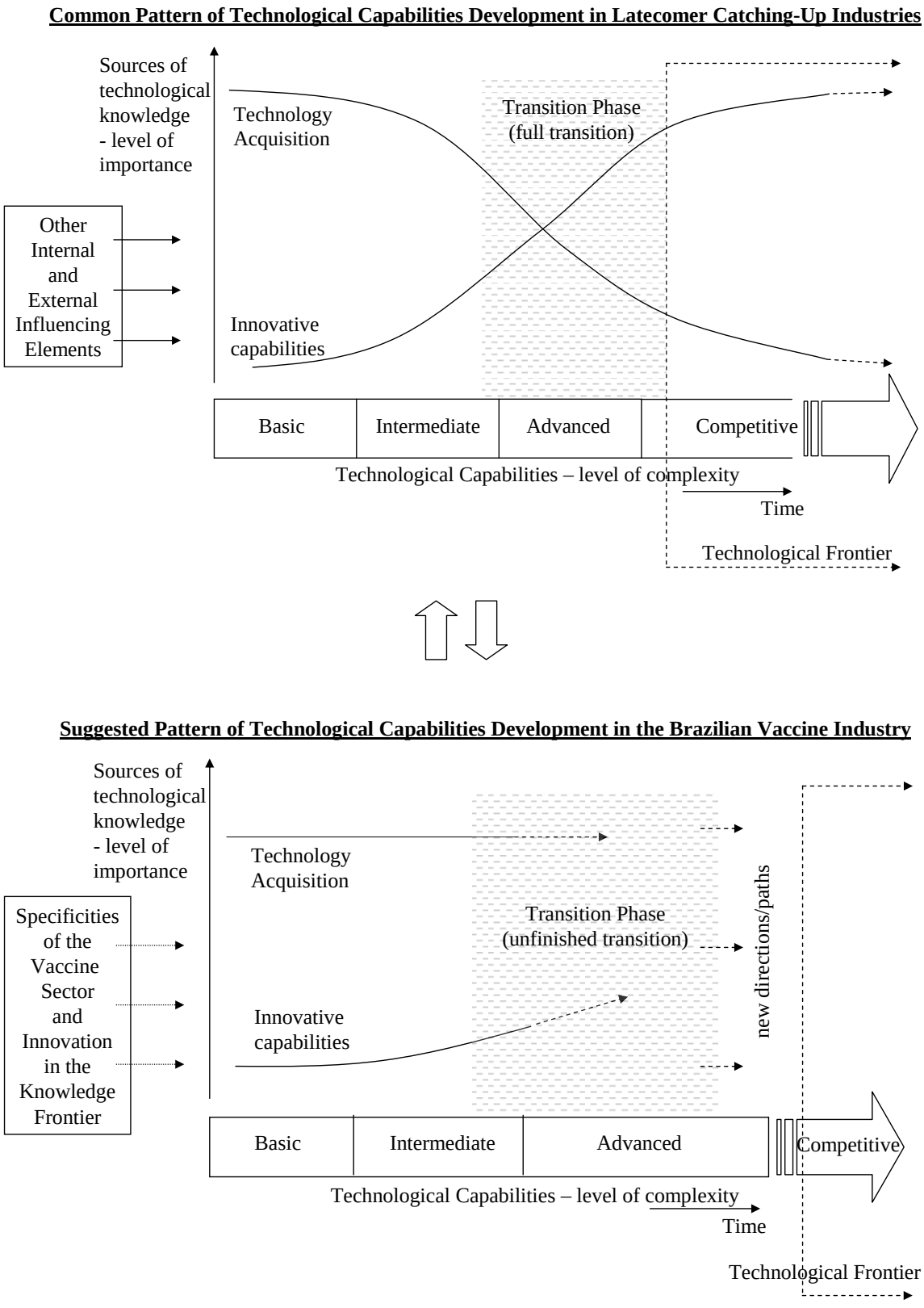
The simple framework draws on these two conceptual issues. It is expected to contribute to the understanding of the general and specific circumstances that have characterized, enabled and hindered the development of the BVI, and work as a benchmark tool in the search for similarities and differences that can characterize new directions/paths in the process of its development. It is represented in Figure 3.2 and is explained in more detail in Sub-sections 3.4.2 and 3.4.3. Complementarily, some key terms used in this research are defined as follows:

"Technological capability" is being employed in this thesis in a broad sense, as employed by Kim (1997:4) and others, as the ability to make effective use of technological knowledge. This is in line with the most common and broad sense captured from the vast range of literature on this subject, and encompasses, at the micro level, the efforts, technical or managerial, of a firm/industry to absorb (acquire, assimilate and use), adapt and change existing technologies as well as generate new technologies.

"Technology acquisition" is used here with a specific sense, and refers to the acquisition of foreign "packaged" technologies – the vaccines. The term "packaged" has been employed by some authors (e.g. Mytelka, 1978; Dahlman and Fonseca, 1987; Kim, 1997) with the meaning of technology acquired with full specifications of the production process, frequently accompanied by training, technical assistance and components and parts.

"Innovative capabilities" refers to the ability to generate innovation inside the formal internal innovating units (e.g. R&D, Design and Engineering), as well as to the absorptive capacity in the way employed by Cohen and Levinthal (1990), with the exception of the acquisition of technology in the sense defined above.

The term "catch-up" is normally employed in this research with a general meaning, i.e. encompassing technological catch-up and market/economic catch-up, as employed in most works. The main concern of this research, however, is with technological catch-up, in the sense employed by Figueiredo (2009).



Source: Own elaboration, based on literature reviewed and on the assumptions raised in this research.

Figure 3.2: The Simple Framework

3.4.2 Pattern of Technological Capabilities Development in Catching-up Industries

The building of the conceptual framework draws on both developing country literature (DCL) and strategic management literature (SML). These two main streams in the literature on innovation and technological capabilities were reviewed in the previous chapter. Based on these streams, this research suggests that the common pattern of technological capabilities development in catching-up firms/industries of latecomer economies may be shaped and expressed by the level of importance of two sources of technological knowledge (acquisition of foreign technology and innovative capabilities) over time, and by the influence of other firms' internal and external elements, as represented in the upper part of Figure 3.2. This needs further elaboration as follows.

This research takes into consideration the fact that the development of technological capabilities is a process of learning inside firms, following the common view amongst many scholars (e.g. Bell, 1984; Bell et al., 1984; Lundvall, 1988; Bell and Pavitt, 1993, 1995; Hobday, 1995; Kim, 1997; Mytelka et al., 1998; Figueiredo, 2001). By definition learning is the action of acquiring knowledge of a subject or matter (OED, 1973:1191). The process of learning is linked to different sources of knowledge, either internal or external, and enhances the stock of knowledge and technological capabilities of firms, as noted by Malerba (1992:84). Technological learning inside firms may also change the path along which technological capabilities proceed over time (Figueiredo, 2001). Thus technological knowledge, and its sources, can be considered as some of the most important elements of firms' technological capabilities development. This is one of the premises of this conceptual framework.

The other dimension considered in the model is related to the catching-up strategy of latecomer firms. Located in places where local capabilities and technological infrastructure are not well developed, latecomer firms start their business through the acquisition of foreign mature technologies (Hobday, 1994; Kim, 1997). [82] , [83] Nevertheless, technology is specific and complex, and the successful absorption of these

[82] As noted by many authors (e.g. Dahlman and Fonseca, 1987; Dahlman et al., 1987; Hobday, 1994, 1995; Kim, 1997; Hobday et al., 2004) at this stage latecomer firms acquire mature technologies from developed countries. A mutual interest is observed in this process, as can be inferred by the life-cycle model of Abernathy and Utterback (see Utterback, 1994). In this model, products at this specific phase compete on the basis of cost rather than on product and process innovation. The technology is then transferred to catching-up countries in order to lower its costs and extend its life-cycle (Kim, 1997:86).

[83] Although this notion was applied by the authors to the Asian context, it applies perfectly to the Latin American context as well.

technologies implies an activity that is rarely costless for its adaptation to local conditions (Pavitt, 1987). This implies the need for the existence of in-house minimal innovative capabilities, as noted by Freeman and Soete (1997). Moreover, in the long run firms need to innovate to be successful (Nelson, 1991; Tidd et al., 2001), and they "cannot mature unless they accumulate the capabilities for technical change" (Bell et al., 1984:121).

Consequently, firms gradually develop more advanced innovative capabilities to adapt and improve existing technologies and to generate new technologies (Mytelka, 1978) over time. This is a long, incremental and painstaking process even for subsidiaries of TNC, according to some studies (Hobday, 1994, 1995).[84] It is also gradual because firms cannot develop all capabilities at the same time (Dahlman et al., 1987). With the development of more advanced capabilities the mode of technology transfer then changes, as firms may acquire technology without a transaction cost – e.g. through reverse engineering (Kim, 1997:103). At this stage, the development of more advanced innovative capabilities increasingly involve what Cohen and Levinthal (1990) define as "absorptive capacity". This refers to the ability to exploit outside sources of knowledge, often critical to the innovative process. At the end, firms will only achieve technological catch-up if they acquire the set of capabilities to improve and create technology (Freeman and Soete, 1997). The development of technological capabilities is also heavily influenced and shaped by other internal and external factors, as shown by several works (e.g. Nelson, 1991; Lall, 1992; Bell and Pavitt, 1995; Kim, 1997; Ernst et al., 1998b), and therefore this aspect is also being considered as relevant in the model.

To sum up, the "pattern of technological capabilities development in latecomer catching-up industries", as represented in the upper part of Figure 3.2, means a commonly observed pattern in which the development of technological capabilities in its basic or initial level of complexity depends heavily on the acquisition of technology (packaged technology), and little on in-house R&D and other sources of knowledge. More complex levels of technological capabilities are, in turn, characterized by the

[84] The works of the author reject the "leapfrogging argument" of technological accumulation in latecomer countries. According to the author this conclusion is strengthened by the fact that it was tested and proved not true in Singapore, a country that supposedly accumulated the most appropriate national conditions for leapfrogging to take place: small population, high educational rates, modern technological infrastructure, etc.

increasing development of in-house R&D and other innovative capabilities, and on more intensive knowledge from other internal and external sources. At the same time, the need for knowledge from packaged technology externally acquired gradually decreases up to the point that the level of importance of the sources of knowledge becomes inverted.

During the transition phase firms develop the kind of capabilities needed to catch-up and to try to compete with the market leaders.[85] High levels of innovative capabilities and knowledge from other sources, new kinds of capabilities, and lower levels of technology acquisition (packaged technology) characterize the highest level – the competitive stage. Moreover, as innovation does not take place in isolation, other elements present in the internal and external environment of the firms/industries, as well as some specificities of each industrial sector, influence this pattern with different intensities and implications across the whole process of technological accumulation; they are very integrated and interrelated.

The lower part of Figure 3.2 suggests a supposed distinct pattern of technological capabilities development in the BVI; this is based on persistent high levels of technology acquisition (packaged technology) and a lower rate of development of in-house R&D and of exploiting other sources of knowledge.[86] It is also suggested that major breakthroughs (radical and incremental innovation) in the knowledge frontier and the scientific, technological, social and economic specificities of the vaccine sector have been critical elements influencing the pattern of technological accumulation in this industry. A longer and unfinished technological transition stage may be related to this distinct pattern. Both parts of the figure embed the constituent elements of this model to serve as a benchmark tool in the search for differences and similarities in the path of development of the BVI.

The sources of technological knowledge, and the other firm's internal and external influencing elements, stand for the key characteristics of technological accumulation

[85] The characteristics of the transition stage are detailed in the next Sub-section.
[86] The existence of initial innovative capabilities, however, seems to be especially important in the vaccine industry.

previously selected from the literature.[87] Some of them were expanded, other were included as they may be of interest for the analysis of the pharmaceutical sector. The analysis of the pattern of technological accumulation will be concentrated on them. Table 3.1 lists these key characteristics. The analytical aspects of each are defined in Sub-section 3.5.2.

Table 3.1: Key Characteristics: the elements for the analysis of Technological Accumulation

Sources of Knowledge	Other Influencing Elements
. Technology Acquisition . Internal Sources of Knowledge . *In-house R&D* . *Design and Engineering* . *Clinical Trials* . Other Sources – Internal and External Linkages . *Operating Capabilities* . *Inter-firm Collaboration/Alliances* . *Consultancy/Hiring Skilled Specialists* . *Universities/Research Institutes* . *Prior Knowledge* . Learning by training – Initiatives and investments	. Organizational Capabilities . Markets . Government Policies, Institutions and Regulation . Innovation in the knowledge frontier . Scientific, technological, social and economic specificities

Source: Own elaboration based on literature review and prior expertise

It is important to highlight some additional considerations about this conceptual framework. Firstly, the common pattern suggested in the model does not ignore the fact that the rate of technological capabilities development may vary considerably across firms, industries, sectors and nations, and that the sequences of development are not as linear as they appear, as well advised by some authors (Bell and Pavitt, 1995; Hobday, 1995; Mytelka et al., 1998; Bessant et al., 2001). In effect, the "common pattern" part of the model seeks to capture the general sense of the catching-up strategy of a great range of latecomer firms, as supported by many empirical works especially in Asia and Latin America. It thus serves as a benchmark model to be contrasted with non-linear

[87] See Chapter 2, Sub-section 2.3.4 (pg. 34-35).

approaches of catching-up only, as described in Sub-section 3.4.4, and not as a description of actual reality.

Secondly, even though the importance of the learning process is highlighted, the model does not intend to support the analysis of the dynamics of the learning process inside firms, as carried out in some works (e.g. Nonaka and Takeuchi, 1995; Figueiredo, 2001).

Thirdly, the model focuses on the segment of vaccines inside the Brazilian vaccine industry. Other segments explored complimentarily by the firms of this industry, such as biopharmaceuticals, serum, blood products and diagnostic reagents, are out of the scope of the model. And finally, even though there are some references to "stages", and the development of technological capabilities is categorized in levels of complexity, this research is not proposing to analyze technological capabilities development in a strict perspective of stages or sequences.[88]

3.4.3 Transition within Innovative Capabilities Development

Differently from the "pattern of technological capabilities" area, the transition phase is still a grey area, as deliberately represented in a rough way in both parts of Figure 3.2. This also needs further elaboration. Generically, transition means "the passage from an earlier to a later stage of development or formation" (OED, 1973:2347), and therefore it can be inferred that it occurs along all the process of technological capabilities development. Notwithstanding, this research draws on the idea initially approached by Dutrénit (2000), and further stressed later by Hobday et al. (2004) and Dutrénit (2007), to define the boundaries and scope of analysis of this transition issue within the BVI. The essence of the transition process approached by both Dutrénit and Hobday et al. is similar, but as they approach the issue in a different way there are some slight differences in the boundaries, characteristics and constraints in both approaches. Rather than divergent, however, these differences are considered here as complementary and as a useful parameter for the analysis of the transition phase of BVI.

[88] The idea of rigid stages or sequences in technological accumulation may be misleading due to the diversity found in different firms and industries, as noted by Bell and Pavitt (1995:88).

The characteristics of the transition process raised by Dutrénit came about mainly from the empirical findings of two works.[89] According to her:

> Those firms (that are undertaking a transition process) have accumulated the minimum essential knowledge base, have developed R&D activities and have acquired advanced innovative TC in certain technical functions. They have different challenges and types of problems from those observed in firms that are still in the process of building-up basic and intermediate innovative TC. (Dutrénit, 2007:130 - sentence between parentheses added)

The embryonic strategic capabilities, as she named this phase, seems to be located somewhere between the upper intermediate capabilities level (when firms have built the minimum essential knowledge), and the lower strategic level (when firms have already built some of the capabilities which will distinguish them competitively). This minimum essential knowledge base is described as the one built by the firm to survive in the market, a long process that lasted from the early 1900s to 1970 in her first case study. It examined a kind of routine production capability, and basic to intermediate innovative technological capability (Dutrénit, 2000:107). The development of embryonic strategic capabilities – the transition process – explained the undertaking of more complex activities based on the increasing importance of internal and external new sources of knowledge, particularly R&D, and on some knowledge management capabilities. However, by the time of the case study conducted by the author, the transition process had already lasted around 25 years and had not been completed by the firm.

In a different fashion Hobday et al. (2004) used a predefined set of capabilities' characteristics to select firms within a technological capability level they elected as of interest for the purpose of analyzing transition. They applied an audit tool in a sample of 25 Korean firms looking for those that had achieved the Type C – "strategic" – capability level defined in this audit tool.[90] The empirical findings confirmed that 19 firms were at the strategic level described in the audit tool, and that they were not yet contributing to move the world technology frontier. It also confirmed that these 19 firms

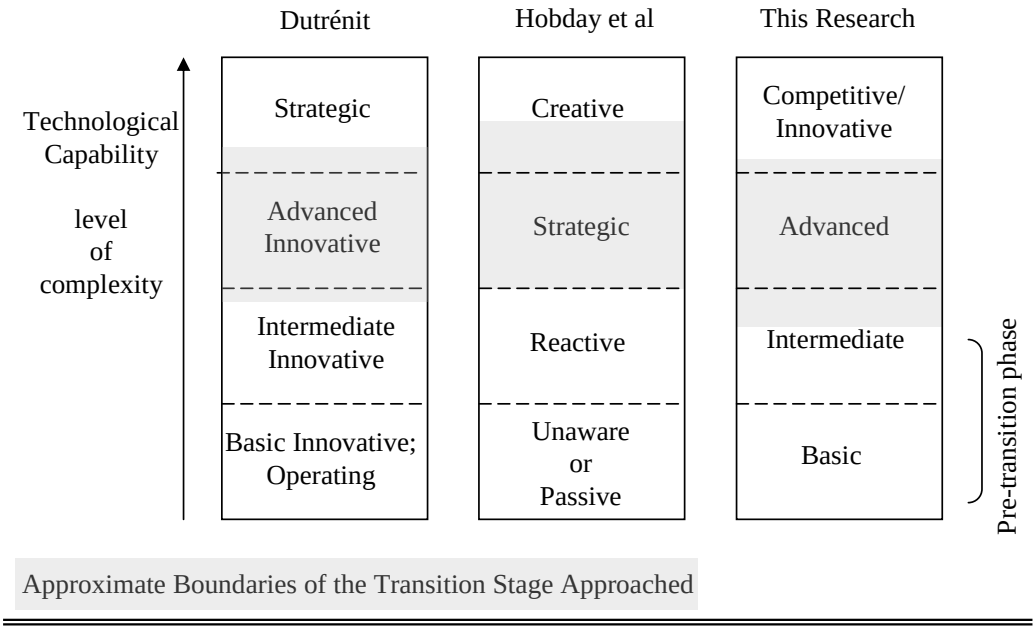
[89] Dutrénit (2000) is a case study of the Glass Container Division of the Mexican Vitro Group. Later on the concept of transition was applied in case studies of two large Mexican firms and a subsidiary of multinational company located in Mexico (Dutrénit, 2007).

[90] The audit tool developed by Bessant et al. (2001) was stressed to some extent in Sub-section 2.3.5 (pg. 37-38) of the previous chapter.

were not uniformly distributed within the strategic category but rather they had different levels of strategic capabilities.[91]

In Hobday et al.'s study, therefore, it is implicit that firms that succeed in overcoming the weaknesses of their capabilities within this level are approaching the innovation frontier, and are supposedly in a transition stage to reach the Type D – "creative" level, the highest level in the scale of the audit tool. Firms categorized as creative are those able to move the international technological frontier forward. Furthermore, firms failing to overcome their weaknesses tend to lose capabilities and become Type B – "reactive". The different terminologies across the stages of technological capabilities adopted in the works of Dutrénit, Hobday et al. and in this research, and the correspondence amongst them, are represented in Table 3.2. The description of the boundaries, characteristics and constraints to the transition process approached in the works of these authors are summarized in Table 3.3.

Table 3.2: Technological Capabilities Levels – different terminologies adopted and transition boundaries



Source: Own elaboration

Based on the contribution of Dutrénit and Hobday et al. discussed above and on the preliminary data gathered, this research is precariously assuming that the BVI is

[91] The firms were spread around the lower, middle and upper band of the strategic level.

currently in a transition process within the development of innovative capabilities. The real constraints and drivers to the development of this industry's advanced innovative capabilities are unknown, as are the boundaries and level of the transition phase. These are the issues raised by research question 2, propositions 3 and 4. This idea is explained in more detail within the Analytical Framework in the next Section.

Table 3.3: Firms in Technological Capabilities Transition Process – Boundaries, Characteristics and Constraints

Dutrénit	Hobday et al.
Boundaries	
. from the lower advanced innovative capabilities, when minimum essential knowledge base was already built, to the building of some strategic capabilities (which distinguish the firm competitively);	. firms that have overcome the reactive approach to technology strategy and are building strategic capabilities to reach the creative capability level, and that are able to compete in/contribute to the world technological frontier;
Characteristics (not exhaustive)	
. minimum essential knowledge base already built (capabilities to achieve more efficient levels of production, improve the quality, upgrade equipments); . accumulation of routine production capabilities; . intermediate innovative technological capabilities in some technical functions and advanced in others; . increasing importance of internal sources of knowledge (especially R&D – applied research, product and process development and minor improvement activities); . integration of knowledge located in different organizational units; . learning from competitors and external sources of knowledge; . acquisition of technology (engineering and know-how to manufacture equipment); . development of innovative capabilities to adapt and keep in operation the technology acquired abroad; . capability to develop linkages with suppliers;	. well-developed awareness of the need for technological change; . highly capable in implementing new projects and taking a strategic approach to the process of continuous innovation; . clear idea of priorities and of resources needed; . strong internal capabilities in both technical and managerial areas; . can implement changes with skill and speed; . consciously develop a strategic framework in terms of search, acquisition, implementation and improvement of technology; . overall strong in-house capabilities, including R&D; . strategic thinking about technology in the medium and long term; . tends to lack the capabilities to re-define or create new market opportunities through new types of technology; . tends to compete within the boundaries of an existing industry, despite having exploited technology efficiently; . sometimes limited in knowing where and how to acquire new technologies beyond the boundaries of their traditional business; . face difficulties to challenging existing business models;

Table 3.3 (cont.): Firms in Technological Capabilities Transition Process – Boundaries, Characteristics and Constraints

Dutrénit	Hobday et al.
Characteristics (cont.)	
. strengthening of capabilities in knowledge management (sharing of internal knowledge and use of external sources of knowledge), process engineering, and investment project management;	. in their own fields they may be at the international technology frontier; . more extensive partnerships with foreign firms; . may benefit from new networks of technology providers and from links with universities; . tends to follow a mixed corporate strategy towards technology; . small and medium size firms tend to seek niche markets and not to seek international leadership positions;
Constraints to complete transition	
. difficulties in the knowledge management processes, especially: . conversion of individual into organizational learning; . coordination of the leaning strategies; . knowledge integration and knowledge creation; . unevenness of the knowledge bases – embryonic strategic capabilities in some areas and lack of knowledge in others; . embryonic strategic capabilities that did not become strategic capabilities: . investment project management; . job changes; . electronic control systems and glass composition; . coupling equipment technology; . imbalance between science and technology capabilities in the national context.	. external shocks (economic crisis) can arrest the pace of change as firms move for shorter-term R&D; . government policies and competitors' strategies, especially in changing circumstances; . own history, cultures and strategies and lack of a strategic mindset; . dependence of foreign capital goods technology and suppliers; . international brand recognition; . stronger market capabilities; . control of foreign distribution channels; . need for a strategic mindset, quite different from that of a firm in catch-up mode; . need for more organizational flexibility (e.g. flatter organizational structures and fast moving project-based organizational structures);

Source: Own elaboration based on Dutrénit (2000, 2007), Bessant et al. (2001); Hobday et al. (2004) and Rush et al. (2007).

3.4.4 New Directions/Paths

A third conceptual issue is considered in this research. It refers to the concept first stressed by Gerschenkron (1962), which suggests that the development of more backward countries present differences from the development of advanced countries, and encompasses innovative initiatives to overcome their disadvantages and barriers to develop. More recent works (e.g. Forbes and Wield, 2002, 2008; Hobday, 2003; Figueiredo, 2009), as discussed in Section 2.4 of the previous chapter (pg. 40-41), have used this concept of new directions/paths inspired in the work of Gerschenkron to interpret the development of firms/industries in developing countries.

This research uses this concept to interpret the pattern of technological accumulation of the BVI. It uses the simple framework developed (Figure 3.2), based on linear patterns of catch-up in latecomer firm/industries, as a benchmark model to look for possible differences and similarities in the pattern of the BVI. It attempts to identify a particular pattern of development and new directions undertaken by this industry in order to develop its technological capabilities and reach the technological frontier.

3.5 The Analytical Framework and the Elements of the Model

This research is proposing the use of a benchmark model integrating two conceptual issues – technological capabilities development in catching-up industries of latecomer countries, and transition within innovative capabilities development – to interpret the development of the BVI and look for differences and similarities in its pattern of development. This model is represented in Figure 3.2 and further stressed in Sub-sections 3.4.2 and 3.4.3 above. The objectives of this Section are to present the analytical framework (Sub-section 3.5.1), and to describe the specific aspects of the elements of this model (Sub-section 3.5.2) in order to support the choice of the research design, the data to be gathered and the analysis to be carried out.[92]

3.5.1 The Analytical Framework

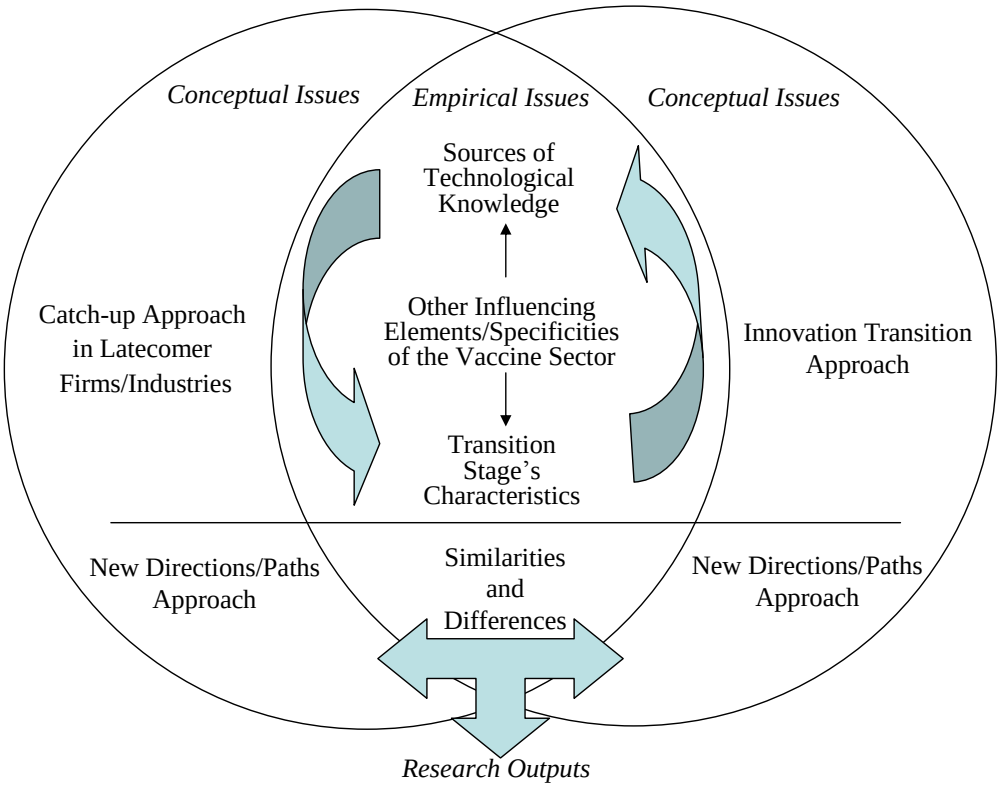
This research argues that the technological development of the BVI can be adequately interpreted by the analysis of two conceptual approaches – technological capabilities in latecomer catching-up industries, and transition within innovative capabilities

[92] The choice of the research design and the data to be gathered is within the objectives of the next chapter. The analyses and discussion are carried out in Chapter 8.

development, integrated in a benchmark model that supports the search for new directions/paths. Drawing on DCL and SML on technological accumulation, a set of key characteristics/elements was identified as shaping the common pattern of technological capabilities development in latecomer catching-up industries. These key characteristics/elements were then categorized in two interrelated groups – sources of technological knowledge and other influencing elements. Based on preliminary data gathered about the international vaccine industry and about the BVI, further elements were added to the conceptual model. In this respect it is assumed that some specificities of the context of the BVI and the persistent strategy of foreign technology acquisition adopted by the firms are possibly giving rise to some differences between the common/linear pattern and the pattern of technological development of the BVI, and that the strategy of foreign technology acquisition is not contributing to shorten the gap to the technological frontier (Research Question 1 Propositions 1 and 2).

The literature was also the source for the development of the second conceptual issue. On this issue it is assumed that the BVI has possibly not developed the innovative capabilities needed to complete the transition phase to date, and that this might mostly be linked to the dynamics in the technology frontier (Research Question 2 Propositions 3 and 4). Also, it is being assumed that the hindrances to the unfinished transition may be related to the persistent strategy of foreign technology acquisition (Research Question 2 Proposition 5). The innovation transition approach is expected to illuminate the micro dynamics of this industry during the transition phase and provide a deeper understanding of its process of technological accumulation.

The analytical framework representing the whole idea described above and supporting the analysis of the empirical information about technological development of the BVI is represented in Figure 3.3.



. Similarities and differences between the pattern of technological accumulation of the BVI and the benchmark pattern based on linear approaches of catching-up;
. The extent of the importance of the technology acquisition strategy;
. Current level of technological capabilities development of the BVI;
. Boundaries, characteristics and constraints of the transition process;
. Possible relationships between the pattern of technological accumulation of the BVI and its unfinished the transition process.

Source: own elaboration.

Figure 3.3: The Analytical Framework

3.5.2 The Specific Aspects of the Elements of the Model

The elements for the analysis of the technological development of BVI were set up in the conceptual framework, Sub-sections 3.4.2 to 3.4.4 and are listed in Table 3.1 (pg. 54-64 and 57 respectively). In this Sub-section the specific aspects of these elements are described. They are arranged in four groups: a) sources of technological knowledge; b) other influencing elements; c) transition issues; and, d) new directions/paths.

a) Sources of Knowledge

- *Technology Acquisition*

It has been common knowledge that the acquisition of external technology has been essential for the development of technological capabilities of catching-up firms in

latecomer/developing countries. In the broad sense employed by the authors, the acquisition of technology takes place through a variety of formal and informal, domestic and foreign mechanisms, and it is a strategy adopted by firms complementary to the development of in-house technological capabilities, as shown by Bell and Pavitt (1995), and Hobday et al. (2004).[93] Some works, however, have indicated opposite findings. Mytelka (1978), for example, has found a correlation between licensing of foreign technologies and low engagement in in-house R&D in some industries of three Andean countries of South America. Her findings are more noticeable in state-owned firms.

Kim (1997) has suggested that a passive attitude towards the learning process in Korean firms is linked to the acquisition of foreign package technologies through licensing from single sources. For the purpose of this research, and in accordance with the conceptual framework proposed, the term here has a narrower sense and refers to the acquisition of foreign "packaged" technologies, as defined in Sub-section 3.4.1 (pg. 52). It represents a very high stage of a firm's technological dependence. This is the type of technology acquisition that tends to decrease in importance as firms develop more advanced technological capabilities. The most common mechanisms of technology transfer in this sense are foreign direct investment (FDI), licensing, joint ventures, turnkey plants and technological agreements.[94] Other mechanisms of technology acquisition, represented here by internal and external linkages, will be investigated within the "other sources of knowledge" item since they, conversely, and along with R&D capabilities, tend to have their importance increased as firms develop more complex technological capabilities, especially in the pharmaceutical industry.

Therefore, this research proposes to investigate the mechanisms used by the BVI to acquire these "packaged" foreign technologies and, more specifically, the importance of these mechanisms along the process of this industry's technological development. The first objective is to find out whether or not the level of importance of this source of technological knowledge performs like the curve in the upper part of the proposed model and, additionally, whether this strategy has been successful to the development of

[93] For a description of several technology acquisition channels see Hobday (1995:35-39), Bell and Pavitt (1995:94-96), Dahlman et al. (1987:768), Freeman (1991:502) and Tidd et al. (2001:252).
[94] Technology transfer mechanisms related to the manufacture of equipment such as OEM (original equipment manufacture) and ODM (original design and manufacture) were not included since they are not related with the case of vaccines.

the industry. The second is to try to identify relationships with other sources of knowledge, with the other elements of the model and with the transition phase.

- *Internal Sources of Knowledge – In-house R&D*

Recognized as the main source of technological knowledge in science-based sectors since the seminal work of Pavitt (1984), R&D is traditionally highly intensive in the pharmaceutical industry (Malerba and Orsenigo, 2002). In this context, R&D capabilities are assumed as essential to competitiveness. However, in latecomer contexts the development of R&D capabilities usually starts much less intensively in the very beginning of the businesses embedded in basic, frequently informal problem-solving activities, especially to help the assimilation of foreign acquired technologies and to adapt them to local conditions, as implicit in the work of Dahlman and Fonseca (1987). Although ignored by some authors, these kinds of informal R&D activities, even those performed in non-R&D units, is admitted by the Frascati Manual (OECD, 2002).

The importance of R&D capabilities tends to strengthen as firms accumulate technological knowledge, consciously engage in more complex innovative activities, and increasingly generate process and product innovation. This requires an increasing allocation of resources in high skilled people, training, R&D facilities and technological management. On the other hand, investments in R&D may be negatively affected by deteriorating economic conditions in the external environment, as noted by some authors (Hobday et al., 2004).

Besides the capabilities for developing new processes and products, Cohen and Levinthal (1989, 1990) suggest another role for R&D – the development of capabilities to exploit outside sources of knowledge – a learning process. This is connected with the strengthening of internal and external linkages. Analyzing the above aspects is being proposed as they may indicate the strengthening of R&D capabilities and, consequently, the gradual increase of its importance to the firm. On the other hand, constraints to the development of these capabilities may signal difficulties in the transition technological process.

- *Internal Sources of Knowledge – Design and Engineering, and Clinical Trials*

Some authors have emphasized the importance of Design and Engineering capabilities to the innovative process (e.g. Dahlman et al., 1987; Lall, 1992; Bell and Pavitt, 1995; Bell, 2007). According to these authors, they are initially developed for project management and for the building and upgrading of industrial facilities, and further developed for scale-up activities, equipment design and project specification amongst others. More than a link between operating and R&D capabilities, they are a necessary basis for building R&D capabilities in some cases, especially in infrastructure sectors and scale-intensive industries, as indicated by Bell (Bell, 2007:63).

This research argues, however, that these capabilities seem to have a different dimension in the vaccine industry and should be investigated in the sense that very specialized engineering is required during some few steps of the R&D process and for the compliance with the tight regulatory requirements of the WHO (World Health Organization), GMP (good manufacturing practices) and GLP (good laboratory practices). Therefore, the importance of the development of these capabilities seems to be linked to some phases of R&D and to the regulatory issues, and may constitute a very specific type of capability in this industry.

Clinical Trials are defined in the Frascati Manual (OECD, 2002:45), and are usually considered as R&D capabilities. This research is proposing to treat them apart from R&D for the following reasons:

1) clinical trials (phases I, II and III) are the last step in the process of developing a vaccine before registration and licensing. In fact, the candidate vaccine is completely developed and produced before clinical trials. Thus the existence of these capabilities within the firm, or of a product within these phases, suggests the development of significant innovative capabilities;
2) clinical trials are currently by far the most expensive phase of the development of a vaccine (Milstien and Candries, 2002), and require capabilities somewhat different from those required for the earlier phases of the vaccine development process (Bomtempo and Baetas, 2005);

3) the complexity and specificity of this phase has led most of the "Big Pharma" to outsource this R&D phase (Milstien and Candries, 2002:75).[95] It seems, therefore, a good qualitative indicator for the development of innovative capabilities in this industry.

- *Other Sources of Knowledge – Internal and External Linkages*

This group encompasses some other formal and informal channels of acquisition of technological knowledge through internal and external links. As noted by Bell and Pavitt (1993:168), one must not assume that firms develop their technological capabilities as isolated actors. The complex structure of networks developed by a vaccine enterprise was an essential component of its success, as shown by Galambos and Sewell (1995), and it was gradually strengthened over time.

Freeman (1991:500) refers to the "multiple sources of information" and to the "pluralistic patterns of collaboration" as a rule rather than an exception in the networks explored by the firms (especially the informal ones) to complement the competencies of their R&D units. The author has also shown that firms enter into collaboration agreements for strategic reasons – e.g. technological complementarity and lead-time reduction – rather than because of lack of financial resources (*ibid.* p.507). Moreover, the accessibility of knowledge is directly related to its appropriability, as noted by some authors (e.g. Bell and Pavitt, 1993; Malerba, 2005).

The modern vaccine industry is recognized as of high appropriability of knowledge – e.g. by patents and by the tacit nature of the knowledge – and therefore of low accessibility, which reinforces the importance of linkages to the access of knowledge. The ability of establishing links and acquiring knowledge at these levels is referred to by Ernst et al. (1998b:21) as "linkage capabilities". Cohen and Levinthal (1989, 1990) call it "absorptive capacity", a critical component of the innovation process and a function of prior knowledge. The existence of substantial flows of technological knowledge from other internal and external sources is a characteristic of the transition process inside firms and of higher levels of technological capabilities, as shown in the

[95] The clinical trials characteristics and capabilities are examined in more detail in Chapter 5.

works of Dutrénit (2000, 2007), Hobday et al. (2004) and Rush et al. (2007), and listed in Table 3.3 on pg. 62-63.

- *Other Sources of Knowledge – Learning by Training*

As stressed before, technological accumulation is a learning process. Learning inside firms takes place in a variety of ways (Hobday, 1994; Malerba, 1992; Bell, 1984; Pavitt, 1991), and some of these processes are already the object of analysis in previous sections – e.g. learning by doing/using (technology acquisition, operating capabilities), learning by interacting/collaborating (internal and external linkages), learning by searching (R&D and other innovative capabilities), etc. The object of analysis now is the explicit initiatives in training. When active, explicit and directed to activities other than operating routines, training is essential to technological change (Bell et al., 1984:121). The initiatives of training undertaken by firms are often more effective than formal education, as some works show (e.g. Bell, 1984; Dahlman and Fonseca, 1987; Bell and Pavitt, 1993, 1995). Therefore, the importance the BVI has been given to this learning mechanism may be also indicative of the reasons for either success or failure in the process of development of more complex technological capabilities.

Along with R&D and other internal innovative capabilities, these other sources of knowledge are represented by the ascending curve of the upper part of Figure 3.2. It is important, however, not only to detect a growing existence of these channels, both formal and informal, but also to determine how effective they have been for the process of innovation in the industry.

b) Other Influencing Elements

In this group, as well as in the sources of knowledge group, a mix of some internal and external elements was selected to be investigated, as they are supposed to contribute to the understanding of the two conceptual issues of the model.

- *Organizational capabilities*

The importance of the organizational dimension for the development of technological capabilities has been the object of analysis within the SML, as stressed in Sub-section 2.3.3 of the previous chapter (pg. 21-24). Within this body of literature the main concern is with the type of capabilities needed to deal with the fast changing

environment and to achieve and/or sustain technological competitive advantage. Thus it refers to the capabilities of firms operating around the technological frontier. Bringing this to the perspective of this research, it is, according to Dutrénit (2000, 2007), the type of capabilities latecomer firms in transition should develop to catch-up. Hobday et al. (2004) also emphasize that the organizational aspects involved in the transition process of Korean firms are as critical as the technological ones.

This is certainly a subject for a whole thesis. In this research, however, for obvious reasons, more limited attention will be given to this issue. This research is concerned with this subject in two dimensions: the awareness of the need of this type of capability to the development of the firms, and the effective existence of initiatives aimed at the strengthening of the managerial capabilities inside firms. The objective is simply to try to understand the extent to which this issue has been affecting the current context of development of the BVI, and the amount of attention the firms have been giving to this matter.

- *Markets*

It is common notion amongst scholars that the market, through competitive pressures, is a basic stimulus that affects the development of technological capabilities. This is the main point about this subject to be approached in this research. The huge Brazilian public market for vaccine, along with government policies against internal competition and protection against outside players, has been an open field for the growth of the BVI. However, the extent to which this has been successful or harmful in promoting the long-term development of technological capabilities within the BVI is a matter to be investigated. [96]

Lall (1992:169), however, calls attention to the potential long delays competition may cause to the development of technological capabilities in infant industries due to the costs of learning during the existence of certain market failures.[97] On the other hand, the

[96] Although export-oriented strategies have been suggested in several empirical studies as the main driver for the development of firms in East Asia, Mytelka et al. (1998:335) show that domestic markets were also important agents for the development of technological capabilities in the region.

[97] The problem of "costs of learning" noted by Lall could be complemented with the "partial appropriability of the returns", as raised by Bell and Pavitt (1993:202).

lack of competitive pressures and rivalry served as non-incentives for the development of firms in centrally planned economies, according to Bell and Pavitt (1993:173).

The strategies and policies of the Brazilian government seem to be benefiting the BVI in another way – by easing the technology transfers agreements from the "Big Pharma", even of those still non-mature technologies. Nevertheless, the dynamics of the international markets, both public and private, and the main players in the world scenario are aspects not to be ignored in the analysis proposed in this research.

- *Government Policies, Institutions and Regulation*

It has been widely agreed that national idiosyncrasies highly influence the system of innovation of the firms, and that the state has an important role in mediating the elements of this system (Lundvall, 1992b; Nelson, 1993). Freeman (1995) has pointed out that national policies remain decisive for the catching-up strategies in developing countries. In this sense, in fact, the role of government is huge. Even though there is no room in this research to investigate this, to some extent some important specific points should be addressed. Besides the policies to protect and stimulate the Brazilian vaccine market, as mentioned in the previous item, greater emphasis should be directed to other aspects of the government initiatives directly encouraging or affecting the vaccine industry. These include the health and vaccination policies, S&T policies, R&D projects funding, and the effects of these policies on the interactions between BVI and other domestic and foreign actors. The regulatory aspects have also highly influenced the pharmaceutical industry. The trend toward increasing regulation threatens vaccine development due to increasing costs and uncertain returns (Milstien and Candries, 2002:77). On the other hand complying with international standards is indicative of well-developed capabilities in many areas of the firms.

- *Innovation in the Knowledge Frontier*

In the last decades there have been major breakthroughs in the development of new vaccines (WHO, 2002b) and the number of firms in this business has declined (Galambos, 1999). Although vaccine R&D is seen as increasingly risky, costly and lengthy (WHO, 2002b), new technologies in the 21st century will guarantee a passage from the golden age to the platinum age of vaccinology (Plotkin and Plotkin, 2004). In addition, the new technologies come protected by patents, which impede the

development in particular domains (Plotkin, 2005c:632).[98] For new entrants it becomes increasingly difficult to catch-up. In turn, it makes them rely more often on technology transfers and licensing (Milstien et al., 2007). In fact, as noted by Gadelha and Azevedo (2003), the BVI has been unable to keep up with international developments. Innovation and development of vaccines in the knowledge frontier is certainly one of the most complex issues influencing the development of the BVI, therefore requiring special attention to the purpose of this research.

- *The Specificities of the Vaccine Sector*

The vaccine sector seems highly influenced by special characteristics that have been raising growing concerns in the international community and have a different appeal in the world economic scenario. The social relevance of the adoption of vaccination, especially in developing and in the poorest countries, along with the high technological complexity of vaccine development and the constraints faced by governments due to the effects of an oligopsonistic market, are possible reasons that have shaped a unique industrial sector. This suggests a different perspective to assess the role of markets, governments and institutions in the development of this sector and of the BVI in particular.

c) Transition Issues

The main aspects of the transition issues approached in this research were stressed in Sub-section 3.4.3 of this chapter, and Sub-section 2.3.4 of the previous chapter (pg. 58 and 29 respectively). This research argues that the characteristics of the transition phase of the BVI are closely linked to, and influenced by, the specific pattern of technological capabilities development of this industry. Therefore, to interpret this transition phase this research will draw on the analysis of the "sources of knowledge" and "other influencing elements" groups proposed above in the light of the specific characteristics of transition, as raised in the works of Dutrénit and Hobday et al and summarized in Table 3.3 (pg. 62-63). The current level of technological capabilities development, and the supposed constraints and/or innovative initiatives to the development of strategic/competitive capabilities in the BVI, are expected to emerge from this way of looking at these events and data. Moreover, an alternative way of assessing the current

[98] The author also emphasizes that patents have an opposite effect – they block collaboration between organizations when both hold intellectual property.

level of technological capabilities of the BVI, as well as of identifying the strengths and weaknesses in the process of development of this type of capability, is a tool to be used complementarily to the above analysis in order to strengthen the findings of this research.

d) New directions/paths

Looking for new directions/paths means to investigate whether the development of the BVI presents innovative initiatives that can be considered as being distinguishing from the common pattern of development identified in linear approaches of catching-up, in an attempt to overcome its disadvantages and barriers. This will be carried out through looking for similarities and differences throughout the analysis of the elements described in items a) to c) above and their relationships. The existence of new directions/paths in the development of the BVI may strengthen the arguments around latecomer development inspired in the ideas of Gerschenkron. It may also disclose new characteristics of latecomer development based on this type of strategy.

3.6 Summary

This chapter describes the motivations of this research and the rationale for the identification of the research problem and for setting the objectives of this research. It also presents the research questions and propositions to be investigated. The conceptual and analytical ideas that nurture the development of this research and the analysis to be carried out are then developed and explained.

The main argument of this thesis is that the specificities of the context of the Brazilian vaccine industry (BVI) may be determining a particular pattern of technological accumulation within this industry, and that interpreting this pattern of development may be useful in understanding how and if the BVI has overcome its disadvantages to develop.

Rather than choosing a single approach amongst the ones stressed in the previous chapter for interpreting the development of the Brazilian vaccine industry, this research is proposing to perform this task in a different and simple way. In this sense it is proposed to integrate two different approaches regarding both the linear catching-up model of industries/firms of latecomer economies and the transition issues involved in

the development of advanced/competitive capabilities. The first reason behind this idea is the attempt to benefit from the broader concepts embedded in the former, along with the more specific ones represented by the latter, in order to interpret the development of the BVI in its entire length, with a focus on its supposedly current transition phase.

The second reason is to provide a benchmark model in the search for similarities and differences in the pattern of development of this industry. This is in order to investigate the existence of new directions/paths in its strategy of development, in line with contemporaneous works that draw on the theory of "backwardness and substitute for missing prerequisites" of Gerschenkron.

This chapter also presents the framework that supports the analysis of the above-mentioned contexts and describes the analytical aspects of the elements of this framework in order to address the research questions and propositions. The next chapter defines the research design and the strategies to the operationalization of the analysis and to answer these research questions.

Chapter 4 – Methodology

4.1 Introduction

This chapter discusses the overall strategy for answering the research questions and achieving the research objectives. It relates to the operationalization of the frameworks and concepts developed in the previous chapter. It explains the research design chosen and the operationalization of data gathering. It is also about the analysis of the data gathered.

The chapter is organized as follows: Section 4.2 explains the rationale for defining the research strategy and design (Sub-section 4.2.1) and the aspects that contributed to the definition of the boundaries of this research (Sub-section 4.2.2). Section 4.3 relates to the operationalization of data and data collection. The topics covered and data selected are presented in Sub-section 4.3.1, and the methods of data gathering are introduced and explained in Sub-section 4.3.2. Section 4.4 shows how the evidence has been analyzed. Section 4.5 summarizes the content of the whole chapter.

4.2 Research Strategy and Design and the Boundaries of the Research

This section introduces the research strategy and design and states why they were chosen (Sub-section 4.2.1). It also explains how the boundaries of the study were defined (Sub-section 4.2.2).

4.2.1 Research Strategy and Design

The general aim of this research is to investigate the circumstances which have been both enabling and hindering the development of the Brazilian vaccine industry (BVI). In the previous chapter the conceptual and analytical frameworks were developed and explained to fit the specificities of this research. This research argues that the BVI might be developing its technological capabilities in a way that is distinct from the common/linear pattern suggested in the literature for most of the catching-up industries of latecomer countries. Additionally, it is also argued that the characteristics of the specific pattern of development of this industry may be setting back the transition to the development of more complex innovative capabilities. The framework proposes to integrate these two conceptual issues (the pattern of technological capabilities

development in catching-up countries, and the transition within innovative capabilities development) as a benchmark model in order to interpret the development of the BVI and address the third conceptual issue – the existence of new directions/paths as an alternative strategy to develop.

In order to interpret how the BVI has developed its pattern of technological capabilities over time (Research Question 1), an investigation of some specific elements of its environment has been suggested, i.e., its sources of technological knowledge and other internal and external influencing elements. To interpret how far this industry has gone to date, how and why (Research Question 2), analyzing the specific issues of its transition phase in the light of the findings of the works of Dutrénit (2000, 2007) and Hobday et al. (2004) has also been suggested. The integration of both conceptual issues means that interpreting the first will help to understand the second, and vice versa. Furthermore, the use of the innovation transition approach intends to throw light on the micro dynamics of a critical phase, that is, when the firms have been developing more advanced technological capabilities. In addition, this model, based on linear approaches of catching-up, is intended to serve as a benchmark to the search for similarities and differences in the pattern of development of the BVI. The expected results are a better understanding of the whole process and the disclosure of the specific characteristics of the process of technological accumulation of the BVI.

The focus on contemporary events of the context of the BVI and the “how” and “why” types of question posed, as shown above, clearly set the stage for an explanatory case study strategy, in line with the definitions proposed by Yin (1981, 2003) for this type of study. More careful explanation is needed, however, to justify the choice for a single-case rather than a multiple-case study design. An initial reason relates to the theory underlying the study and the type of questions and propositions posed. They are of an holistic nature and address a more general phenomenon of the industry, as shown in the previous paragraph.

A second reason comes from the analysis of the preliminary data gathered about the structure of the BVI. Even though the Brazilian vaccine market may be considered expressive when compared to the world market, the BVI comprises only four

manufacturers.[99] These manufacturers are public, address the public market only and supply different products to the National Immunization Programme (PNI).[100,101,102] Two of these manufacturers have supplied over 97% of the PNI local purchases and the great majority of the products purchased. Also, these two manufacturers were the only firms to introduce new products in the last two decades, most of them based on the acquisition of foreign technology.

From the above facts one can consider these two biggest manufacturers as highly representative of the industry and, consequently, the focus of this research was concentrated on them.[103] If the two reasons are put together and described from a different viewpoint, the findings of each of unit of analysis were expected to contribute to the general purpose of the research and would not be used for comparisons between them. These constitute what Yin (2003:40-46) considers as some of the rationales for designing a single and embedded case study – a single case-study with multiple units of analysis. This design was then adopted for the purposes of this research.

Still relating to the research design, another important perspective was considered here. This research essentially focuses on the dynamics of building up technological capabilities over time. Investigating the pattern of technological capabilities development means trying to understand how a sequence of events has unfolded over a period of time. Similarly, investigating transition within innovative capabilities development means a temporal examination of events being changed. The order of the sequence of events is thus relevant to interpreting the phenomena. These characteristics basically require an event-driven explanation and characterize the need for a process approach in order to adequately address the research questions (Van De Ven and Poole, 1995; Van de Ven, 2007). This was also taken into consideration here.

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[99] The figures about the world and the Brazilian vaccine markets as well as the details about the manufacturers are presented in Chapter 6.

[100] The smallest of the manufacturers – the Ataulfo de Paiva Foundation - is not public but a non-profit private organization (see Sub-section 6.2.4 on pg. 140).

[101] One of the two biggest manufacturers – the Institute of Technology on Immunobiologicals (Bio-Manguinhos/Fiocruz) – also supplies some vaccines for the United Nations Children's Fund (UNICEF) and for the Pan American Health Organization (PAHO).

[102] Supplying different products for the PNI means that the manufacturers have not, so far, competed with each other.

[103] However, some data from the other two manufacturers were also occasionally considered.

Additionally, this research has taken a retrospective account because technological capabilities usually develop over a long period of time, sometimes over decades, as noted by some authors (Dahlman et al., 1987; Hobday, 1995), making it useless to observe the events in real time over a short period. This seems especially true in the field of vaccine, which is characterized by long cycles of technological development as stated by Galambos and Sewell (1995). According to Van de Ven (2007:208), knowing the outcomes of a process in advance may be helpful for interpreting events that have already unfolded.

This research is also qualitative as it relies mainly on wordy rather than on numerical evidence (Eisenhardt, 1989; Miles and Huberman, 1994). However, some quantitative data were also collected, since they proved useful in helping qualitative analysis in certain situations. Furthermore, multiple forms of data collection, such as interviews, a survey and secondary sources (e.g. government publications, firm's institutional folders, annual reports, academic theses and dissertations, specialized magazines and firms' and other institutions' web pages) were used.[104] This research also benefited from a small number of informal conversations that were useful, especially to check the need for further data. According to some authors (Hakim, 1987:63; Yin, 2003:97), the use of multiple sources of data strengthens the outcomes of a case study and makes this type of research design very powerful.

4.2.2 The Boundaries of the Study

The boundaries of the research were defined in two steps: before and after the fieldwork. Before the fieldwork some preliminary data about the history and contemporaneous facts on vaccination in Brazil were determinative. Firstly, a threshold was defined: the establishment of the National Immunization Programme (PNI). Created in 1973 by the Ministry of Health (MOH) the PNI was the driver for the transformation of the Brazilian vaccine industry (BVI) and of immunization in Brazil.[105] Therefore, the period of analysis of this research starts in the mid-1970s, when the public market started growing faster, public demands received poor answers from the manufacturers and, consequently, public investments in new industrial facilities took place, technology transfer processes became a continuous technological strategy, and the vaccines began

[104] More details about data collection and sources of data are presented in Sub-section 4.3.2.
[105] The PNI and the success of the immunization initiatives in Brazil are described in detail in Chapter 6.

to be produced by the BVI under tighter quality control standards. Notwithstanding, some interesting and useful historical facts about this industry have also been used to illustrate and give sense to the arguments.

Secondly, the four national producers and the public market were defined as comprising the scope of the study. The private market is dispersed and supplied only by the biggest international pharmaceutical companies ("Big Pharma") and little information is available (Temporão, 2002). Moreover, there is no technological activity involved since the "Big Pharma" do not produce vaccines locally but import all the vaccines they sell in Brazil.

During the fieldwork it became clear that the two smaller national producers would be of minor interest for the purposes of this study.[106] Even though their few products have been important to PNI so far, they constitute very old technologies and both producers have been carrying out only basic R&D activities within this field. Therefore, only limited data were collected from them. On the other hand the two other producers – the Instituto de Tecnologia em Imunobiológicos (Bio-Manguinhos/Fiocruz) and the Instituto Butantan – were confirmed as meeting the characteristics proposed in this research. Moreover, figures proved these manufacturers are highly representative of the BVI, as stated in the previous sub-section and presented in Chapter 6.[107] Focus was therefore directed on them.

An additional point should be restated here. The firms comprising the BVI also explore other segments of Immunobiologicals (e.g. serum, biopharmaceuticals and diagnostic reagents).[108] For the purpose of this research, however, only the vaccine segment is being discussed. As stated in the previous chapter (Sub-section 3.4.2 on pg. 58) the conceptual model developed does not encompass the general strategy of diversification of the firms but the strategies to the vaccine segment only.

[106] They are the Fundação Ataulfo de Paiva and the Instituto de Tecnologia do Paraná (TECPAR). See details about both manufacturers in Sub-section 6.2.4 on pg. 140 and 141, and some comparative data of the four manufacturers in Table 6.6 on pg. 143.
[107] Details about both manufacturers in the same sub-section (pg. 137-140) and Table referred to in the previous footnote.
[108] Vaccine is the main segment of three of the four firms. See Sub-section 6.2.4 (pg. 135-143) of Chapter 6 for more details about this issue.

4.3 Operationalizing Data and Data Collection

In Chapter 3 the frameworks were developed, their elements were set up and some analytical aspects of these elements were defined. This section is about the data to be gathered (Sub-section 4.3.1) and the methods of data collection (Sub-section 4.3.2), in line with the research design chosen.

4.3.1 Operationalizing Data

The main concern of this stage was to select the type of data to be gathered which could provide an evolving picture of the evidence as well as being meaningful for qualitative analysis. A second concern was about the amount of data to be collected in order not to overload the analysis. It is acknowledged that some new portions of data tend to emerge during the fieldwork as a dynamic in qualitative research (Miles and Huberman, 1994).[109] A third concern was about the accuracy of the data and triangulation, a matter that is discussed in more detail in the next sub-section.

In the previous chapter the selected elements for the analysis of the technological capabilities development of the BVI were arranged in four groups: a) the sources of knowledge; b) other influencing elements; c) transition issues; and, d) new directions/paths. Some analytical aspects of these elements were then defined in order to orient the better choice for data.[110] The elements of group d) above are embedded in the analysis of the elements of the other groups.

The topics of information chosen were therefore arranged within the first three groups and specified by each element. Tables 4.1 and 4.2 present the topics and types of data selected to constitute the evidence of both (i) the sources of technological knowledge and (ii) the other internal and external influencing elements, respectively. They were primarily intended to address the analysis of the pattern of technological capabilities development concept, but they have also helped the analysis of the other conceptual issue – transition within innovative capabilities development. For specifically addressing this latter issue other strategies were also adopted and they are explained in item (iii).

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[109] In this research the importance of the aspects of the transition phase within the development of more complex innovative capabilities became more evident during the fieldwork, and led to a higher emphasis on this issue in order to strengthen the understanding of the development of the BVI.

[110] See Sub-section 3.5.2 on pg. 66-75.

(i) Sources of Knowledge

Table 4.1: Topics and Types of Data about Sources of Knowledge

Elements	Topics Covered / Types of Data Selected
Technology Acquisition	. sources of technology of each product launched in the market (foreign technology or in-house development); . mechanisms of technology transfer used; . gap between the launching of each technology in the international market and its launch in the Brazilian market; . aspects of the strategy of technology acquisition;
R&D (including clinical trials)	. domain of capabilities required to develop a vaccine; . investments in R&D; . personnel employed; . sources of knowledge exploited; . existence of process and product innovation; . existence of candidate products in clinical trials; . existence of clinical trials activities and capabilities developed; . strategies for innovation;
Design and Engineering	. main activities and capabilities developed
Internal and External Linkages	. existence and importance of links between Operating and Innovative areas; . existence of capabilities flowing from Operating (acquired technology) to Innovative areas; . existence and results of links and alliances between firms within the BVI; . existence and results of links and alliances between the BVI and external firms, research institutions (including universities) and other institutions; . existence and importance of links with suppliers; . use of consultancy and/or skilled specialists in technological activities; . importance of prior knowledge; . strategies for collaborating.
Learning by Training	. awareness of the importance of learning; . mechanisms of formal technological training; . training embedded in technology transfer processes; . on-the-job training; . investments in training;

Source: own elaboration.

(ii) Other Internal and External Influencing Elements

Table 4.2: Topics and Types of Data about Other Influencing Elements

Elements	Topics Covered / Types of Data Selected
Organizational Capabilities	. project management experience; . existence of awareness to the development of managerial capabilities; . existence of initiatives to strengthen the managerial capabilities;
Markets	. main figures; . dynamics of the Brazilian public market; . international and Brazilian markets as an opportunity and as a threat; . actors of the markets;
Government Policies, Institutions and Regulations	. existence and adequacy of policies stimulating this industry, especially innovation; . impact of regulation on the development of innovative capabilities; . existence and importance of institutions in the national and international contexts to the development of this industry;
Innovation in the Knowledge Frontier	. breakthroughs within vaccine development and alternative strategies adopted by the BVI;
Social and Technological Specificities	. evidences which could possibly characterize the vaccine as a singular sector.

Source: Own elaboration.

(iii) Transition Issues

As stated earlier, some of the evidence for the analysis of the transition within the innovative capabilities development concept is embedded in the topics listed in Tables 4.1 and 4.2. However, to address the issues raised by Research Question 2 and its propositions in more detail, drawing on the approach on innovation transition reviewed in the literature, this research made use of other types of data. The objective was to select the type of data that could help the identification of the level of complexity of the innovative capabilities developed by the BVI to date, and of the boundaries, characteristics and constraints of the transition phase of this industry. Thus the data selected mirrored the results of other experiences approached in the works on innovation transition as described in Table 3.3 on pg. 62-63.

As a complementary tool for the analysis of the transition phase this research made use of a survey. The Simple Survey Tool developed by Bessant et al. (2001) is one of the

three audit tools designed by the authors for assessing technological capabilities of firms. This tool provides a quick assessment of the level of technological capability and points out strengths and weaknesses across the nine dimensions listed in Table 4.3. Its adoption proved successful and useful in some previous works related to innovation transition (e.g. Hobday et al., 2004; Rush et al., 2007) and, therefore, it was considered adequate for the purposes of this research. One further advantage of this survey was to cover several points of the interview questions by a larger distributed population. Conversely, the result of the interviews helped to explore the issues of the survey in more detail and at greater depth.

Table 4.3: The Nine Dimensions for Assessing Technological Capabilities

1 – Awareness
2 – Searching
3 – Building core technological competences
4 – Technology strategy
5 – Assessing and selecting technology
6 – Technology acquisition
7 – Implementing and absorbing technology
8 – Learning
9 – Exploiting external linkages and incentives

Source: Bessant et al. (2001).

4.3.2 Operationalizing Data Collection

Data to cover the topics listed in Tables 4.1 and 4.2, and those about transition issues, were collected through a variety of ways and in two rounds. Most of data were collected in the first and main round. A second round was undertaken mainly to address missing points and to clarify possible inconsistencies. However, the survey, two new interviews, and an extension of one previous interview were also carried out during this second round of fieldwork.

Given the high specificity of the topics to be addressed, a large body of data was gathered through semi-structured interviews. This type of interview has proved to be appropriate as it allows a combination of guided questions with a certain freedom in questioning and answering. In addition, it provides a closer interaction with the

interviewees. As long answers were expected, and since there was no objection by the interviewees, the interviews were all audio recorded. This allowed more attention to be paid to the answers during the interviews, a quicker managing of the interviews conducted, a later review and pre-analysis of data gathered in order to search for missing points during these interviews, and easier access to the data gathered during the data analysis phase.

A short protocol adapted from Yin (2003:67-77) was used as a guide to the interviews and as a source of general information about the research to the interviewees. The research protocol was constituted of two parts. The first part comprised the specific information to help with the interviews, such as the agenda of the process (e.g. prearranged interviews, date, place, interviews planned to be arranged on the site, contacts), general information about the research (e.g. research questions, propositions, topics of interest), background information about the firm of each interviewee and the interview questions. The second part comprised the general information to make the interviewees aware of the objectives of the research, as well as the terms for requesting permission to audio record the interview and for stating the strict use of data gathered during the interviews for the purpose of the research only.

The interviews were primarily designed to cover four different themes: Policies, Strategies/Management, Operating Capabilities and Innovative Capabilities. A set of 20 interviews was conducted initially. They lasted 90 minutes each on average. Some of the interviews covered more than one subject since the interviewee showed familiarization and a willingness to contribute to other themes. Two interviewees spontaneously approached issues about markets. A further two interviews were conducted later on other specific themes (Clinical Trials, and Engineering and Design) to complement information gathered through documentation and other sources and to address specific issues of the research. One previous interview was complemented during this second set of interviews. Due to the small number of firms and consequently the small number of interviews, emphasis was given to selecting senior actors as interviewees inside and outside the firms. Table 4.4 presents the number of interviews by each of the subjects approached. The list of interviewees with their current and previous positions is presented in Annex A.

Besides the interviews and a few informal meetings this research benefited from a wide and rich variety of sources of data. Some recent studies about this industry proved highly useful and eclectic, providing both historical and contemporaneous facts besides discussing proposals for the development of the BVI (e.g. Benchimol and Teixeira, 1993; Benchimol, 2001; Brasil, 2003; Buss et al., 2005; Azevedo and Gadelha, 2007). Papers, government documents (e.g. Laws, Ministerial Acts), theses, dissertations, institutional folders, annual reports and the Internet are also amongst the vast range of sources of data used. Technical information, information about investments, personnel and the main projects undertaken within the R&D area of the two biggest firms was requested and provided by the firms in most cases. Some figures about this industry were also provided by the Coordination of the PNI/Ministry of Health.

Table 4.4: Number of Interviews by Subject

Subject	No. of Interviews[1]
Policies	6
Strategies/Management	7
Operating Capabilities	4
Innovative Capabilities	9
Clinical Trials	3
Engineering and Design	1
Market	2

[1] Some interviewees approached more than one subject.
Source: Own elaboration.

With regard to the survey, this was conducted in the biggest firm of the BVI across all of its working areas. The firm was chosen not only because of its relevance within the context of the industry but also due to logistical reasons and the higher probability of obtaining a good response rate. In this sense there were 123 valid responses representing 10.6% of the total number of employees of the firm, and 22.9% of the employees in positions requiring graduation as the minimum background, to whom the survey was directed.[111] The questions formulated for the audit tool by the authors were kept for the survey, but some variables about the population were introduced (e.g. area

[111] There were 140 responses in total of which 17 were not considered due to high blank responses (16 questionnaires) and due to lack of coherence (1 questionnaire). The percentage was calculated over the number of employees in August 2009, as provided by the Human Resources Department of the firm.

of work – R&D/Production/Engineering/Quality/Management; years in the firm – less than 10/between 10 and 20/over 20; type of post – manager/non-manager; and highest qualification – graduation/specialization/MSc/PhD).[112] The results of the survey are presented in Chapter 7 on pg. 201-206. The questionnaire and the analytical tables are reproduced in Annex B.

Finally, the choice of the sources of data embedded the concern with triangulation. This research has tried to avoid bias and strengthen the reliability and validity of data using many different methods. As shown before, the use of multiple sources of evidence was one method used. In this case, this strategy was adopted not only for gathering a wider variety of data but also for looking for convergences and discrepancies in the evidences gathered. Yin (2003:98-100) emphasizes that data triangulation of multiple sources happens only when there is a convergence in the facts addressed. Van de Ven (2007:284-285) distinguishes between reliability and validity in triangulating data. He notes that convergence of data addresses only the reliability of data. Validity, instead, is obtained from different perspectives of the phenomenon approached.

The selection of senior actors as interviewees was another strategy. Most of the interviewees are managers in high positions inside the firms and have been working in the BVI for many years. Furthermore, many of them started working in the BVI around the beginning of the main period covered by this research (1970s).[113] However, in addition to the other sources of data, this research made use of some quantitative figures to help to corroborate some of the data gathered through interviews and to avoid what Miles and Huberman (1994:41) call "elite bias".[114] Moreover, the survey provided data from a broader and varied population, as stated before, allowing the analysis of some points approached in the interviews from other perspectives.

4.4 Analyzing and Interpreting Data

The analysis of the data was carried out in three main steps. The first one started almost simultaneously with the data collection during the fieldwork, drawing on some methods described by Miles and Huberman (1994:50-53) for organizing early analysis. Although

[112] The authors emphasize that diversity in the population surveyed brings a more representative view from inside the firm and can be very informative (Bessant et al., 2001:10).
[113] The profile of the interviewees is presented in Annex A.
[114] For "elite bias" the authors mean "talking only to high-status respondents".

it had been only a primary analysis this proved an arduous task as the main concern was not to delay the data collection including the period planned for the interviews. On the other hand the exact objective to raise feedback from the material already collected in order to detect possible inconsistencies, address missing points before the end of the fieldwork, and improve the approach for the subsequent interviews, if needed, by adding possible contradictory ideas. As a matter of fact the pre-analysis of some data provided by the firms before starting the set of interviews, was key in determining the need for more emphasis on the transition issues and led to the strengthening of the interview questions in the same direction. In addition, it led to the search for more data that could more accurately address the transition context of the development of the firms.

The second step in the process of data analysis was the longest and most laborious one. It consisted of organizing all the data according to the elements and topics selected, and defined for the characterization of the level of importance of the sources of knowledge and of the influence of other internal and external elements, as described in Tables 4.1 and 4.2. Data were also organized in order to represent the chronology of the events since this process approach is fundamental for interpreting development and change in organizations across time, as noted by Van De Ven and Poole (1995).

This generated large draft tables, or what Miles and Hubeman (1994:90) describe as "display". In this specific case the drafts were arranged in a format inspired in the "time-ordered matrix" format described by these authors as appropriate to track sequences, processes and flows (*ibid.* p.119-120), and they contributed to the building of the empirical chapters (Chapters 5 to 7). During this phase some doubts and missing points were raised. They were clarified during the second round of data collection. The survey was also carried out during this second round of fieldwork. These new data were also analyzed during this second step of data analysis.

The last step of the data analysis referred to the linking of the conceptual issues approached in the literature review, and organized within the frameworks developed with the empirical evidence gathered in order to address the research questions and their propositions. This will be described in Chapter 8. In this sense the integration of the catch-up approach with the innovation transition approach was put forward, as proposed,

allowing the interpretation of the data in three dimensions, and serving as a benchmark model to the search for new directions/paths. The first dimension has a broader view based on the former approach, the second has a more detailed view, focusing on a specific stage of technological capabilities development, as provided by the innovation transition approach, and the third dimension refers to the search for innovative initiatives across the first two dimensions.

The explanations offered were all built taking into account the order of the events and were always illustrated by empirical evidence. For analyzing one specific proposition (Proposition 2) the results of the survey and some of the dimensions (along with their underlying themes), approached in the audit tool referred to in item iii of Sub-section 4.3.1, were adapted and successfully used. The claims for the conclusion are presented in the last chapter (Chapter 9).

4.5 Summary

The present chapter has presented the strategies adopted to deal with the conceptual and empirical issues of this research that made possible the achievement of the research objectives. In this sense it has described the methods for choosing the research design, for defining and collecting data as well as the ones for analyzing them. The next chapter starts a set of three empirical chapters where the evidence collected and organized is presented.

Chapter 5 – Vaccine and Innovation on Vaccine

5.1 Introduction

This chapter is the first of three dedicated to the description of the empirical issues of this research. This first chapter shows how and why vaccine and vaccination have achieved a place of distinction in the worldwide public health scenario and why there is much still to be done in this field.[115] Special attention is given to the dynamics of innovation on vaccines. It also shows the complexity of dealing with vaccines and the capabilities required to develop and manufacture vaccines.

The chapter is organized into five sections. Section 5.2 presents the facts that characterize the importance of vaccines today and some paradoxical aspects of their existence. It also outlines the history of vaccine worldwide and in Brazil in particular. Section 5.3 describes the main breakthroughs that characterize the innovation on vaccines. Section 5.4 describes the steps of developing and manufacturing vaccines and the capabilities involved in these complex processes. Section 5.5 briefly outlines some tendencies in vaccine innovation. Section 5.6 summarizes the concept of the whole chapter.

5.2 Facts and History

This section describes some facts that have made vaccines one of the most important tools for public health as well as some hindrances for its development, manufacture and administration (Sub-section 5.2.1). The history of vaccine and vaccination in the world and in Brazil since its inception is also briefly approached in this section (Sub-sections 5.2.2 and 5.2.3).

5.2.1 Vaccine – Key Facts and Paradoxes

Vaccine is acknowledged by the World Health Organization (WHO) as one of the public health interventions – together with clean water – that has achieved the greatest impact in world health (WHO, 2002a; Plotkin and Plotkin, 2004). Immunization is also frequently cited as one of the most cost-effective public health interventions (e.g. WHO,

[115] This research uses the terms “immunization” and “vaccination” interchangeably and with similar meaning, as already mentioned in the footnote 1 (pg. 3).

2002a; Plotkin and Plotkin, 2004; Blume, 2005; Orenstein et al., 2007). These two statements explain the importance that vaccines and vaccination have achieved in the world today.

> Vaccines are the keystone of the fight against pathogenic microbes. It is vital to develop new vaccines continuously, as well as to improve existing vaccines. (Kieny and Girard, 2005:5706).

Indeed, empirical data can better illustrate the importance of the vaccine. Nowadays, over 26 serious infectious diseases are preventable by vaccine (a non-exhaustive list of human infectious diseases preventable by vaccine is shown in Table 5.1). Millions of lives are saved every year across the world, 3 million of them children (Andre, 2003), and the risk of disabilities caused by infectious diseases has shown a significant reduction by immunization programmes (WHO, 2002b). The most important achievement in the field of vaccinology was against smallpox, declared eradicated from the globe by the WHO in 1979 (Plotkin and Plotkin, 2004; Blume, 2005). The worldwide eradication of poliomyelitis is expected soon (WHO, 2006), and the incidence of measles and maternal and neonatal tetanus has been dramatically reduced in the poorest countries (WHO, 2002b). Moreover, the use of existing vaccines is considered the solution for increasing microbial resistance caused by the use of antibiotics and antivirals (Vandersmissen, 2002:S105). Table 5.2 shows an estimation of the cost-effectiveness of vaccination.

Notwithstanding, vaccines cross the boundary that divides two paradoxical worlds. On the dark side social interests have been frequently dazzled by economic, scientific, political, technical and managerial reasons. The wider benefits of existing vaccines have not reached millions of children, especially in poorer countries or poorer regions of wealthier countries. Estimations from the WHO (2002b:vii) indicate that one-quarter of world's children are still unprotected against preventable infectious diseases, and 2 million die every year from those diseases. Other studies estimate that 25% of global mortality, especially amongst children younger than five years, is still due to infectious diseases. This contributes to the great disparity in average life spans between rich and poor countries (Kieny et al., 2004:1931).

The high price of some vaccines is one of the alleged reasons. The persistence of mortality and morbidity caused by some diseases where vaccines are widely available at low cost, such as measles and tuberculosis, however, indicates other reasons of programmatic and scientific nature respectively, as noted by Vandersmissen (2001:1611-1612). Vaccine shortages have frequently happened even in developed countries, as described by Hinman et al. (2006), and they have resulted not only from the lack of resources to purchase vaccines but also from interruptions in supply due to technical problems, higher-than-expected demands or manufacturer's withdrawals from the business for economic reasons.

Table 5.1: Non-exhaustive list of human infectious diseases preventable by vaccine

. *Anthrax*	. *Poliomyelitis (Types I, II, III)*
. *Cholera*	. *Rabies*
. *Diphtheria*	. *Rotavirus*
. *H. Papillomavirus (several Types)*	. *Rubella*
. *Haemophilus influenzae b*	. *Plague*
. *Hepatitis (A, B)*	. *S. Pneumoniae (several Serotypes)*
. *Herpes Zoster*	. *Smallpox*
. *Influenza (several Types)*	. *Tetanus*
. *Japanese Encephalitis*	. *Tuberculosis*
. *Lyme*	. *Typhoid Fever*
. *Measles*	. *Varicella*
. *Mumps*	. *Whooping Cough*
. *N. Meningitidis (several Serogroups)*	. *Yellow Fever*

Own elaboration. *Source*: NIH/NIAID (2007:Appendix B)

Recent events have once more raised these concerns and exposed some of the paradoxes of this phenomenon. In July 2009, when officially reported cases of the pandemic Influenza A (the new H1N1 virus or swine flu) quickly reached almost 100,000 cases across the world, with more than 400 deaths in just a few months, the WHO considered the spread of the pandemic virus unstoppable by means of intervention other than vaccine, and its Strategic Advisory Group of Experts (SAGE) on immunization recommended the vaccination of the population for all countries (WHO, 2009b). The specific vaccine for this type of virus was still not available, however, and it was

estimated that it would not be available for three or four months.[116] SAGE's recommendations also took into consideration the fact that production capacity of the vaccine by the manufacturers would be insufficient for world demand, particularly in the first months, and then priorities for distribution should be defined by individual governments. Moreover, SAGE advised that each country's strategy should reflect their availability of resources to buy and ability to access the vaccine. Implicit was the prediction that many more people would inevitably die from this preventable disease, and the poorer countries would have more difficulty in obtaining the vaccines.

Table 5.2: Some estimations of the cost-effectiveness of vaccination

Rubella	Each US$1 spent in vaccination saves nearly US$8 in costs associated with the treatment of the disease in the US;
Poliomyelitis	US$1.5 billion/year in costs with vaccines, treatments and rehabilitation would be saved when the disease is eradicated, according to WHO estimations;
MMR	US$21 is saved for every dollar spent with this vaccine in the US, according to the US Institute of Medicine;
Smallpox	Its eradication has saved US$1.3 billion/year in treatment and prevention costs;
Pneumococcus	The introduction of the vaccine has been associated with a 39% reduction in hospital admissions due to pneumonia from any cause.

Source: NIH/NIAID (2003), Bloom et al. (2005) and WHO (2009a).

Furthermore, even though vaccines and vaccination have achieved this high level of importance and acknowledgement over more than 200 years, some anti-vaccine movements have taken place in many parts of the world. These were frequently based on unscientific reasons or even scientifically disproved (WHO, 2002b; Offit, 2005).[117,118] This has caused important impacts on public health, such as the resurgence of some diseases and distrust in vaccines (Andre, 2003), to drug companies, with rising

[116] An effective vaccine against influenza has been available since the 1940s but, as there are hundreds of different viruses causing influenza, production depends on the identification and isolation of the influenza virus strain each season. The process is similar for this new swine flu virus.

[117] The existence of anti-vaccine movements is not recent. Since the times of Jenner in the 18th century (see sub-section 5.2.2 for more details about Edward Jenner and his discovery), when some people were afraid of becoming cow-like hybrids if they were inoculated with the bovine material for the immunization against smallpox (Andre, 2003), there have been reports about these movements. In Brazil, a movement known as "The Rebellion of the Vaccine" took place in 1904 against a government law obliging the population to be vaccinated against smallpox (Benchimol, 2001). More recently, there have been several unproven associations between vaccines and heath conditions. Andre (2003:595) lists some of these associations in countries such as Scotland, Japan, Canada, France UK and US.

[118] Adverse events post-vaccination have occurred, however, and are largely described in the literature. See, for example, Andre (2003), Plotkin and Plotkin (2004) and Hinman et al. (2006).

liability risks and possibility of litigation (Vandersmissen, 2002), and of R&D costs due to tighter regulatory issues (Wilson et al., 2007).[119,120]

> … no medical product is 100 percent (sic) safe or effective. Vaccines have been proven, over decades, to be one of the safest and most powerful disease prevention tools available (FDA, web page, accessed in 9/2009).[121]

In fact, and paradoxically, the main and biggest manufacturers and developers of vaccines nowadays are a few multinational pharmaceutical companies. These companies mainly make their revenue and profit from the drug market, which is estimated to be more than 50 times larger than the vaccine market, and considered much more profitable and much less risky (Gréco, 2001; Vandersmissen, 2002; Plotkin, 2005c; Hinman et al., 2006). The forces which have caused manufacturer's withdrawals from the vaccine market are still present (Vandersmissen, 2002).[122] Moreover, even though 60% of the demand for vaccines in volume terms is in poor countries (Blume, 2005), the new vaccines are often developed to address diseases of the developed world and are, in many cases, not suitable for the same disease in developing countries (WHO, 2002b; Mahoney et al., 2007).[123]

From the scientific point of view, however, there is a prolific way and great expectation for the near future in terms of new vaccines and vaccination, as noted by many authors (e.g. Galambos, 1999; Andre, 2003; Plotkin and Plotkin, 2004; Plotkin, 2005b). Besides, as several important infectious diseases are still not preventable by vaccines (e.g. malaria, HIV, hepatitis C, Dengue, SARS, leishmaniasis and avian influenza), and new ones have emerged through mechanisms such as mutation, transformation and

[119] A typical example of impact on the firms is the case of the Lyme vaccine. This recombinant vaccine, the first against the disease, was linked to some adverse effects and, although never proven, this fact negatively impacted on the sales and led the manufacturer (GSK) to withdraw the vaccine in 2002, a few years after its licensing (Plotkin, 2005c; Wilson et al., 2007).

[120] Most authors do not associate the tightening of regulatory requirements to the existence of anti-vaccine movements, but to the evolution of good clinical and manufacturing practices (e.g. Andre, 2003), or to the need to ensure the potential safety of the vaccines (e.g. Milstien and Candries, 2002). Plotkin (2005a), however, mentions the societal aversion to risk as causing the regulators to apply the "principle of precaution" on the tightening of the regulatory requirements.

[121] http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm133806.htm

[122] The industry and the economics of vaccine are better developed in Chapter 6.

[123] According to the report of the WHO, different types and often more dangerous forms of organisms prevalent in developing countries, especially amongst children suffering from malnutrition, may cause the same disease found in developed countries. This is one of the constraints to the adoption of some new vaccines in poorer countries (WHO, 2002b:xi). Mahoney et al. (2007:4004) give the example of the 7-valent Pneumococcal conjugate vaccines, which serotypes covered are the ones prevalent in developed countries and its effectiveness in developing countries is still not proved.

interspecies transfers, much needs to be done and new technologies will evolve from old ones, according to Plotkin (2005a).

> By helping to reduce the burden of disease, new, improved and more accessible vaccines will contribute to international efforts to achieve the Millennium Development Goals and to global efforts to reduce poverty, and should lead to a safer and more equitable world (Kieny and Girard, 2005:5706).

5.2.2 History at a Glance

Curious procedures, such as the blowing of powdered pox crusts into people's nostrils in ancient China or the intake of snake venom by Indian Buddhists in the 7th century, are described in the literature as some of the earliest attempts at immunization (Hilleman, 2000; Gréco, 2001; Plotkin and Plotkin, 2004). However, documented initiatives of systematic "variolation", the introduction of dried material from smallpox pustules into healthy individuals, date from the 17th century (Bazin, 2003; Plotkin and Plotkin, 2004). The technique of variolation spread to many parts of the world during the 18th century, when smallpox became the most terrible disease, but it could lead to several fatal reactions and further contagions from newly variolated people; this meant that people were hesitant to use this method (Bazin, 2003; Plotkin, 2005b).

The word vaccine was coined by the English doctor Edward Jenner in 1798, following the completion of his successful experiments on preventing smallpox (BBC, web page, accessed in 11/2007).[124] Indeed, this was the first scientific attempt to control an infectious disease (Plotkin and Plotkin, 2004). Besides being a result of scientific work, the "vaccine" developed by Jenner was innovative as it used another known infectious disease, cowpox, as the principle to immunize against smallpox.[125] The great advantage of Jenner's discovery over the variolation technique was that cowpox was a less aggressive illness in humans. The sciences of vaccinology and immunology were born then (Hilleman, 2000).

After Jenner the road to the development of new vaccines was not an easy one. The achievements were thanks to advances in science and revolutions in vaccinology, as approached by Plotkin (2005a). Almost 90 years later, the development of the second

[124] Available online at www.bbc.co.uk/history/historic_figures/jenner_edward.shtml .
[125] The work of Jenner – "Variolae Vaccinae" – was published in 1798 by the Royal Society (see web page cited in the previous footnote).

human vaccine was then made possible. The French scientist Louis Pasteur developed the rabies vaccine in 1885 following his successful experiments in modifying the virulence of microorganisms.[126] Shortly after, still in the 19th century, new vaccines were developed for typhoid, plague and cholera thanks to another new technique of dealing with microorganisms – the inactivation.[127]

During the last century the world saw great advances in the development of new vaccines, major discoveries have become vaccines, and vaccination has become the greatest ally in reducing mortality and controlling several infectious diseases. In the 1920s and 1930s new vaccines against seven different infectious diseases were introduced. Table 5.3 presents the chronology of vaccine introduction in the world by each of the main technological approaches discussed in the next section. However it was after World War II, when most of the currently used vaccines were introduced, that the golden age of vaccine development was reached (Plotkin and Plotkin, 2004). During the war, and in the first decades after the war, the United States became the driver for breakthroughs in vaccinology and for the development of new vaccines since the most advanced European countries were recovering from the devastation of the war (Galambos, 1999). According to Hilleman (2002:25) the "modern era vaccines" were starting.

In the 1950s and 1960s the vaccine business – development, production and marketing – was carried out mainly by the public sector and small enterprises. From the 1970s onwards, again pushed by breakthroughs in science (and with the development of new and more technologically sophisticated vaccines, the tightening of manufacturing practices and the increasing costs of R&D, manufacturing and marketing), the actors have changed. Large pharmaceutical enterprises now dominate the scene (Blume and Zanders, 2006) whilst several smaller manufacturers have left the market (Hinman et al., 2006).

[126] Just before the development of the rabies vaccine, Pasteur developed other vaccines against diseases such as chicken cholera and anthrax. However they were developed for animals and were not to be administered to humans. These vaccines are acknowledged by some authors as the first vaccines using the same agent that caused the disease, and different from Jenner's vaccine (Plotkin and Plotkin, 2004).

[127] The isolation of bacteria and viruses, the "germ theory", and the concepts of antibodies and cellular immunity are described in the literature as important advances in science that made the development of vaccines possible after the rabies vaccine of Pasteur in the late 18th century (Bazin, 2003; Plotkin and Plotkin, 2004). The discoveries of Jenner and Pasteur were, in fact, considered totally empirical as they didn't know how the vaccines actually generated protection (Bazin, 2003; Orsenigo et al., 2006).

More than 200 years after they were first developed, the history of vaccine is still under construction. The list of diseases for which there is still no vaccine is far bigger than the one with diseases currently covered by licensed vaccines (Plotkin, 2005c:631). On the other hand, the number of general strategies and specific technical approaches for making new vaccines has expanded quickly and become limitless, as noted by Galambos (1999:S9).

5.2.3 Vaccines and Vaccination in Brazil – the beginning of the history

The history of vaccine and vaccination in Brazil is long and interesting. It began in the early 1800s, just after the arrival of the Portuguese Royal Family to settle in Rio de Janeiro.[128] Amongst the initiatives which started the social, political and economic transformation of Brazilian society was the creation of the "Junta Vacínica da Corte" in 1811, a state maintained Institution responsible for disseminating the use of the "Jennerian" vaccine against smallpox (Fernandes, 1999).[129]

Many years later, in the late 1890s, an unknown infectious disease arrived in Brazil through Santos harbour and quickly spread among the population. Bubonic plague was identified by two young physicians, Oswaldo Cruz and Vital Brazil, and the shortage of serum, only produced at that time by the French Pasteur Institute, led to the creation of two new institutions – the Oswaldo Cruz Foundation (Fiocruz) in 1900 and the Butantan Institute in 1901 (Benchimol and Teixeira, 1993).[130] The young physicians were named to organize and direct the new institutions.[131]

Shortly after their inauguration both institutes were able to produce immunobiologicals for several diseases such as Bubonic Plague, Smallpox, Rabies, Diphtheria and Cholera, as well as carrying out important research in the health area that achieved international acknowledgement. It is clear from the literature that both institutes were, at that time,

[128] The Portuguese Royal Family arrived in Brazil in 1908 with 15,000 members of Portuguese society escaping from Napoléon's invasion of Portugal.

[129] The Junta Vacinica da Corte was created with similar orientation to European Institutions such as the English Vaccine Institute and the Chambon of Paris (Fernandes, 1999:31).

[130] Oswaldo Cruz, 27 years old, had recently arrived from France where he attended the Microbiology Course in Pasteur Institute. Vital Brazil worked for the Bacteriological Institute of São Paulo and attended a specialization in laboratory work in Paris.

[131] The Butantan Institute was created by the Government of São Paulo State. The creation of the Oswaldo Cruz Foundation was an initiative of the Government of Rio de Janeiro City. Shortly after, it passed to the Federal Government sphere.

closely connected with the scientific communities of Europe, the United States and Cuba. It is also clear that they followed different paths. While Fiocruz opted for diversifying its activities, carrying out research in parasitological diseases, production of biologicals and teaching, the Butantan Institute specialized in ophiology – research and production of anti-ophidian serums (Benchimol and Teixeira, 1993). In the first decades of the 20th century Brazil was close to the frontier in terms of development and production of biologicals.

Table 5.3: History of vaccine and vaccination in Brazil – key facts 1808 – 1969

Year	Fact
1808	The Royal Portuguese Family arrives in Brazil escaping from Napoléon.
1811	The Junta Vacínica da Corte is created by D. João VI to disseminate the vaccination against Smallpox in the country.
1846	The Instituto Vacínico do Império is created, restructuring the activities of Junta Vacínica da Corte and to introduce the new vaccine against Smallpox developed in Europe in the early 1840s.
1894	The Instituto Vacínico Municipal is created and definitely introduced the new vaccine.
1900	The Oswaldo Cruz Foundation (Fiocruz) is founded (named Instituto Serumtherápico Federal), primarily to produce the serum to fight against Bubonic Plague.
1900	The Ataulfo de Paiva Foundation (FAP) is created (named Liga Brasileira contra a Tuberculose) to fight against Tuberculosis.
1901	The Butantan Institute is inaugurated in São Paulo (named Instituto Serumtherápico de São Paulo) with the same objective as the creation of Oswaldo Cruz Foundation.
1920	The Instituto Vacínico Municipal is incorporated with the Oswaldo Cruz Foundation.
1930	Ataulfo de Paiva Foundation starts the production of the oral BCG vaccine.
1937	Yellow Fever vaccine – Oswaldo Cruz Foundation starts its production in collaboration with, and with technology developed and transferred by, the Rockefeller Foundation (USA).
1942	The Institute of Technology of Parana – Tecpar is created.
1960	Fiocruz starts the production of the new smallpox vaccine developed in-house.[132]
1966	The Smallpox Eradication Campaign begins in Brazil.

Sources: Benchimol and Teixeira (1993); Fernandes (1999); Ministério da Saúde (2003) and FAP (web page, accessed in 05/2008).

During the following decades, especially between the end of World War II and the early 1970s, innovation in vaccines in advanced countries experienced a new and astonishing

[132] Fiocruz was acknowledged by World Health Organization (WHO) as an international supplier of smallpox vaccine to the world campaign of eradication of the disease started in 1967. It also exported this new smallpox vaccine for some Latin American countries during this campaign (Benchimol, 2001).

era with several discoveries and the development of new and safer vaccines (Galambos, 1999). During this period, the conditions of the Brazilian manufacturers deteriorated and they lagged far behind the international technological context (Homma et al., 2003). The lost competitiveness of the Brazilian pharmaceutical industry as a whole was due to the lack of investment in R&D (interview 19).

The second phase of this history starts in the early 1970s with the re-emergence of the Brazilian vaccine industry and of some manufacturers. This period is the main focus of this research and it is approached in detail in the next two chapters.

5.3 Innovation on Vaccines

In this section the advances in vaccinology and the technological breakthroughs that gave sustainability to innovation on vaccines are detailed in Sub-section 5.3.1. In Sub-section 5.3.2 the actors of the innovation on vaccines are briefly introduced. The last sub-section is dedicated to the demonstration of some specificities and complexities of and capabilities needed in the process of developing vaccines (Sub-section 5.3.3).

5.3.1 Cycles and Breakthroughs

Historians have described the advances in vaccinology and the development of vaccines in many different ways. The “waves” or “revolutions” of Plotkin (2005a, b), the “steps in immunization” by Bazin (2003), the “eras” of Galambos (1999) or the “breakthroughs” of Hilleman (2000) have made the history in this field both clear to understand and interesting to read, as briefly reviewed in Sub-section 5.2.2.

According to Galambos and Sewell (1995), the process of innovation in the vaccine industry has been characterized by a long cycles pattern. Since Pasteur’s time the authors identified four cycles that exerted major influences in the subsequent development of vaccines. The first, in the late 18th century and beginning of 19th century, was the original bacteriology cycle that influenced the development of most of the new vaccines until the 1930s. The second long cycle, the virology, exerted strong influence in the development of viral vaccines from the mid-1950s to the late 1970s. The third, the new bacteriology of polysaccharide capsules, has influenced the innovation of new bacterial vaccines from the early 1970s, and the fourth, based on advances in

recombinant DNA technology and molecular genetic, has been the main source of innovation since the mid-1980s.

Indeed, science and technology have evolved *pari passu* in the field of vaccinology. Along with other advances in science, new approaches in dealing with microorganisms were of fundamental importance to the development of new and improved vaccines, and they are in close proximity with the long cycles described by Galambos and Sewell. The most important scientific and technological breakthroughs are briefly described below. They are not necessarily in chronological order as some of them came about contemporaneously. Table 5.4 outlines the main strategies used to develop most of the vaccines over time.

a. Attenuation

Regarded as the first major advance in vaccinology since Jenner's vaccine, the attenuation of live microorganisms, developed by the French scientist Louis Pasteur, was a serendipitous discovery (Plotkin, 2005a).[133] The process of attenuation consists of the artificial modification of the virulence of a microorganism in order to induce the protection against the disease caused by the microorganism as well (Bazin, 2003). Attenuation of live microorganisms has been the concept for the development of several human vaccines since then.[134,135] First was the rabies vaccine, developed by Pasteur in 1885. Tuberculosis and Yellow Fever, in the early 20th century, and Varicella and Rotavirus, in recent times, are examples of other vaccines made of attenuated live microorganisms. Therefore, the importance of attenuation persists to the present time, since the use of live microorganisms to make vaccines has advantages for preventing some specific diseases. They may elicit broader immune responses, may require fewer doses and produce generally longer lasting protection (Ellis, 1999:1597).

[133] Pasteur left a chicken cholera culture exposed to air on the bench by chance during his summer holiday in 1879. When he returned he decided to inoculate it into chickens but it did not cause the disease. Further experiments with fresh cultures proved the same; chickens had received protection against the disease (Plotkin and Plotkin, 2004; Plotkin, 2005b).

[134] This research will focus on human vaccines only.

[135] The process of attenuation has been improved over time as new technologies have been introduced to the process. See items c and d about virus cell culture and tissue culture.

b. Inactivation

A new and equally important process of dealing with microorganisms was announced in 1886, only six years after the publication of Pasteur's discovery of attenuation. The Americans, Daniel Elmer Salmon and Theobald Smith, of the US Department of Agriculture, had developed the process of inactivating microorganisms.[136] In their successful experiment they killed salmonella bacteria by heat and injected them into pigeons which were then protected against the same disease (Bazin, 2003). As well as the process of attenuation, the process of inactivation made possible the development of many vaccines, and the concept of non-living vaccines was further developed later on.[137] The first human killed vaccines developed were for Typhoid, Cholera and Plague, just few years after the development of the process (Plotkin and Plotkin, 2004). More recently important vaccines such as inactivated polio vaccine and hepatitis A vaccine were developed using the technology of inactivation (Plotkin, 2005b).

c. Cell Culture

The next major advance took place only in the early 1930s and is represented by the development of the process of virus cell culture. The process consists of growing viruses in embryonated hens' eggs. Until that time the only way of cultivating viruses was in live animals such as ferrets, mice and rabbits; this was considered an obstacle to the development of new virus vaccines (Bazin, 2003). Furthermore, the process developed by the American Ernest Goodpasture, of the Vanderbilt University, proved to be cheaper and safer (Plotkin and Plotkin, 2004), and a new means of attenuating viruses (Plotkin, 2005b). New vaccines, such as a safe and effective yellow fever vaccine and the influenza vaccine, were developed by using this process shortly after. This was the transition time to the new era of vaccine (Hilleman, 2002).

d. Tissue Culture

The tissue culture of cells may be considered the next important advance in terms of process. Tissue culture is a process of cell culture *in vitro* with the use of a growth medium, instead of in hen's eggs as in the traditional method. It was developed by

[136] There were some disputes over the rights for this discovery. Pasteur argued that results of experiments on inactivation were first obtained in his Institute since his disciples Roux and Chamberland had published similar results shortly after the Americans but his claim was proven to be untrue (Bazin 2003).

[137] Other technologies of nonliving vaccines were approached in the following decades. See item e about toxoids and sub-unit vaccines.

scientists at Harvard University just after World War II and opened the way for the development of a safe poliomyelitis vaccine (Blume, 2005).[138] From this discovery the culture of many viruses was also achieved and many other vaccines were developed including Measles, Rubella, Mumps and Varicella (Plotkin, 2005b). However, several other cells would still not grow *in vitro* hindering the development of many vaccines (Bazin, 2003). In addition to allowing the development of new vaccines, the tissue culture method has several advantages over the traditional cell culture method. It's cheaper, much more efficient and safer as the vaccine is free from egg protein, which may cause some adverse effects in people with sensitivity to egg products. Important vaccines, however, such as yellow fever and influenza, are still produced by the traditional method since, to date, it has not been possible to improve their production method because of technological reasons.

e. Toxoids and Sub-unit Technologies

The early 20th century was also the stage for further developments on the technology of inactivated vaccines. In the 1920s a new process of inactivating bacterial toxins by the use of chemicals (formalin) made the development of diphtheria and tetanus toxoids possible (Plotkin and Plotkin, 2004). The process was developed by the British immunologist Alexander Glenny, of Wellcome Physiological Research Laboratories, even though this discovery is also claimed by the German Gaston Ramon who worked at the Pasteur Institute (ODNB, web page, accessed in 11/2007).[139] Later on, as whole cell vaccines were considered dangerous and technology advanced, it became possible to separate and use sub-units of organisms in the development of several vaccines (Plotkin, 2005b; Bazin, 2003). Examples of sub-unit technologies developed are the extracts of infected tissues, capsular polysaccharides, purified or recombinant proteins and, more recently, protein-conjugated capsular polysaccharides (Plotkin, 2005b). The sub-unit vaccines have some important advantages as they are unable to replicate in the host and therefore cannot revert into pathogenicity. Furthermore they are generally less reactogenic, non-transmissible and usually more feasible technically (Ellis, 1999:1597).

[138] The work "Cultivation of the lansing strain of poliomyelitis virus in cultures of various human embryonic tissues" was published in 1949 by Enders et al in the journal Science.
[139] Available on line at http://www.oxforddnb.com/view/article/33424 .

Table 5.4: Main Technological Strategies for Developing Vaccines and Vaccines Developed Over Time[1]

Attenuation (Live)	Inactivation (Killed)		Genetic Engineering	Combination[2]
	Whole Organisms	Sub-units – Extracts, Toxoids, Protein or Polysaccharide		
18th Century				
Smallpox (1798)[3]				
19th Century				
Rabies (1885)	Typhoid (1896) Cholera (1896) Plague (1897)			
1920s and 1930s				
Tuberculosis/BCG (1927) Yellow Fever (1935)	Pertussis (1926) Influenza (1936) Rickettsia/Typhus (1938)	Diphtheria (1923) Tetanus (1927)		DT (1926)
After World War II				
OPV (1958) Measles (1963) Mumps (1967) Rubella (1969) Adenovirus (1971) Varicella (1984) Typhoid (1989) Rotavirus (1998) – withdrawn new Rotavirus (2006) Zoster (2006)	IPV (1955) Rabies/cell culture (1976) Hepatitis A (1991)	Japanese encephalitis (1944) Meningococcal (1972) Pneumococcal (1976) Hepatitis B (1981) Acellular Pertussis (1981) Hib (1985) Hib conjugate (1987) Typhoid Vi (1994) MCCV (2000) PCV (2000) Anthrax (2002)	Hepatitis B (1986) Lyme (1998) – withdrawn Human Papillomavirus (2006)	DTPw (1957) DT+IPV (1961) DTPw+IPV (1966) MMR (1971) DTPw+IPV+Hib (1988) DTPa (1994) DTPw+HBV (1996) Hib+HBV (1996) DTPa+Hib (1997) DTPa+IPV+Hib (1997) DTPa+HBV+IPV (2000) DTPa+HBV+IPV+Hib (2000) HAV+HBV (2001)

1. Not exhaustive. 2. The strategy of combination may bring together components developed by other different strategies (e.g. DTPa – whole organisms and sub-unit). In this column only combination of vaccines for different diseases were considered. 3. Between parentheses the approximate year of introduction of each vaccine in the market. For some of the most recent vaccines the dates are based on the approval by FDA. Legend: OPV – Oral Polio Vaccine; IPV – Inactivated Polio vaccine; Hib – *Haemophilus influenzae b*; MCCV – Meningococcal C Conjugate Vaccine; PCV – Pneumococcal Conjugate Vaccine; DTPw – Diphtheria, Tetanus and whole cell Pertussis; MMR – Measles, Mumps and Rubella; DTPa – Diphtheria, Tetanus and Acellular Pertussis; HAV – Hepatitis A Vaccine; HBV – Hepatitis B Vaccine.
Source: Adapted from Plotkin and Plotkin (2004). Other sources: Jordan (2002); Hilleman (2002); Andre (2003); Plotkin (2005b); Wilson et al. (2007) and FDA (web page, accessed in 09/2009).

f. Combination

Little has been said by the authors about the process of the combination of vaccines during the 20th century. Combination is a process by which immunogens for different diseases are combined into a single product. Vaccines made of different types of virus, or different Serotypes/Serogroups of bacteria of the same disease, are also considered combined vaccines.[140] The process was first developed in 1926, when the French scientist from the Pasteur Institute, Gaston Ramon, and his colleague Christian Zoeller combined the Diphtheria and Tetanus toxoids (DT) (Pasteur, web page, accessed in 11/2007).[141] The DTP (Diphtheria, Tetanus and Pertussis), DT+IPV (DT combined with Inactivated Polio vaccine), DTP+IPV, MR (Mumps and Rubella), MMR (Mumps, Measles and Rubella) and Meningococcus AC are examples of other combined vaccines commonly in use before the 1980s (Andre, 2003; Hilleman, 2002). However, combined vaccines have been more emphasized as recent discoveries (Plotkin, 2002) or a candidate for the next revolution in vaccinology (Plotkin, 2005a) since the development and licensing of more complex combinations has been achieved since the late 1980s. In fact, the importance of combined vaccines has increased recently as they reduce the costs of public campaigns, diminish the suffering of children and ease the vaccination coverage.

g. Genetic Engineering

It seems to be common sense amongst many authors that the advent of molecular biology and genetic engineering in the 1950s provided a dramatic influence on vaccine development (Bazin, 2003; Galambos, 1999; Plotkin, 2005b, a; Milstien, 2005). However, even though there have been many achievements in this field, and many vaccine candidates are already in Phase III trials, only a few human vaccines against widespread disease and developed by using this technology are currently in use. The first one is the recombinant Hepatitis B vaccine, which was licensed in 1986. Besides being the first recombinant vaccine developed, recombinant Hepatitis B vaccine is also acknowledged as the first human vaccine against cancer (Hilleman, 2000). In 1999 a recombinant Lyme vaccine was licensed by the FDA but it was withdrawn from the market three years later due to low acceptance (Plotkin and Plotkin, 2004). Quite

[140] DTP is an example of a combined vaccine using immunogens for three different diseases (Diphtheria, Tetanus and Pertussis). The Oral Polio Vaccine and the Inactivated Polio Vaccine are combined vaccines using three different types of virus of the same disease.

[141] Available on line at http://www.pasteur.fr/infosci/archives/f-bio.html .

recently the technology for producing a Human Papillomavirus vaccine (HPV) by genetic engineering was developed by scientists at the National Cancer Institute (NCI) in the USA and licensed to two pharmaceutical companies. The vaccines were then developed and licensed by the FDA in 2006 and 2008. Amongst the advantages are that genetic vaccines elicit cellular immune responses and have a standardized method of production (Ellis, 1999:1597). In addition, the use of genetic engineering technology provides opportunities for the construction of inactivated antigens and for rational attenuation of organisms through direct mutation.

h. Adjuvants and Delivery Systems

Innovation on vaccines is also approached here in a broader perspective. In parallel to the development of the technologies to deal with microorganisms described above, are other important technologies that have been developed to enhance the power of vaccines. *Adjuvants* are molecules developed to enhance, accelerate, modify or prolong the immune response to the vaccine antigens (Vogel and Alving, 2002:39). They are a necessary component of many vaccines (Liu, 2002). Non-live vaccines and highly purified or recombinant antigens, for example, need adjuvants to enhance their immunogenicity (Ellis, 1999; Vogel and Alving, 2002). The first type of adjuvant, the Gel-type, was first described in the 1920s, and remains the most common in use so far.

New delivery systems have been developed to both enhance immunity and the comfort of the patient. The most common way of administering vaccines are the subcutaneous or intramuscular injections. Oral vaccines, however, have existed since the 1950s. The first one was the Oral Polio Vaccine developed by Sabin. Rotavirus is a more recent example of oral vaccine. Another mucosal means of administering vaccine today is the intranasal. An intranasal vaccine against influenza A and B has been registered in the US since 2003 (FDA, web page, accessed in 9/2009).[142] In addition to not requiring the use of needles and syringes, reduced adverse effects, immunization directly at the site where many infections start and the possibility of administration by non-healthcare professionals are amongst some of the advantages of these types of delivery system (Liu, 2002).

[142] http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094047.htm .

5.3.2 The Actors

Innovation on vaccines must also be approached from another important perspective: the actors of the process. When we approach the innovation on vaccines in its full extent it becomes clear that it is full of specificities, even within the pharmaceutical industry whose subsectors are considerably different (Nightingale and Mahdi, 2006). Vaccine R&D has often been characterized by the involvement of quite complex network of relationships and collaboration amongst multiple actors (Galambos and Sewell, 1995; Galambos and Sturchio, 1996; Galambos, 1999; Wilson et al., 2007). Two distinct periods are being highlighted here: the periods before and after WWII. Within the period from Pasteur until WWII there is a lack of comprehensive data specifically focusing on this issue (Wilson et al., 2007). However, it is possible to point out a predominance of research and public institutions and non-profit organizations as the main actors of the process even though a limited participation of small private companies is also identified.[143,144]

Yet the most recent period, post-WWII, was driven by the massive investments of the US government in vaccine research and development, and by a new network of public, private and non-profit organizations supporting vaccine development and distribution. Amongst the latter were organizations such as the United Nations, the World Health Organization and the World Bank Group (Galambos, 1999:S8). From this time on it is possible to devise a new division of labour in the process of vaccine R&D (Mazzucato and Dosi, 2006). For the majority of vaccines developed since then, basic research has been carried out by universities and public or non-profit research institutions, often financed by public funds. On the other hand, technological development, clinical trials, licensing and manufacturing have been conducted by industry, as noted by Wilson et al. (2007).

Four models of vaccine development are then identified by these authors to characterize the role of each actor in this period:

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[143] This idea draws upon the events approached and in the literature cited in the previous sections of this chapter. Galambos and Sewell (1995) and Galambos and Sturchio (1996) are exceptions of works approaching this issue from an historical perspective.

[144] The few companies dedicated to the business of biologicals were small at that time (Galambos and Sturchio, 1996). The large and integrated pharmaceutical companies of the first half of the 20th century were dedicated to the development and manufacturing of drugs (Galambos and Sturchio, 1996; Mazzucato and Dosi, 2006).

a. predominantly private sector development;
b. public (or non-profit) sector vaccine design, with a handover to the private sector for trials and manufacturing;
c. predominantly public sector development; and
d. coordination by a non-profit entity (*ibid.* p.1).

Table 5.5 lists some vaccines developed after WWII by each of the development model described by the authors.

Table 5.5: Models of Vaccine Development – Actors and Vaccines

Vaccine Development Model Vaccine Developed
a. Predominantly Private Sector development
Cholera, inactivated (1952)
Mumps, live (1967)
Hepatitis B, plasma-derived (1981)
Hepatitis B, recombinant (1986)
Typhoid Vi polysaccharide (1992)
Pneumococcal conjugate, 7-valent (2000)
b. Public Sector vaccine design, with handover to the private sector for trials and manufacturing
Measles, live (1963)
Rubella (1967)
Pneumococcal polysaccharide (1977)
Typhoid, live oral (1981)
Hib polysaccharide (1985)
Hib conjugate (1988)
DTaP (1991)
Hepatitis A (1991)
Cholera, live oral (1994)
Varicella (1995)
Lyme disease (1998)
Rotavirus (1998)
Influenza, live attenuated intranasal (2003)
HPV (2006)
Rotavirus, live oral pentavalent (2006)
Zoster (2006)
c. Predominantly Public Sector development
Influenza (1945)
Mumps, inactivated (1948)
Adenovirus (1957)
Polio, oral trivalent (1963)
Anthrax (1970)
Meningococcus polysaccharide (1974-5)
Adenovirus, live oral (1980)
Meningococcus (types B and C) (1989)
Japanese encephalitis B, killed (1992)
d. Coordination by a Non-profit Entity
Inactivated polio (1955)

Source: Adapted from Wilson et al. (2007:20).

Other actors have been of growing importance in this process. The boom of biotechnology firms (Biotechs) since the 1980s is a phenomenon that has directly affected the network of innovation. Apart from drugs against cancer, vaccine development and manufacturing has been the main business of these firms (Milstien, 2005).[145] Along with universities and public research institutions, biotechs concentrate their capabilities mainly on upstream research, (Mazzucato and Dosi, 2006), as they lack the essential capabilities to compete with the "Big Pharma", even though some clinical and financial successes have taken place (Nightingale and Mahdi, 2006). Within this new network of innovation the diffusion of technological knowledge from the Biotechs to the "Big Pharma" has often been through alliances (Rothaermel, 2001; Nightingale and Mahdi, 2006).[146]

Indirect actors have also exerted important influence in the process of vaccine innovation today. The national regulatory authorities have provided increasingly tighter regulations and guidance both to the pre-marketing and post-marketing phases (Baylor and McVittie, 2002).[147] Government agencies, such as the NIH in the US, have provided significant financial resources for vaccine R&D. Non-governmental organizations, such as UNICEF, GAVI Alliance and IAVI, have also provided important support and funds for the development and distribution of vaccines.[148]

5.3.3 Developing Vaccines – Complexities, Steps and Capabilities

Whatever the technology used, the process of development of a vaccine is very complex and long. The average time for the development of a product is estimated to be between 10 and 15 years but it can take longer (Homma et al., 2003). A vaccine against HIV, for example, has been pursued unsuccessfully for more than 20 years.[149] As time has passed, technical requirements to license a human vaccine have become stricter, and new pre-clinical and clinical trials have been required in order to make the products safer. The

[145] The boom of Biotech firms has its origins in the US Bayh-Dole Act in 1980, which allowed universities and small enterprises to patent discoveries and license them to the large pharmaceutical firms even when the research had been financed by the public funds of NIH (Mazzucato and Dosi, 2006).
[146] The case of Biotechs is also approached in Chapter 6, Sub-section 6.2.2 (pg. 125-128).
[147] Food and Drug Administration (FDA) in the USA, European Medicines Agency (EMEA) in Europe and Agência Nacional de Vigilância Sanitária (ANVISA) in Brazil are examples of national regulatory authorities.
[148] These and other actors are also approached in the section about Government and Institutions in the next chapter on pg. 151-161.
[149] The Jordan Report 2000 (NIH/NIAID, 2000:85) reports HIV vaccine studies funded by NIAID since 1987 involving a great range of actors.

investments required became huge and returns uncertain, which makes the business too risky (Hinman et al., 2006). Estimations suggest that the cost of vaccine development ranges between US$300-800 million (Plotkin, 2005c),[150] and few manufacturers have managed to accomplish all the stages of a vaccine's development (Orenstein et al., 2007). In fact, most projects fail. Table 5.6 below outlines the status of vaccine R&D in 2006 and the probabilities of launching in each of the R&D phases.

Table 5.6: Vaccine R&D Projects – Status and Market Entrance Probabilities

Basic Research	Pre-clinical	Clinical Trials I	Clinical Trials II	Clinical Trials III	Registration
Status of Vaccine R&D in 2006 – 448 Vaccine Projects / 115 Target Agents(1)					
84	180	68	63	53	-
Market Entrance Probability(2) - %					
-	22	39	54	68	96

Own elaboration
(1) *Source*: NIH/NIAID (2007:Appendix A). Data refers to publicly available information only. HIV projects not included.
(2) *Source*: Struck (1996).

The complexities of vaccine development may be illustrated in other ways. Compared with drugs, there is no bioequivalence procedure for vaccines, which means that there are no "generic" vaccines and therefore any new or improved vaccine should go through at least limited clinical trials (Milstien et al., 2007). Moreover, as briefly approached in footnote 123 of Sub-section 5.2.1 (pg. 95), the same disease may be caused by different microorganisms due to specific population characteristics (WHO, 2002b:xi), which makes the development of potential globalized vaccines technologically challenging (Milstien and Candries, 2002).

According to Homma et al (2003), the typical process of development of a vaccine comprises seven main steps. However, these authors emphasize that this process is far from being linear since the need to return to previous steps is not uncommon. Additionally, as pointed out by Bomtempo & Baetas (2005), the frontiers of these steps are flexible since some activities are superposed. The basic steps are summarized as

[150] The cost of the development of the live attenuated influenza vaccine may have exceeded US$ 1 billion (Orenstein et al., 2007).

follows, based on Homma et al. (2003) and Bomtempo & Baetas (2005), and represented in Figure 5.1.

Step 1 – Discovery/Invention: in this first step basic research is performed in very well equipped laboratories and by very skilled and multidisciplinary researchers and technicians to set up a scientific understanding of the etiology of the disease, the interactions between human being and pathogen, and the immune response of the human being. Researches on new adjuvants and molecules are also performed within this step. Infectology, biochemistry, epidemiology, immunology and microbiology are amongst the main capabilities required. Molecular biology, genetic engineering and studies on the genome are increasingly used technologies in this phase.

Step 2 – Pre-development studies: this step includes studies on the identification and analyses of the antigen(s), on the modification of its virulence and on the determination of its stability and immunogenicity. In addition, material is specified and several studies are repeatedly performed in the same conditions and parameters in order to standardize the methodology of production, to obtain the biological and physic-chemical characterization, to test the reproducibility, to establish the parameters of scaling-up and, in short, to show its technical feasibility to become a product. Similar capabilities are required in this step.

Step 3 – Candidate Vaccine and Pre-Clinical Trials: in this step a candidate vaccine is designed, developed and produced for the pre-clinical studies. This includes adjuvants selection, vaccine presentation (e.g. liquid or freeze-dried, intramuscular or oral) and formulation parameters. The pre-clinical trials consist of evaluating the inocuity, reactogenicity, toxicity and immunogenicity of the potential vaccine to determine the level of risk of inoculating it in humans. The tests are performed in selected *in vivo* animals especially grown for use in research, and in laboratories that comply with Good Laboratory Practices (GLP). Veterinarians are amongst the professionals performing these activities.

Step 4 – Vaccine for Clinical Trials: since an acceptable level of risk in administering the potential vaccine in humans is demonstrated in the pre-clinical trials phase, experimental lots of the vaccine are produced to be tested in clinical trials. The lots are

produced in pilot plants that simulate the same conditions of production facilities.[151] The scale-up process encompasses an industrial dimension and Good Manufacturing Practices (GMP) are required. The commercial feasibility is determined in this phase. New capabilities are incorporated for the development of these activities, amongst them engineering (chemistry, biochemistry, production, economic), marketing and regulation. In this phase the seed lot is prepared to assure the reproducibility of subsequent lots. All the parameters defined in this phase cannot be modified after the clinical trials otherwise new trials will be required.

Step 5 – Clinical Trials: these trials are very complex and sensitive since they are carried out on human beings. With the introduction of new regulatory and safety standards, clinical trials have become the major expense in the process of development (Milstien and Candries, 2002) and may take several years to be carried out. They are divided into three distinct phases:

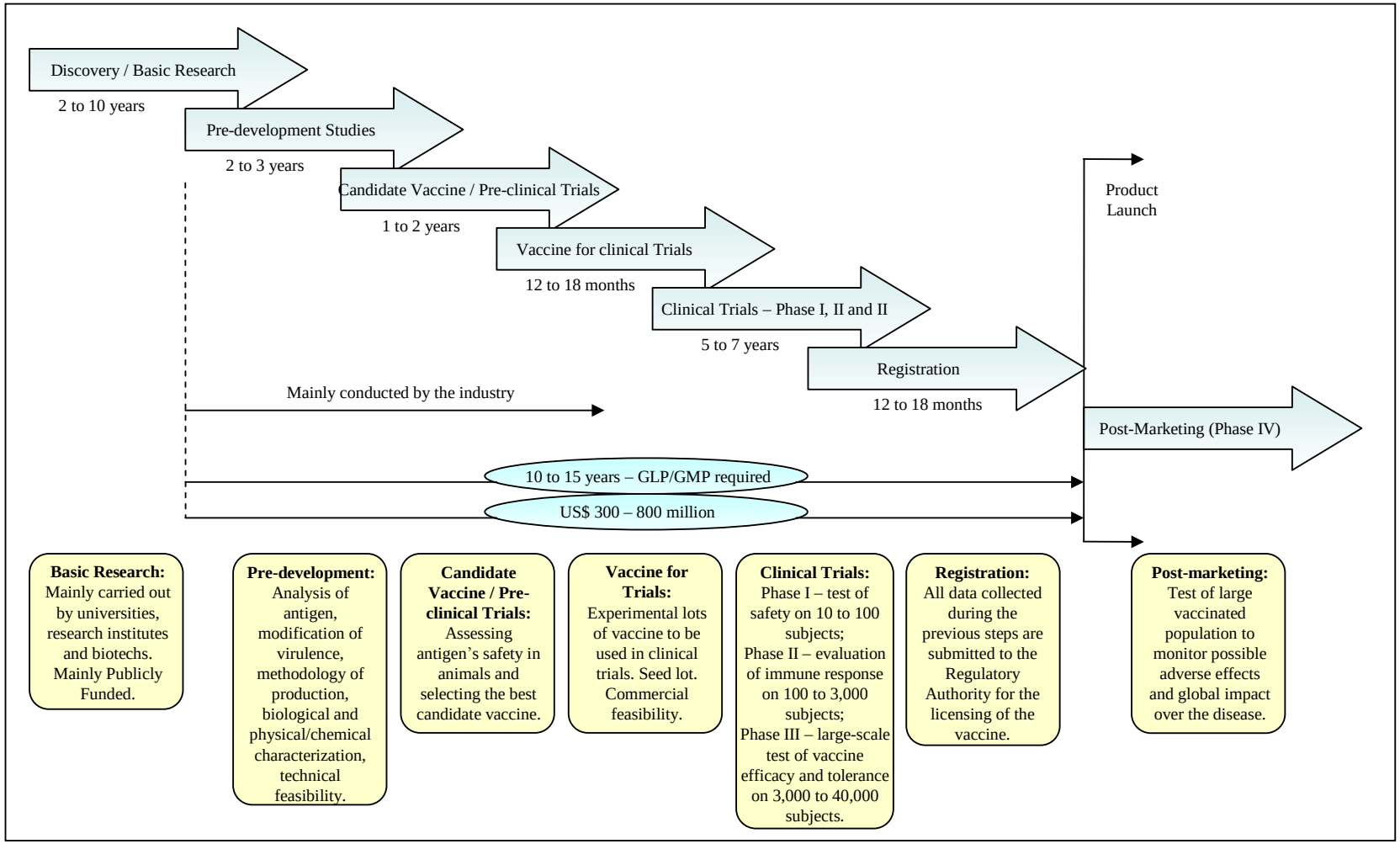
- Phase I: the safety of the vaccine is tested in a small number of adults and healthy volunteers;
- Phase II: the immunogenicity of the product is tested in an amplified population. In this phase the real product is compared to a placebo and the adverse effects studies are extended;
- Phase III: the efficacy of the vaccine is the main purpose of the tests in this phase, which are carried out on a larger population preferably from endemic areas. The immunogenicity and adverse effects studies are complemented in this phase.

When performing clinical trials for an improved vaccine, the old one should be used as a reference during the tests: Good Clinical Practices (GCP) should be observed during these trials (Milstien, 2005). The capabilities required for performing clinical trials are somewhat different, as shown by Bomtempo & Baetas (2005), and include ethical procedures. Moreover, they are restricted to a limited number of research centres (WHO, 2002b). There is a trend, therefore, to outsource the clinical trials to specialized organizations also called Contract Research Organizations (CROs) (Milstien and Candries, 2002).

[151] The vaccine for Clinical Trials Phase III is produced in the production facilities (interview 11).

Step 6 – Registration – Detailed documentation about the development, production and quality control methodology, and pre-clinical and clinical trials results, must be submitted to the regulatory authority in order to obtain the license to market the product. Once licensed the product cannot be modified in any of its characteristics otherwise new studies must be carried out and the results re-submitted to the regulatory authority. For this step, deep knowledge about the regulation is required.

Step 7 – Post-Marketing Trials: also called Clinical Trials Phase IV, this step is performed after the commercialization of the licensed vaccines and consists of testing a large population of vaccinated people to monitor the results of the vaccination with regard to both any adverse effects – rare or delayed adverse reactions not detected in smaller trials – and to the global impact over the disease. The tetravalent rhesus-based recombinant rotavirus vaccine, for example, was withdrawn from the market after some adverse risks were identified in the post-licensure tests (Hinman et al., 2006; Milstien and Candries, 2002).



Own elaboration. *Source*: Homma et al. (2003), Leal (2004), Moreira (2005) and Plotkin (2005c)

Figure 5.1: Developing a Vaccine: Key Steps and Aspects

5.4 Manufacturing Vaccines

The previous section has shown the complexity of the innovation process on vaccine. Manufacturing vaccines is also very complex on technological grounds.[152] Vaccines are biological substances and their manufacture is considerably different and more complicated than drugs manufacture, which involves chemical systems rather than biologic systems (Gréco, 2001; Hinman et al., 2006). Moreover, vaccines are administered to healthy people, often children, which requires higher standards of safety than those for substances which are administered to sick patients (Offit, 2005; Milstien et al., 2007). As they are biologically variable, the characterization and reproducibility of the product is very difficult, and their safety and efficacy must be consistently shown (Gréco, 2001; WHO, 2002b). This requires strict conditions for the manufacture of each batch and the whole process must comply with Good Manufacturing Practices (GMP); it is tightly controlled by regulation authorities (Milstien et al., 2007).[153]

> Each step of the production process must be documented and validated. (Milstien and Candries, 2002:74).

> Every single step in the manufacture of vaccines is extremely challenging. (Sheridan, 2005:1359).

Additionally, the technological knowledge required to manufacture a vaccine is eminently tacit, not easily communicated by codified documents (patents or routines) and, therefore, costly and time consuming to acquire (Milstien et al., 2007).[154]

The manufacture of a vaccine can take up to 22 months and the quality control tests are responsible for approximately 70% of the vaccine's total manufacturing time (Sanofi Pasteur, web page, accessed in 7/2009).[155] Vaccines may be classified as viral or bacterial, depending on their etiological agent (Barbosa, 2009). Two main independent

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[152] In this chapter vaccine manufacture is shown under the technological perspective only. Other aspects related to this issue are presented in Chapter 6, about the industry of vaccine.

[153] Good Manufacturing Practices (GMP), as proclaimed by the World Health Organization (WHO) is much broader than simple manufacture procedures. It implies the implementation of a whole quality system that encompasses organizational structure, procedures, processes and resources, managed and supervised by an internal quality assurance area. The manufacturer of pharmaceuticals should be licensed by the local regulatory authority, and assumes total responsibility for the quality of the product (WHO, 2003).

[154] The main way vaccine manufacturing knowledge has been acquired by the Brazilian vaccine industry during technology transfer processes is outlined in Section 7.2.2 on pg. 167-172.

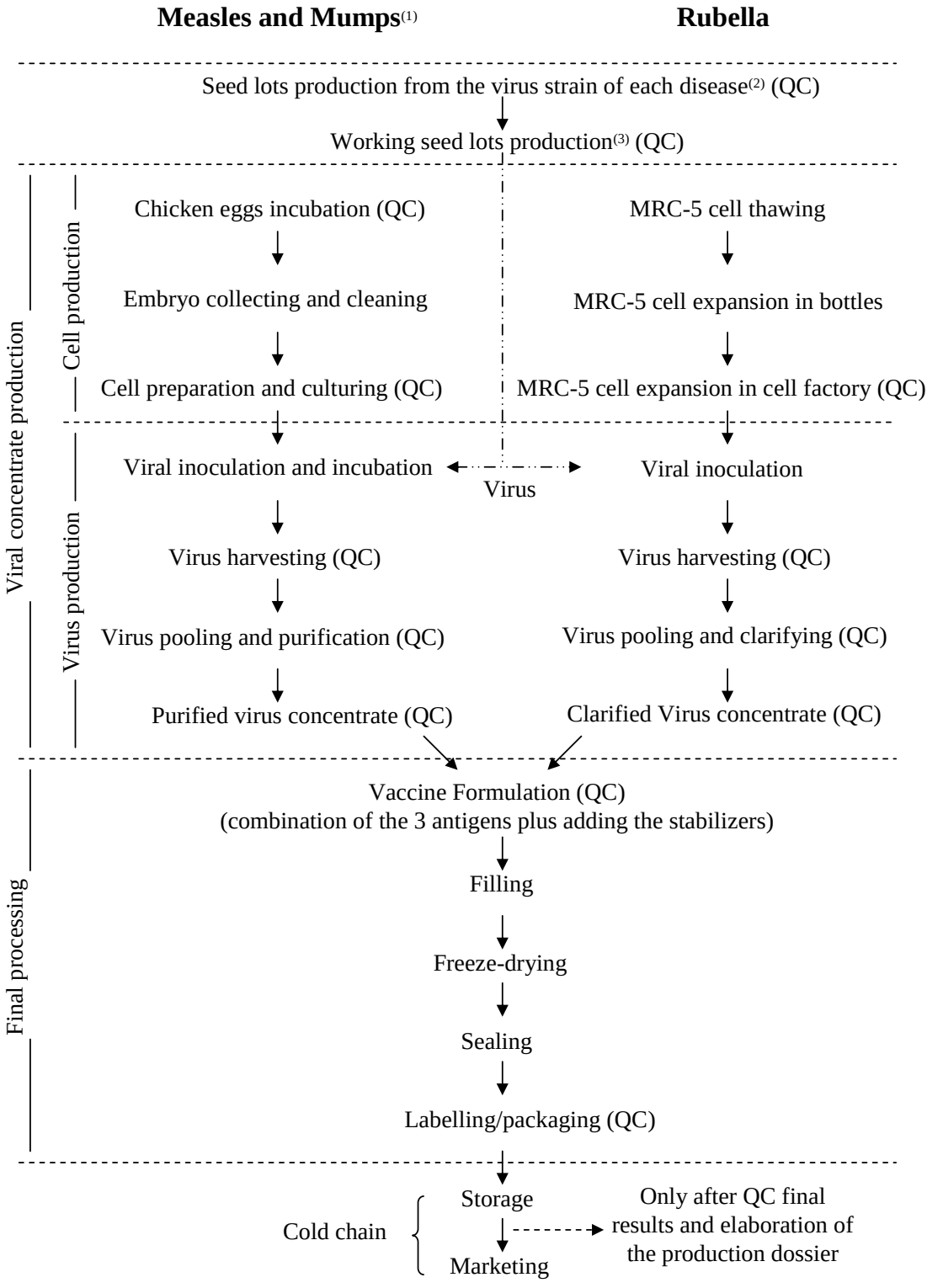
[155] http://www.sanofipasteur.com/sanofi-pasteur2/front/index.jsp?siteCode=SP_CORP&codeRubrique=25

stages can be identified in the process of manufacturing a vaccine: the vaccinal (viral or bacterial) concentrate production and the final processing. The first stage is considered more technologically complex, while the second predominantly involves the domain of capabilities to deal with large industrial equipment in a controlled environment (Temporão, 2002).

At the end of the first stage the concentrate produced may be stored for long periods, often frozen at very low temperatures to retain its physical characteristics. The facilities for the vaccinal concentrate production are built specifically to fit to the technological characteristics and design of the vaccine (e.g. viral, bacterial, attenuated, inactivated etc.). Yet the facilities for final processing are generally multi-purpose and usually encompass technological processes for different types of vaccine presentation (e.g. vials, ampoules, syringes, liquid, freeze-dried, etc.). The main production steps of the triple viral vaccine (Mumps, Measles and Rubella) are represented in Figure 5.2 for illustration.

At the end of the final processing steps the vaccine batch must be kept stored in cold chambers until the release of the final QC tests. As noted by a "Big Pharma" manufacturer, the cold chain must be assured through all stages, including the distribution.[156]

[156] See previous footnote for the reference.



(1) Measles and Mumps viral concentrate production are similar processes but performed independently. (2) The seed lot is prepared during the development of the vaccine. (3) working seed lot is produced from time to time and use to last several years. (QC) Quality Control tests performed at the end of the steps except for chicken eggs, which are performed before.

Own elaboration. *Source:* Data kindly provided by the Department of Viral Vaccines of Bio-Manguinhos/Fiocruz.

Figure 5.2: Main Production Steps of the Triple Viral Vaccine – MMR

Quality control tests are also technologically complex and of fundamental importance to the manufacturing process. They are performed from the beginning and across all the manufacturing processes of the batch. Several different tests are performed at the same time for most of the production steps. QC tests are also performed on materials that are used in direct contact with the vaccine – e.g. reagents, vials, stoppers, etc. – and on some indirect materials – e.g. cardboards and labels for packaging (interview 11).[157] QC results are stated in the production dossier, which must be kept for tracking if needed. Table 5.7 lists the amount of QC tests performed during the production process of the MMR vaccine, not including tests in stabilizers, reagents and other raw materials.

Table 5.7: Amount of QC Tests Performed During MMR Vaccine Manufacturing

Production Step[1]	Vaccine Component / Amount of Tests		
	Measles	Mumps	Rubella
Chicken eggs	2	2	-
Cell cultured/expanded	7	7	7
Virus harvested	5	-	5
Virus pooled	13	13	11
Virus purified/clarified	4	4	4
Vaccine formulated	3		
Final product	15		
Q.C. Tests total amount	**102**		

[1] Refers to the production steps described in Figure 5.2.
Own elaboration. *Source*: Data kindly provided by the Department of Quality Control of Bio-Manguinhos/Fiocruz

5.5 The Future of Innovation on Vaccines

Advances in many fields are pointed out as the drivers for the development of new vaccines. Recent and future remarkable discoveries on immunology, genomics and proteomics, and a broader and more intensive use of molecular biology and genetic engineering, will allow the development of safer and less reactogenic vaccines, new combinations, new adjuvants, new delivery systems, the enlargement of target groups and vaccines for non-infectious diseases (Hilleman, 2000; Plotkin, 2005a). Furthermore, partnerships will be the strategy used by successful manufacturers to gain access to new technologies and markets (Milstien, 2005).

[157] According to the interviewee, direct materials outside of the correct specifications may cause changes in the physical characteristics of the product. Yet the case of indirect materials, products outside of the correct specification may cause damage in the machines of the production line.

On the other hand, R&D on vaccines will face challenging pressures. Growing regulatory requirements, cyclical pressures on governments and non-governmental organizations (NGO) and tighter sales margins, are increasing the costs as well as reducing the number of manufacturers able to invest in new vaccines (Galambos, 1999; Andre, 2003). Moreover, Intellectual Property Rights (IPR), although important to protect and encourage innovations, have not only prevented investigations but also collaboration in particular domains (Plotkin, 2005c). In some developing countries, which emerging manufacturers have tried to move from incremental to radical innovations, IPR has led the manufacturers to technology transfers and licensing agreements to have access to new technologies (Milstien et al., 2007).

All in all, it is expected that during this new era the number of vaccines will double (WHO, 2005). However, the future of innovation on vaccines resides, according to Galambos (1999), on strengthening and not weakening, the three-sided networks – government/non-government organizations, research institutions and private companies – that have been responsible for the sequence of breakthrough innovations during the 20th century.

5.6 Summary

This chapter has inaugurated the description of the empirical issues of this research. More specifically, it seeks to bring to light evidence about the specificities of the field of vaccine in order to allow the building of a link between them and the development of technological capabilities in the BVI, in light of the analytical framework developed in Chapter 3. The issues were described in social, historical, scientific and technological perspectives with evident economic implications across all of them.

Under the social perspective the importance achieved worldwide amongst governments and health authorities by the use of vaccines and consequent reduction of infectious diseases is emphasized. In addition, it is shown that the increasing access to vaccines has been advocated more recently to be linked to the reduction of poverty and inequity across the world. Yet the contrast between the international and Brazilian historical perspective, shows that Brazil has a long tradition in dealing with vaccines and that it was close to the technological frontier in this field in the first half of the 20th century.

The section about innovation on vaccines describes the long cycle pattern of the process, and the scientific and technological breakthroughs that made the development of several vaccines since late the 1800s possible. The almost exclusive role of academia and public institutions in the innovation process of vaccines up to the mid-20th century is also highlighted. On the other hand it was shown that the subsequent period presents a new division of labour in the process of vaccine R&D, with basic research being carried out predominantly by academia, strongly supported by public funds, and downstream development by the "Big Pharma". In this regard, the huge costs of R&D due to tighter requirements to license a human vaccine have favoured the hegemony of the "Big Pharma" in this field. The last sub-section of this section and the following section show how the processes of developing and manufacturing vaccines are complex, requiring very specialized technological capabilities that are costly and time consuming to developed, and constituting an important entry barrier in this sector.

Finally, some expectations about the future of innovation on vaccines raised by experts in this field are presented. As suggested, they encompass a scenario of increasing technological complexity, requiring the domain of new scientific and technological capabilities and new strategies to compete in more competitive markets.

The next chapter continues to examine the empirical issues by addressing the dynamics and organization of the vaccine industry, the markets and their drivers and the role of government and institutions in the support of the development of this sector.

Chapter 6 – Vaccine Industry, Markets and Institutions in Brazil and in the International Context

6.1 Introduction

The last chapter approached the characteristics and complexities of vaccines and of the innovation on vaccines under historical, social and, in particular, scientific and technological perspectives. The focus in this chapter is on the dynamics and economics of the vaccine industry, with the emphasis on its organization, markets and institutions. These have driven important implications on the development of technological capabilities in the field of vaccines.

The organization, dynamics and trends of the vaccine industry are approached in Section 6.2. The markets and economics, with an emphasis on the structure of the Brazilian market, are the issues in Section 6.3. Section 6.4 presents the other actors and the current role of the intricate network of institutions that has been one of the pillars of sustenance to the development of the vaccine industry over time. However, although this gives details of the proposed organization of the chapter, some issues overlap across the sections. Section 6.5 summarizes the whole chapter.

6.2 The Vaccine Industry

In this section the organization and dynamics of the vaccine industry are depicted. For the purposes of this thesis, the industry was divided into three main groups: the aspects of the "Big Pharma" – the global players – are presented in Sub-section 6.2.1. The next sub-section describes the characteristics of the most recent phenomenon of the vaccine industry – biotech firms. Sub-section 6.2.3 approaches the smaller, but of growing importance, firms – private, public and emerging local players. This group includes the Brazilian vaccine industry.

6.2.1 The "Big Pharma"

The "Big Pharma" firms are represented here by the few large and global pharmaceutical companies that have participated and dominated the vaccine business during the last decades: Sanofi-Aventis (Sanofi-Pasteur), GlaxoSmithKline (GlaxoSmithKline Biologicals), Merck & Co. (Merck Sharp & Dohme), and Wyeth

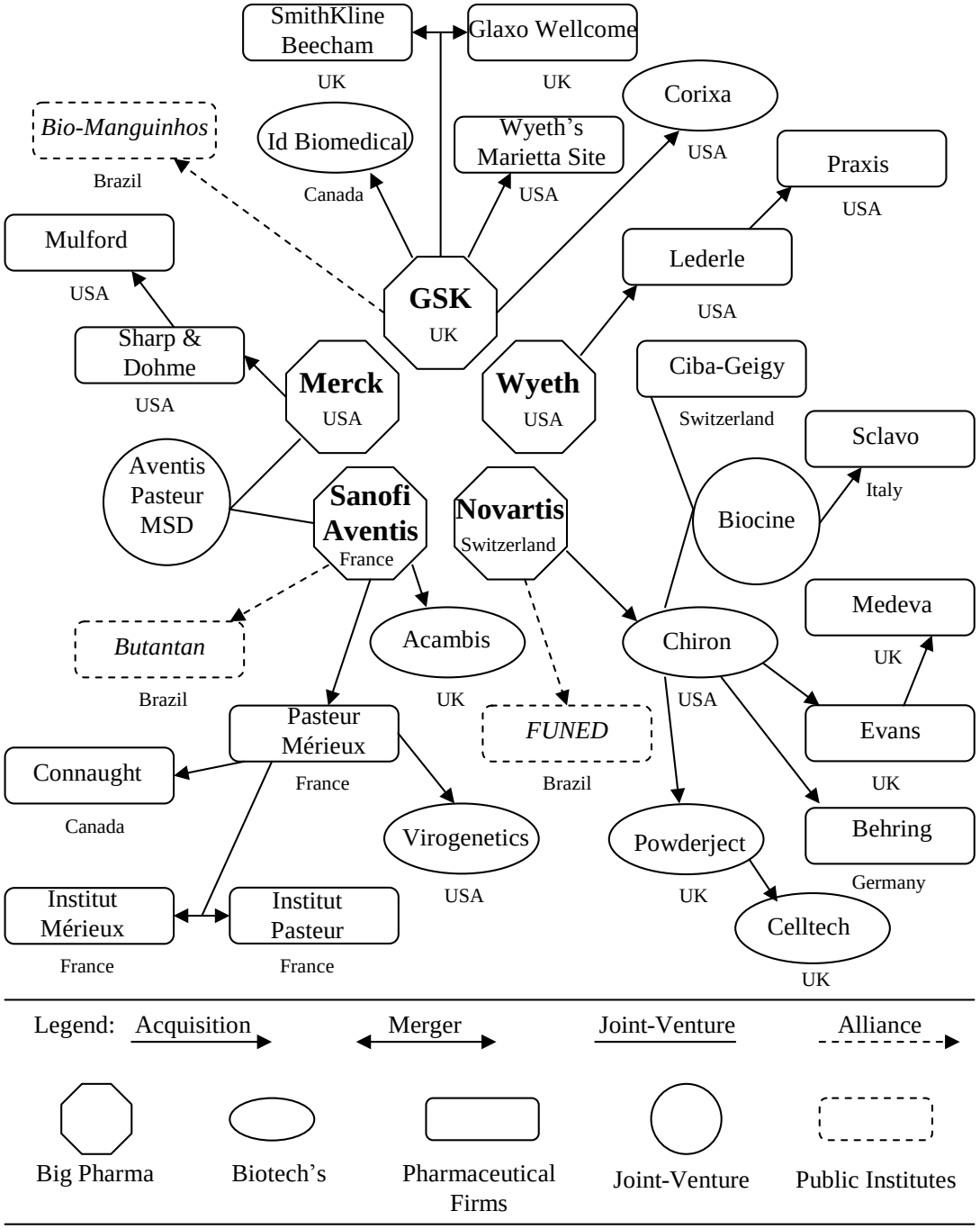
(Wyeth Pharmaceuticals).[158] Novartis (Novartis Vaccines) has recently been attempting to join this group following their acquisition of Chiron in 2006. Altogether the sales of the four leading companies in 2000 represented almost 80% of the global market of vaccines, and around 85% when Chiron is included (Gréco, 2002). Recent estimations show that this picture remains unchanged.[159]

This oligopolistic core of the few large pharmaceutical companies in the vaccine business has its origins in the post-war era. Massive government investments in basic biomedical research, especially in the US (Galambos and Sturchio, 1996), breakthroughs in virology and vaccinology (Galambos and Sturchio, 1998; Galambos, 1999), development of new vaccines – e.g. inactivated polio and influenza – (Offit, 2005), opened new markets and awoke the interest of the larger pharmaceuticals to vaccines in the 1950s and 1960s. From the 1970s to the mid-1980s the number of private manufacturers decreased sharply due to the lower profit margins generated by the tightening of the manufacturing standards, liability concerns, high investments needed for R&D (Galambos, 1999; Hinman et al., 2006), and the need to internationalize the business (Gréco, 2001). Mergers and acquisitions then became more frequent and, according to Offit (2005:623), the number of manufacturers in the vaccine business declined from 26 in 1967 to 17 in 1980 and to only 5 in 2004.[160] In this process, even public producers dedicated only to national needs and some major pharmaceutical companies dropped out, as noted by Gréco (2001). An illustrative picture of the dynamics of acquisitions, mergers and alliances of the vaccine industry pushed by the current "Big Pharma" is presented in Figure 6.1.

One reason for the current success of the few large pharmaceutical companies who decided to pursue the business of vaccines is certainly the organizational capabilities developed by their parent companies in the drug business. As indicated by Mazzucato and Dosi (2006), the capabilities to manage the process of R&D, including large-scale clinical trials, applying and getting registration of products from regulatory authorities,

[158] Between parentheses are the vaccine divisions of the "Big Pharma". Wyeth Pharmaceuticals includes the drugs and biopharmaceuticals businesses. Wyeth is in the process of merging with Pfizer.
[159] Based on the firms' Annual Reports, freely available at their web pages (GSK, web page; Merck, web page; Novartis, web page; Sanofi Aventis, web page; Wyeth, web page).
[160] According to Mowery and Mitchell (1996:195) between 1966 and 1977 one-half of commercial vaccine producers quit the business in the USA , a trend that continued in the 1980s and led to price rises paid both by public and private purchasers.

and marketing and distribution developed by the large and vertically integrated pharmaceutical companies since the 1930s, has been one of the main entry barriers in the pharmaceutical industry.



[1] This figure presents only some selected events of the dynamics of the vaccine industry. By obvious reasons it would be impossible to represent it in its full extent.
Own elaboration. *Source*: Galambos and Sewell (1995), Mowery and Mitchell (1996), Sheridan (2005), Hinman et al. (2006) and the web pages of the five "Big Pharma" companies.

Figure 6.1: Mergers, Acquisitions and Alliances in the Vaccine Industry[1]

Besides these distinct technological and organizational capabilities, the "Big Pharma" firms have other specific characteristics that differentiate them from other groups acting in the vaccine business. Firstly, as private companies and major global players they are profit oriented, which means that the objective of their shareholders are fundamentally economic (Vandersmissen, 2001). Although scientific progress may restrict their decisions, the costs, risks and return on future sales drive the investment decisions of the vaccine manufacturers (Batson, 2005), and have been one of the causes of the decrease in the number of pharmaceutical companies in the vaccine business (Offit, 2005; Coleman et al., 2005).[161]

Secondly, they invest significantly in R&D as a percentage of sales and, according to the Mercer Consultants' report (Mercer Management Consulting, 2002), since the 1990s these investments are estimated to be at the same level of R&D investments of the broader pharmaceutical business. Moreover, according to the same report, the development pipeline of the "Big Pharma" is constituted of increasingly complex vaccines, especially the genetically engineered recombinants, the conjugate and the combined vaccines (*ibid.* p.14). On this matter it is important to highlight that the "Big Pharma" companies do not usually carry out basic research. Conversely, they benefit from a wide network of alliances with universities and research institutions (Galambos and Sewell, 1995; Wilson et al., 2007).

Thirdly, as noted by Mowery and Mitchell (1996), they also access technologies and markets through the dynamic strategies of mergers, acquisitions, joint ventures and strategic alliances (see Figure 6.1).[162] Indeed, the "Big Pharma" can spend up to a quarter of their R&D budgets with their network of alliances (Nightingale and Mahdi, 2006). Fourthly, high revenues from vaccines allow them to afford the characteristic permanent high investments needed for R&D and manufacturing infrastructures. Table 6.1 presents some facts and figures of these large pharmaceutical firms.

According to the Mercer report (Mercer Management Consulting, 2002:13-14), some significant differences in terms of strategy, even within the "Big Pharma" group, can

[161] This point is approached in more details in Section 6.3.
[162] "Big Pharma" companies also go through mergers and acquisitions to increase the manufacturing capacity, as shown by Sheridan (2005).

also be identified. These differences or trends are region specific and refer to the two big vaccine markets: the US and Europe. The US-based multinational producers – Merck and Wyeth – mostly focus on higher profit margin proprietary products through a narrower range of products for high-income customers, and their scale of production is low. On the other hand, the strategy of the European-based multinational producers – Aventis, GSK and Chiron – encompasses a broader range of products for a wider range of buyers and their scale of production is high.[163]

Table 6.1: Illustrative Facts and Figures of the "Big Pharma"

Facts & Figures	"Big Pharma"			
	Sanofi-Aventis	GSK	Merck	Wyeth
R&D investments[1] (% of total sales)	16.1	14.9	20.5	14.9
Vaccine R&D expenditures (US$ million)[2]	653	491	722	323
Vaccine revenues (as % of total revenues)[3]	13	10	17	12
Blockbusters	. Influenza . Paediatric combinations	. Hepatitis . Paediatric Combinations	. Papillomavirus . Viral combinations, . Rotavirus	. Pneumococcal conjugate
R&D personnel	19,089[1]	1600 scientists[4]	N/A	N/A
Headquarter	Europe (France)	Europe (UK)[5]	North America (USA)	North America (USA)

[1] Average from 2006 to 2008 for the whole company business.
[2] Estimative based on the percentage of vaccine revenues to total revenues and global R&D expenditures in 2008. The values in pounds Sterling and Euro were converted into US dollars using the average rates of exchange provided by the Federal Reserve.
[3] In 2008.
[4] Only for the vaccine business.
[5] The headquarter of GSK Biologicals is in Belgium.
Own elaboration. *Source*: The Annual Reports of the four companies.

6.2.2 The Biotechs

The biotechnological firms are being approached as a distinct group due to their highly specific characteristics and trajectory, and to their importance in the context of vaccine

[163] Originally, Chiron is a US-based biotech, which expanded its business to Europe before being acquired by Novartis. See Figure 6.1 for illustration.

development and manufacturing in the last decades. According to Milstien (2005),this has not previously been fully taken into account.[164]

The rise of the first biotech firms took place in the 1970s filling a gap in the market caused by the recently posed challenge to the large enterprises by the new technological regime – the biotechnology transition (Galambos and Sturchio, 1998). At that time, most of the early biotech firms were founded by academic scientists involved in University entrepreneurial activities, as also noted by these authors.[165] The boom of the biotech firms, however, took place after the US Congress enacted the Bayh-Dole Act in 1980. Under this Act, universities and small enterprises financed by public funds – e.g. funds from NIH – were allowed to patent their discoveries and license them to the large pharmaceutical companies (Mazzucato and Dosi, 2006; Milstien and Kaddar, 2006). The rapid growth in the number of biotech firms, however, was circumscribed essentially to the US and eventually to the UK (Garavaglia et al., 2006). In fact, over 90% of the existing biotech firms involved with pharmaceuticals in the 1990s were concentrated in the US, many of which dealt with vaccine development (Mowery and Mitchell, 1996).[166] Milstien (2005) adds that vaccines have been the second target of biotech firms' R&D pipeline, just behind cancer drugs.

Nowadays several biotech firms are effectively participating in the vaccine market with their own products and/or services, exploring, in particular, some niche opportunities opened by the vacuum left by the "Big Pharma" (Sheridan, 2005). Milstien (2005) points out, for example, that US stockpiles of vaccines against bioterrorism diseases have been one of the main targets of biotech firms. Some biotech firms, however, have

[164] It may seem confusing to set up a distinct group of biotech firms when approaching the vaccine industry. If we draw on the definition employed by Hodgson (2006:635), biotech firms encompass those with a commercial application of biological organisms, biological systems or biological processes, in activities such as R&D, manufacturing or services. In a broad sense all the vaccine firms fall into this group. However, the objective of the proposed distinction is to focus on the dynamics of those more recent firms that have, as their main characteristic, the employment of molecular genetics and recombinant DNA technology – the new biotechnological paradigm – instead of "traditional" biotechnology, as a foundation to carry out their business. This research, therefore, approaches biotech firms in the same sense as Galambos and Sturchio (1998).

[165] According to the authors, with the emergence of the new biotechnology, scientists who were normally providers of technical expertise to private ventures started carrying out a dual role – inventors and entrepreneurs, frequently holding University positions (*ibid.* p.257).

[166] As data presented by Mowery and Mitchell may be considered relatively old for a dynamic sector such as biotech, this picture has probably changed. A study by Lawrence (2006) about the biotech sector in general, shows that in 2005 Europe concentrated more biotech firms than the United States although the latter still dominated the healthcare category.

expanded their business to other niches and, in some cases, have been acquired by large pharmaceuticals, or even by other biotech firms. Table 6.2 presents a list of selected biotech firms, their alliances, situation and the main products or services marketed.

In fact, the dynamism of biotech firms has been one of the drivers for their quick technological and commercial success. Besides the very close connection with universities and research institutes and their high skilled staff, biotech firms are characterized by the highest R&D intensity within the science-based sector, as they invest up to 50% or more of their total revenues in R&D (Global Forum for Health Research, 2001; Milstien, 2005).[167] For some authors (e.g. Sheridan, 2005) biotech firms may be challenging the hegemony of the "Big Pharma" companies. Nightingale and Mahdi (2006) point out, however, that biotech firms, with few exceptions, lack the essential capabilities – financial, marketing and technical – to compete with the "Big Pharma" in the global market and they therefore need to form alliances to survive.[168]

Even though alliances have been one of the biotech firms most important strategies, in the vaccine business they are not the only one. According to Sheridan, as their R&D pipeline matures biotech firms face tough decisions on manufacturing and frequently go through one of two options: either to outsource the manufacturing of their products to existing manufacturers, or to develop the in-house manufacturing capabilities needed.[169] An alternative path chosen by some biotech firms to raise their working capital has been the initial public stock offerings (IPOs) (Galambos and Sturchio, 1998) or other financial transactions such as private investments in public equities and debt financing (Lahteenmaki and Lawrence, 2006).

In the fields of vaccine development and manufacturing, some biotech firms can be found outside the US/Europe-axis. India, China, Cuba, Australia and Thailand host some of them (see list in Table 6.2). In fact, a more recent analysis of the biotech sector

[167] The report of the Global Forum for Health Research (2001:14) lists two biotech firms investing over 50% of their revenue in R&D: ALZA (67%) and Genentech (55%).

[168] This trend is confirmed in a recent WHO report. Biotech firms are expected to play an increasing role in vaccine R&D, but they have limited ability to penetrate some downstream functions such as Phase 3 Trials, industrialization and commercialization. Some large biotech firms that manage to reach the market are usually taken over by the "Big Pharma"; a recent example is Genentech, which was taken over by Roche in 2009 (WHO, 2009a:22). See Figure 6.1 and Table 6.2 for other examples.

[169] According to the author, the partnership for outsourcing is through contract manufacturing organization (CMO) to retain product exclusivity.

has shown that the Asia-Pacific region has shown a rapid increase in the number of biotech firms (Lawrence, 2006). In Brazil the situation is different. A recent study carried out by a specialized institution has mapped 71 biotech firms, 12 of which are in the field of human health (Fundação Biominas, 2007). This study, however, has not identified any biotech firm dealing with vaccine development or manufacturing.[170]

Table 6.2: Selected Biotech Firms in the Vaccine Business

Biotech Firm	Major Products/ Services	Alliances	Remarks
	US/Europe-based biotech firms		
Acambis (UK)	Typhoid, Smallpox	Baxter, Aventis-Pasteur, Berna Biotech	Acquired by Sanofi-Pasteur
Bavarian Nordic (Denmark)	Smallpox	GSK, Powderject, IDM Pharma	-
Berna Biotech (Switzerland)	Influenza, Typhoid[1], Hepatitis A and B	Corixa, Orphan Europe, Chiron, Solvay	Acquired by Crucell
BioPort (USA)	Anthrax[1], Rabies[1]	-	-
Chiron (USA)	Rabies[1], Meningitis C conjugate, Influenza, DTaP	-	Acquired by Novartis
Crucell (The Netherlands)	Vaccine development Commercialization of vaccines of acquired firms.	Chiron, MedImmune, Merck, Sanofi-Pasteur	Acquired Berna Biotech
ID Biomedical (Canada)	Influenza[1] Vaccine development	-	Acquired by GSK
MedImmune (USA)	Influenza (FluMist)[1]	ViroNovative, Wyeth, GSK	-
Powderject (UK)	Influenza, Yellow fever, BCG, Cholera, IPV	CSL, Acambis, GSK	Acquired by Chiron
VaxGen (USA)	Development of biodefense vaccines, outsource of manufacturing facilities	Kekutsuken, Celltrion Incheon	-
	Other countries-based biotech firms		
Bharat Biotech (India)	Hepatitis B, TyPhoid	Wyeth	-
CSL (Australia)	DT, Influenza, Plague	Merck, Chiron	-
Heber Biotec (Cuba)	Hepatitis B, Hib, DTP-Hepatitis B, DTP-Hepatitis B-Hib	Panacea Biotec	-
Panacea Biotec (India)	DTP-Hepatitis B-Hib	Heber Biotec, Chiron	-
Sinovac (China)	Hepatitis A+B, Hepatitis A, Influenza	-	-

[1] Vaccines licensed by FDA.

Source: Milstien (2005), Sheridan (2005), Milstien et al. (2007), The Jordan Report (NIH/NIAID, 2007).

[170] Other studies, however, indicate a Brazilian incubated biotechnology firm, FK Biotecnologia, as developing anti-cancer vaccines. See Ferrer et al. (2004) and Rezaie et al. (2008).

6.2.3 Local Manufacturers: private, public and emerging

In this sub-section attention is drawn towards those vaccine manufacturers who, with a few exceptions, have primarily dedicated their business to fulfil requirements in their local markets. These manufacturers were the main source of vaccines until the 1970s and 1980s (Gréco, 2001; Milstien and Candries, 2002). Until that time the vaccines commonly used by immunization programmes were decades old, as were the production methods employed, and which were widely available (Milstien et al., 2007).[171] According to Milstien et al. (2007), these factors made it easier to establish several public producers in developing countries.

From this time on the "Big Pharma" began to dominate R&D and the commercialization of vaccines, and the number of smaller and local manufacturers started to decrease.[172] The situation was more pronounced amongst the public manufacturers, which used to be the arm of governments in developing countries for the supply of the low cost vaccines, but it was also recurrent in the USA and Europe. In the USA the two major public manufacturers are the most relevant examples: the Massachusetts Public Health Biologics Laboratories is currently producing limited quantities of a few old vaccines, and the Michigan Department of Public Health is no longer producing any vaccine (Hinman et al., 2006). According to Mowery and Mitchell (1996), in the 1990s in Europe public manufacturers were fighting to survive. In Latin America the situation was even more dramatic since only Brazil and Cuba continued regular local production of vaccines in the late 1990s (Homma et al., 2003).[173] Table 6.3 lists the active manufacturers in Latin America (LA) in the early 1990s and the first part of this century, after most of them stopped regular production. The causes for the decline of local manufacturers have already been approached in Sub-section 6.2.1 as they were exactly the opposite of the ones contributing to the rise of the "Big Pharma".[174]

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[171] When the Expanded Programme on Immunization (EPI) was created by the WHO in 1974, the vaccines commonly in use were Smallpox, BCG, DTP, Polio and Measles (WHO, 2002a). See Table 5.4 in the previous chapter (pg. 104) for more details about the technology and dates of introduction of these vaccines.

[172] The declining of private manufacturers has already been approached in Sub-section 6.2.1. See also Footnote 160 in this chapter.

[173] According to the authors, Mexico was trying to sell its only public producer (Birmex) to an MNC.

[174] The decline of local manufacturers took place in different times depending on the region of their markets. In the USA and Europe it started in the 1970s, as noted by Galambos (1999) and Hinman et al. (2006). In developing countries, whose immunization programmes delayed the introduction of new available vaccines, it started in the mid-1980s or later, as is the case of the Latin American vaccine manufacturers, as pointed out by Homma et al. (2003).

One consequence of the decline of local producers was the shortage of basic vaccines for national immunization programmes, and stockpiles in both developed and developing countries. As they became low margin products, the "Big Pharma" firms naturally drove their production to the new, more complex and more profitable vaccines (Batson, 2005; Hinman et al., 2006), and the remaining local producers were unable to cope with the demand.[175]

Table 6.3: LA Vaccine Manufacturers in the early 1990s and in 2000s

Country	Manufacturer[1]
Argentina	Instituto Malbrán Laboratorio Central de Salud Pública de La Plata
Brazil	***Fundação Ataulfo de Paiva*** ***Instituto Butantan*** ***Instituto de Tecnologia em Imunobiológicos (Bio-Manguinhos/Fiocruz)*** ***Instituto de Tecnologia do Paraná*** Instituto Vital Brazil
Chile	Instituto de Salud Pública
Colombia	Instituto nacional de Salud
Cuba	***Instituto Finlay***
Ecuador	Instituto de Higiene y Medicina Tropical Leopoldo Izquieta Pérez
Mexico	Gerencia General de Biológicos y Reactivos (currently ***Birmex***)
Uruguay	Instituto de Higiene Dr Arnaldo Berta
Venezuela	Instituto Nacional de Higiene Rafael Rangel

[1] Manufacturers with current regular production are in bold italic.
Source: Adapted from Homma et al. (1995). Other sources: Homma et al. (2003) and DCVMN (web page, accessed in 10/2009).

Notwithstanding the above picture, smaller manufacturers have been re-emerging in the past few years and some of them are now even supplying the international vaccine market (Mercer Management Consulting, 2002; Milstien et al., 2007). Besides the concerns with vaccine shortages, growing worldwide concern with the inequity between rich and poor countries regarding access to basic and new vaccines (WHO, 2002b), as well as with the "regionalization" of circulating pathogens (WHO, 2002b; Blume, 2005), has raised the awareness of governments and non-government organizations to the importance of the role of emerging manufacturers.[176,177,178]

[175] Vaccine shortages have taken place for many other reasons, but this issue is out of the scope of this research, even though it was briefly approached in Sub-section 5.2.1 of Chapter 5 (pg. 93). See Coleman et al. (2005), Hinman et al. (2006) and Orenstein et al. (2007) for detailed analyses on this issue.
[176] From this point on the "smaller" and local manufacturers, either public or private, will be termed as "emerging" interchangeably, as they have been approached in recent literature. This may sound strange as many of them are, in fact, old established institutions that managed to survive and are re-emerging after

The rise and growth of emerging manufacturers has been captured in some studies (e.g. Milstien et al., 1997; Mercer Management Consulting, 2002; Boston Consulting Group, 2005), and this phenomenon seems to overlap with the decline of many larger manufacturers. These studies' findings are highly representative of the real characteristics of emerging manufacturers and indicate several factors contributing to or hindering the development of their capabilities.[179]

The study of Milstien et al. (1997) was carried out in 31 manufacturers from 13 countries.[180] Seven critical elements for viability were assessed. These elements were proposed based on the characteristics of successful producers. Based on the scores achieved the manufacturers fell into three categories: viable, potentially viable and low viability (or probability of becoming viable). Only five manufacturers were considered viable whilst fifteen fell into the second group and eleven into the low viability group. Amongst the main findings, three of them draw the attention: a) the fundamental importance of government commitment to the viability of the manufacturers; b) the size of the national population as important but not critical for the success of local manufacturers; and[181] c) the rationalization of facilities within countries as a means of increasing the viability of production.[182] Moreover, the authors add that the current technological standard of vaccine and vaccine production requires a new and expensive quality system where quality assurance capabilities are of higher importance. The current acceptance of product quality is not based on quality control tests alone, but also

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experiencing a period of decay or hibernation. In this research, therefore, "emerging" simply refers to the current growing importance of these smaller manufacturers in the international scenario.

[177] The regionalization of circulating pathogens means that the same disease may be caused by different forms of organisms due to specific regional characteristics. See Sub-section 5.2.1 of the previous chapter (pg. 95 and footnote 123) for more information about this issue.

[178] Milstien et al. (1997) point out that a study in the mid-1990s revealed that 50% of the doses of vaccines acquired by national immunization programmes all over the world had been locally produced.

[179] These studies were commissioned to guide governments, non-governmental organizations and donors in the strategies and/or investments needed to strengthen the development of new and the supply of current vaccines for national immunization programmes in the poorest and developing countries.

[180] The authors point out that there are vaccine manufacturers in more than 55 countries but many of their facilities do not meet the quality standards for a reliable vaccine manufacture. The manufacturers assessed were established in Bangladesh, Brazil, Egypt, India, Indonesia, Iran, Mexico, Nigeria, Pakistan, Philippines, South Africa, Senegal and Thailand.

[181] According to the authors this finding is confirmed by the existence of some successful small private producers in industrialized countries where the national population is not large. Viability seems to be more related to total GNP and some government support in this case.

[182] Rationalization was a hypotheses raised by the authors when analyzing the critical elements of three manufacturers in the same country who had ranked as potentially viable or below. The idea consisted in the combination of capabilities and strengths of those manufacturers that might result in a new viable scored producer (Milstien et al., 1997:1362).

by a quality assurance system. This is across all the production steps through documentation, environment control, validation of equipment and operational procedures, and ensures product safety and production consistency.

One critical point raised was the access to new technologies. As most are now protected by Intellectual Property Rights (IPR), national producers need to enter into agreements with the "Big Pharma" to access them or wait until the patents expire. Before entering into these agreements, however, manufacturers need economically viable facilities with assured quality. Table 6.4 summarizes some of the characteristics of the manufacturers assessed.

> To stay current, national producers must upgrade technology and increase budgets and investments, but those which serve relatively small markets will find they are unable to compete with large scale producers who can take advantage of economics of scale (Milstien et al., 1997:1359-1360).

Table 6.4: Common Characteristics of Viable, Potentially Viable and Low Viability Vaccine Manufacturers

Main Characteristics	Manufacturers Categories		
	Viable	**Potentially Viable**	**Low Viability**
Support from government	Strong	Low commitment to long-term viability (e.g. week NRA[1]).	No commitment.
Technical and Managerial Skills	Strong	Ability to produce traditional vaccines; No commitment/ability to cope with change; Need to improve management and legal structures.	Weak (even for old products).
Quality System	Proven track records with the current vaccines;	Track record (quantity element) for some traditional vaccines; Quality assurance system often not in place.	Lack of independent NRA[1].
Facilities	Make changes to be able to meet new demands.	Investments in some extent to facilities upgrade.	Decaying facilities; Lack of adequate maintenance.
Other	Likely to need alliances and joint-ventures to be successful in the long term.	Viability does not depend on investments in buildings and equipments alone.	Investments in facilities alone unlikely to change the situation.

[1] National Regulatory Authority

Own elaboration. *Source*: Milstien et al. (1997:1361-1362).

The Mercer report (2002) focuses mainly on the economics of markets, and vaccine development and production, which are issues to be approached in more detail in the next section. However, some aspects presented in the report about the dynamics and characteristics of emerging manufacturers deserve to be mentioned here. First, and consistent with other studies, the report states that these manufacturers have been expanding capacity significantly, improving production scale and widening the range of products offered. They have benefited from their cost advantage and different objectives from the large multinationals to increasingly supply basic vaccines for international public sector procurement on a profitable basis. Second, and in an opposite way, as they often lack the innovative capabilities of the large multinationals, their key challenge is to access and/or develop the new technologies increasingly procured by international agencies and low and middle-income countries.

The Boston Consulting Group's report (2005) analyzes 18 emerging manufacturers (public and private) and 6 multinational corporations (MNCs) in order to assess the characteristics of potential suppliers to the GAVI priority needs, to identify the constraints faced by these manufacturers in the production and development of these priority vaccines, and to point out possible actions to GAVI partners to ensure security and quality of supply.[183,184] The emerging manufacturers assessed in this study are located in Brazil (2), China (5), Cuba (2), India (5), Indonesia (1), Korea (2) and Mexico (1). Some of the findings of this study show the contrast between both groups of manufacturers. For instance, emerging manufacturers are focused in the vaccine business whilst the MNCs are focused in other products.[185] Moreover, even though the emerging manufacturers assessed have been responsible for half the volume of vaccines produced, this volume represented only 8% of the total sales of vaccines of both groups. This finding reinforces the fact that the portfolios of emerging manufacturers are constituted of older products.[186]

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[183] The six MNCs assessed in the study of BCG include the five "Big Pharma" addressed by this research in Sub-section 6.2.1 plus the Berna Biotech, which was addressed in Sub-section 6.2.2.

[184] GAVI Alliance is a public-private partnership. Its role and importance are stressed in Sub-section 6.4.1.

[185] In 2004, an average of 66% of the total revenue of emerging manufacturers assessed came from vaccine sales whilst it represented only 6% for MNCs in the same year. However, higher figures were raised by this research for MNCs in 2008, as shown in Table 6.1, which can probably indicate a shift in MNCs' strategy.

[186] According to the report, however, emerging manufacturers are starting to invest in the development of more technically challenging vaccines (e.g. rotavirus), but not in the most scientifically challenging ones (e.g. HIV). Furthermore, emerging manufacturers can be more successful in innovation focusing the local markets needs (e.g. heat stable vaccines).

Other findings of this study are very indicative of the growing position of emerging suppliers. Within this group the study identified a few manufacturers that are export-focused rather than dedicated to the local market.[187] However, most of them address their entire production only to local markets, or only a small percentage of their production to export markets. Amongst those assessed some were identified as having technical and production capabilities to supply high quality vaccines. However, they were considered rather unrealistic in terms of timelines of product development, which denotes a certain weakness in innovative capability and project management. IPR capabilities have not been a barrier, but they are of growing importance to the firms' innovative capabilities. Amongst the main needs of the emerging manufacturers are assistance with regulatory issues, WHO pre-qualification, and mechanisms to access new technologies.

The need for mechanisms to strengthen the capabilities for production and development, and to ease the access to new technologies, is a point already being addressed by the main emerging manufacturers. In 2001 most of them formed an alliance and the Developing Countries Vaccine Manufacturers Network (DCVMN), an international non-profit and public health driven organization, was created. After some years in existence, the DCVMN has been considered by some as the main representative of emerging manufacturers in the international scenario (Jadhav et al., 2008). Some of the members have WHO pre-qualification, which means that they comply with WHO required standards for producing vaccines and are able to sell their products to international organizations (e.g. UNICEF, GAVI, PAHO). According to Milstien (2005), obtaining WHO pre-qualification is indicative of their viability. Other members are still pursuing this status. The two main Brazilian vaccine manufacturers are members of DCVMN but with a different status. The list of members is shown in Table 6.5. Other aspects of DCVMN are stressed in Sub-section 6.4.1.

[187] The few export-oriented manufacturers are located in India, Korea and Indonesia, and the UNICEF and middle-income countries are the main markets to them.

Table 6.5: Developing Countries Vaccine Manufacturers Network – DCVMN

Vaccine Manufacturer/member	Country	Category[1]
Bio Farma	Indonesia	FM
Bio-Manguinhos/Fiocruz	Brazil	FM
Bionet-Asia Co., Ltd	Thailand	FM
Finlay Instituto	Cuba	FM
LG Life Sciences	Korea	FM
Panacea Biotec	India	FM
Serum Institute of India	India	FM
Bharat Biotech	India	PFM
Biological E Ltd	India	PFM
Birmex	Mexico	PFM
Indian Immunobiologicals Ltd	India	PFM
Instituto Butantan	Brazil	PFM
JGAD	China	PFM
The Biovac Institute	South Africa	PFM
Zydus	India	PFM
CNBG	China	AM
INNOVAX	China	AM
IVAC	Vietnam	AM
Queen Saovabha Memorial Institute	Thailand	AM
Razi Vaccine & Serum Research Institute	Iran	AM
TIANYUAN Bio-Pharma	China	AM
VABIOTECH	Vietnam	AM
VACSERA	Egypt	AM

[1] FM – Full Member (manufacturers with WHO pre-qualification and with a fully functional National Regulatory Authority – NRA); PFM – Prospective Full Member (manufacturers of countries with fully functional NRA and working towards attaining status of WHO pre-qualification); AM – Associate Member (manufacturers committed to become viable but from countries with no fully functional NRA).
Source: DCVMN (web page, accessed in 10/2009).

6.2.4 The Brazilian Vaccine Industry (BVI)

Brazil has a century-old tradition in the vaccine industry.[188] In this sub-section some introductory aspects and a general overview of the current manufacturers of the Brazilian vaccine industry during the second phase of its history is presented.[189] The

[188] The primordia of the Brazilian vaccine industry and the first phase of its history were approached in Sub-section 5.2.3 of Chapter 5 (pg. 98-100).
[189] The second phase of the history of BVI starts in the early 1970s after the creation of the National Immunization Programme (PNI). The reason for establishing this threshold is stressed in Sub-section 6.4.2.

development of technological capabilities of the two main manufacturers of this industry is depicted in the next chapter.

Of the four current manufacturers, three are public and one is a private non-profit organization. They have been the only local manufacturers to supply the public market with human vaccines since the early 1980s.[190] In 1981 the then biggest Brazilian vaccine manufacturer, Sintex do Brasil, a private company receiving foreign capital, stopped the production of vaccines and sera due to the tighter requirements imposed by the local regulatory authorities and the high investments needed to comply with the new requirements. This left the Brazilian government faced with an insufficient vaccine supply by the existing smaller public producers, which also ran their production under precarious conditions at that time (Gadelha and Azevedo, 2003; Ponte, 2007).

Successes and failures have marked the trajectory of these manufacturers since then. Huge investments from the Brazilian government through the Programme of National Self-Sufficiency in Immunobiologicals (PASNI) from the mid-1980s to the late 1990s, and a growing and assured public market coordinated by the National Immunization Programme (PNI) of the Ministry of Health, have attempted to create the foundations for the development of Brazilian manufacturers.[191] Much was achieved, but weaknesses amongst the articulation of governmental policies have limited the intended success (Gadelha and Azevedo, 2003; Gadelha, 2005). Moreover, some studies consider the high dependence of central government vaccine purchases is considered of high risk for the manufacturers (e.g. Castanhar et al., 2005). The same authors point out, however, that the size and rapid growth of this public market and possibilities of internal and international cooperation open a window of opportunity to these manufacturers. Consequently, the development of these four manufacturers has not been balanced and remarkable differences can be noticed between the two bigger manufacturers and the two smaller ones. Table 6.6 presents some data about these current manufacturers. Other general information and characteristics are described below:

[190] A fifth small public manufacturer, Instituto Vital Brazil, provided small quantities of tetanus toxoid to the public market for some years, but it ceased production in the 1990s, as indicated in Table 6.3. Recently, the Ministry of Health announced that the "Big Pharma", Novartis, started building a vaccine production industrial plant in the city of Recife, in the north-eastern region of Brazil, with completion forecast for 2010 (interview 10).

[191] The aspects of the Brazilian public market are approached in more detail in Section 6.3. Both PNI and PASNI are also approached in Section 6.4.

Instituto de Tecnologia em Imunobiológicos (Bio-Manguinhos/Fiocruz): the biggest Brazilian vaccine manufacturer by sales, Bio-Manguinhos/Fiocruz is an Institute of the Oswaldo Cruz Foundation (Fiocruz), a century-old institution linked to the Ministry of Health, and the most prominent biomedical and biological research institution in Latin America (Moreira, 2005).[192] The creation of Bio-Manguinhos/Fiocruz by Fiocruz in 1976 was motivated by the desire to centralize and organize the production and development of immunobiologicals then carried out since the beginning of the 20th century by different research laboratories across the institution, according to the same author (*ibid.* p.15). Besides human vaccines the institute manufactures diagnostic reagents and biopharmaceuticals. Its current mission is *"to contribute to the improvement of Brazilian public health standards, through technological research focused on product development and production of immunobiologicals, in order to respond to the demands originated by the national and worldwide epidemiological situation"* (Bio-Manguinhos, web page, accessed in 11/2009), which states its public and local main purposes.

Being part of a huge research institution with an internationally acknowledged scientific community seems, however, has not yet made a great difference to Bio-Manguinhos/Fiocruz in terms of innovation on vaccines. This is because the source of technology for the great majority of its current products is foreign, obtained through technology transfer agreements. Notwithstanding, several successful incremental innovations and recent product innovations have been achieved and are the result of increasing investments in in-house R&D activities, as noted by Milstien et al. (2007), and of a growing network of partnerships (Bio-Manguinhos, 2009b).[193] On the other hand, the technology transfer agreements have been a successful strategy of Bio-Manguinhos/Fiocruz to quickly acquire technological capabilities and fulfil some of the needs of the PNI, as shown by Moreira (2005) and Barbosa (2009).

[192] The Oswaldo Cruz Foundation (Fiocruz) is a complex and large institution with 15 technical institutes carrying out activities such as basic research, education, hospitals with clinical research, technological development and production of immunobiologicals (Bio-Manguinhos), and of medicines and drugs, quality control, animal breeding and scientific and historical information. Its headquarters are in Rio de Janeiro in an 800,000-square metre campus. It is also present in other sites in Rio de Janeiro and in another six Brazilian states. Moreover, it employs over 7,500 employees (Fiocruz, web page, accessed in 11/2009).

[193] This network includes partnerships with several other institutes of Fiocruz.

The manufacturer is currently supplying eight products to PNI – Yellow Fever, Meningococcal A+C and C, OPV, Hib, DTP+Hib, MMR and Rotavirus vaccines. The production lines for the two first vaccines are WHO pre-qualified, and the institute have exported the surplus of production of both vaccines to United Nations (UN) Agencies.[194] Recently a new technology transfer agreement was announced for the production of a 10-valent Pneumococcal conjugate vaccine to be supplied to PNI from 2010 (Bio-Manguinhos, web page, accessed in 11/2009).[195] Currently, several products are in the R&D pipeline (Milstien et al., 2007; Bio-Manguinhos, 2009b), some in the late stages of development (Bio-Manguinhos, 2009b).[196] The manufacturer fully complies with the GMP requirements being annually inspected by the national authority.

The legal status of Bio-Manguinhos/Fiocruz, submitted to the tight rules of the public administration in Brazil, has been long recognized by some as inadequate for the management of an enterprise of its size, complexity and rapid growth (Castanhar et al., 2005). As a consequence, the institute has resorted to continuous processes of labour outsourcing and to the support of a non-profit foundation linked to Fiocruz to carry out vaccine exportation and some activities such as procurement (partially) and training, amongst others (interview 10).

The manufacturer largely benefited from the resources provided by PASNI to modernize the facilities and build a new large industrial plant in the 1990s, as shown in Table 6.10 in Sub-section 6.4.2. Significant investments in infrastructure, however, have also been made on a continuous basis. To perform its activities Bio-Manguinhos/Fiocruz relied on an approximately 35,000 square metre facility built in 2007 (Bio-Manguinhos, 2008), and new facilities are under construction to strengthen the quality of the current products and accommodate the production and development of new vaccines (interview 21).[197]

Instituto Butantan (Butantan): internationally acknowledged by its scientific and technological activities and production of serums in the ophidian area (Mello, 2000),

[194] Bio-Manguinhos/Fiocruz is currently the world biggest producer of yellow fever vaccine.
[195] Available at http://www.fiocruz.br/bio/cgi/cgilua.exe/sys/start.htm?infoid=964&sid=227, in Portuguese only.
[196] See Figure 7.3 on pg. 179 for a list of selected R&D projects of both Bio-Manguinhos/Fiocruz and Instituto Butantan.
[197] The total area includes facilities for activities other than vaccines.

Butantan is currently the second largest supplier of vaccines for the local public market. Together with Bio-Manguinhos/Fiocruz it supplied 67% of the total needs of PNI and 98% of the human vaccines locally purchased by PNI in 2006 (see Table 6.6). Figures released by institutional materials of Butantan (e.g. Instituto Butantan, 2007; Fundação Butantan, 2007) place the institution as the biggest vaccine manufacturer in number of doses produced and supplied. This public institution is linked to the São Paulo state's Secretary of Health and is headquartered on a large campus in the city of São Paulo (Instituto Butantan, 2000). In addition to vaccines and serums, Instituto Butantan also manufactures biopharmaceuticals and blood products.

Currently Butantan is supplying the PNI with six products, all different from the ones supplied by Bio-Manguinhos/Fiocruz.[198] They are, in order of introduction in the production line, the BCG, DTP, DT, dT, Hepatitis B, Influenza and Human Rabies. Butantan's development strategy has mixed in-house development with technology transfers. The first four products were developed in-house from old and widely available technologies. The recombinant Hepatitis B was the first and the only vaccine of the newer generation to be completely developed in-house in Brazil. Although Influenza and Rabies were introduced through technology transfer agreements, Rabies was substituted by a further improved in-house developed vaccine. This manufacturer also fully complies with GMP requirements (interview 6).

Butantan's R&D pipeline also has several vaccines being developed, most with a wide range of collaborations and partnerships (Fundação Butantan, 2007). Investment in R&D has significantly increased in recent years, mainly thanks to research grants from São Paulo state's S&T support agency (Milstien et al., 2007).

In the 1980s and 1990s, PASNI also contemplated giving the manufacturer resources to modernize and build new facilities for vaccine production (Temporão and Gadelha, 2007). It was the only manufacturer to direct part of these resources to build R&D facilities – the Biotechnology Centre – (see Table 6.10 in Sub-section 6.4.2), which, in turn, made the development of the recombinant Hepatitis B vaccine possible (Gadelha and Azevedo, 2003; Temporão and Gadelha, 2007). Butantan's potential technological

[198] The tetravalent (DTP+Hib) vaccine produced by Bio-Manguinhos/Fiocruz is a partnership with Butantan, which supplies the bulk of DTP to the former.

capability is recognized as one of its strengths amongst the Brazilian manufacturers (Temporão, 2002).

In order to grant more administrative flexibility, a non-profit foundation – Fundação Butantan – was created in 1989 to support Butantan's financial, procurement and personnel management (Instituto Butantan, 2000), but it participated effectively in the Institute's strategic decisions.[199]

Fundação Ataulfo de Paiva (FAP): this traditional private and non-profit organization, acknowledged by the Brazilian government as being a public utility, is at the other side of the BVI. Although it is the main supplier of the BCG vaccine to PNI, it is a small manufacturer of a sole product of old technology, which imposes clear financial and technological restrictions to its management (Castanhar et al., 2005). Therefore, its participation in the Brazilian vaccine public market is tiny (see Table 6.6). Butantan, a significantly stronger institution on scientific, technological and financial grounds, which implies a real threat for the continuity of its business, also produces the BCG vaccine.

Despite having the managerial flexibility characteristic of private firms, in contrast to the other three manufacturers, FAP's financial fragility is an important limitation to the development of its activities and its ability to invest in R&D, quality, and the modernization of its production facilities (Castanhar et al., 2005).[200] In this regards, although they have received financial resources from PASNI for the building of a new industrial plant (which could increase its production capacity and enhance the quality of its production process that is still not fully compliant with GMP), the new facilities are still not operative and require further investment for their completion (Limonta, 2005).[201]

[199] The Four-Year Plan 2007-2010 of the Institute was elaborated by the chairman of the Fundação Butantan, a former general director of the Institute, influential researcher and charismatic character amongst its workers, as revealed by the general director of the Institute in a interview to a magazine published by Butantan (Instituto Butantan, 2007:26).
[200] According to the authors, due to its private nature FAP cannot count on financial aid from government like the other manufacturers and need to resort on bank loans, which become its situation still more dramatic (*ibid.* p.256).
[201] See table 6.10 in Sub-section 6.4.2.

Instituto de Tecnologia do Paraná (Tecpar): Tecpar is a public institution linked to the Paraná state government. Even though it is a vaccine manufacturer its main business is in the field of technical and technological services provided for other firms installed in the Paraná state. Tecpar is a medium sized firm, but a small vaccine manufacturer and does not dominate any recent technology. Curiously it is not currently supplying any human vaccine, but only a canine rabies vaccine to PNI. In the past Tecpar supplied PNI with three human vaccines: DTP, dT and human rabies, the two first introduced through an unfinished technology transfer agreement with a "Big Pharma"; production of these had to be stopped due to quality problems raised by PNI over the product (interview 8). The human rabies vaccine was supplied from 1986 to 2002 and, according to the same interviewee, production of this was also interrupted due to complaints over the side effects of its old technology.

Tecpar's weakness in the vaccine field is attributed to its low tradition and technological commitment to vaccine R&D (Temporão, 2002). One of the interviewees pointed out the reasons for Tecpar's poor performance in the field of vaccines today in more detail. Firstly, the institute hasn't structured any formal area for vaccine R&D and there are few researchers allocated to these activities. Secondly, the lack of capability in molecular biology has been the main hindrance to the development of new vaccines (interview 8). In 2001, however, the IBMP – a molecular biology institute – was created on the campus of Tecpar through a partnership between Tecpar and Fiocruz, but there have been no successes in the vaccine field so far. Through other cooperation initiatives, however, Tecpar has been developing a new human rabies vaccine and it is expected to be launched soon, according to the interviewee. Moreover, with a partnership with Bio-Manguinhos/Fiocruz, Tecpar established the Tetanus Monomeric Protein (PMT) production process, a component used by Bio-Manguinhos/Fiocruz in the conjugation process of its Hib vaccine, and has been supplying this product regularly to that manufacturer.

Tecpar's managerial capabilities were pointed out by some authors as one of its strengths when compared to the other vaccine manufacturers (Temporão, 2002; Castanhar et al., 2005), but this has not translated into success in the vaccine business. Tecpar also benefited from PASNI resources to modernize and build new facilities, as

shown in Table 6.10, but the new facilities for the DTP vaccine were not completed and were adapted for the production of PMT (interview 8).

Table 6.6: The Brazilian Vaccine Manufacturers

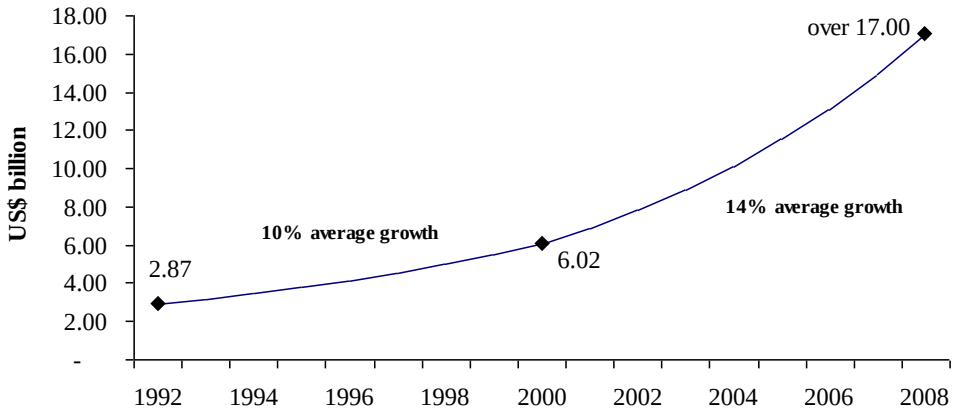
Manufacturer[1]	Start Date	Legal Status, Owner	Size of Manufacturer		Main Product Line	Other Product Lines	Number of Vaccines Marketed 2008	Human Vaccine Market 2006	
			Employment	US$ Sales[5] (in million)				Markets Explored	Market Share[9]
Bio-Manguinhos/Fiocruz[2] (Rio de Janeiro)	1900	Public, Brazilian Federal Government	1102[3]	316.8[3]	Vaccines	Biopharmaceuticals; Diagnostic Reagents	8	Local public and Export (Unicef, PAHO)	38.9% (56.9%)
Instituto Butantan (São Paulo)	1901	Public, São Paulo State Government	1020[4]	158.1[6]	Vaccines	Hyperimmune Sera; Vaccine bulk, Blood products	6	Local Public	28.1% (41.1%)
Fundação Ataulfo de Paiva (Rio de Janeiro)	1900	Non-profit Organization of Public Utility	155[4]	4.0[7]	Vaccines	-	1	Local Public	1.4% (2.0%)
Instituto de Tecnologia do Paraná (Curitiba)	1942	Public, Paraná State Government	566[3]	16.5[8]	Technical and Technological Services	Vaccines; Tetanic Monomeric Protein; Antigens	1	Local Public	0% [10]

[1] The city where the manufacturer is established is given in parentheses.
[2] Bio-Manguinhos was inaugurated in 1976 as a separate Institute within the Fiocruz structure.
[3] In 2008.
[4] In 2004.
[5] Encompasses all businesses of the firms. Values converted into $US using the average annual exchange rate published by the Central Bank of Brazil.
[6] In 2009.
[7] In 2006.
[8] Sales of canine rabies vaccine only in 2008.
[9] Local market share excluding imported vaccines are given in parentheses.
[10] Currently not marketing human vaccines.
Sources: Limonta (2005); CGIES/CGPNI (2007) and data collected during the field work.

6.3 Markets and Economics of Vaccine

Vaccine markets and economics have been analyzed in several studies and papers in recent years. This section seeks to present selectively the main aspects of the international and Brazilian vaccine markets revealed in these studies, and/or raised in data gathered during fieldwork, in order to bring to light some possible elements that might be influencing or affecting the development of BVI. Further economics of vaccine development and production are also approached amid the data.

The global vaccine market is, in fact, "a series of markets", in the words of Milstien and Candries (2002), or highly segmented, according to the report of Asian Development Bank (2001). This segmentation has two dimensions, as stated in this report: an international dimension, with the market segmented between industrialized and developing countries, and a national dimension, constituted by the public and private sectors. In a global perspective the vaccine market has presented an impressive average growth of 10% in the 1990s, having reached US$ 6bn in 2000 (Mercer Management Consulting, 2002).[202] This trend was expected to continue or accelerate in the early part of this century, according to some authors (e.g. Gréco, 2002; Mercer Management Consulting, 2002; Milstien and Candries, 2002). In fact, recent estimates point to a global vaccine market of over US$ 17bn in mid-2008 (WHO, 2009a), representing an average growth of 14%. According to the same report, this makes it one of the fastest growing sectors of industry. Figure 6.2 illustrates the global market growth.[203]



Own elaboration. *Source*: Mercer Management Consulting (2002) and WHO (2009a).

Figure 6.2: Global Vaccine Market – Figures and Growth

[202] According to the report, growth was calculated in nominal terms, i.e. with no inflation adjustment.
[203] In fact, an examination of the four "Big Pharma" firms' sales published in their annual reports, shows that only their vaccine sales, all together, exceeded US$ 16 billion in 2008.

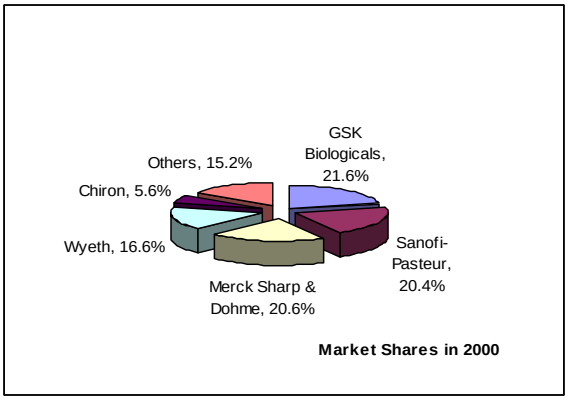
In terms of volume, however, the average growth was only 1% in the first period, the difference explained by the increase in the average price of the vaccines supplied due to the introduction of some enhanced pediatric vaccines, and especially of proprietary products in the market (Mercer Management Consulting, 2002).[204] Table 6.7 shows the product segmentation of vaccines and the impact of "blockbusters" in the market.

Table 6.7: Vaccines by Product Segment

Basic Pediatrics	Enhanced Pediatrics	Proprietary Pediatrics	Adult/Travel
. *OPV*	. IPV	. Pneumococcal conjugate[1]	. Hepatitis A
. *DTP*	. DTaP	. Meningococcal conjugate[1]	. *Yellow Fever*
. *BCG*	. *Hepatitis B*	. Varicella[1]	. Typhoid
. TT	. *Hib*	. *Rotavirus*[2]	. *Influenza*
. Measles	. *MMR*	. HPV[2]	

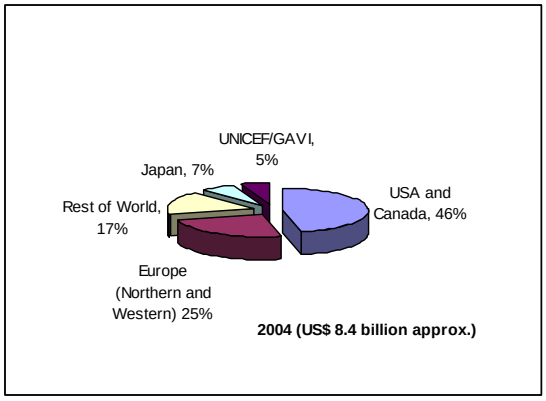
Vaccines in italics are those currently produced by the manufacturers of BVI. The Pneumococcal conjugate is planned to be introduced in 2010.
[1] These vaccines represented approx. 30% of the market value and 1% of the market volume in 2000.
[2] Recent proprietary products not in the market in 2000 - see Table 5.4 in the previous chapter (pg. 104).
Source: adapted from Mercer Management Consulting (2002).

As stated before (Sub-section 6.2.1) the "Big Pharma" firms are the main suppliers of this market and their revenues represent over 80% of this global market.[205] The main markets, in terms of value, are located in the private sector of developed countries, where the products in their early lifecycle are launched (Vandersmissen, 2001). Figures 6.3 and 6.4 illustrate these statements.



Source: Adapted from Gréco (2002)

Figure 6.3: Manufacturer's Market Share

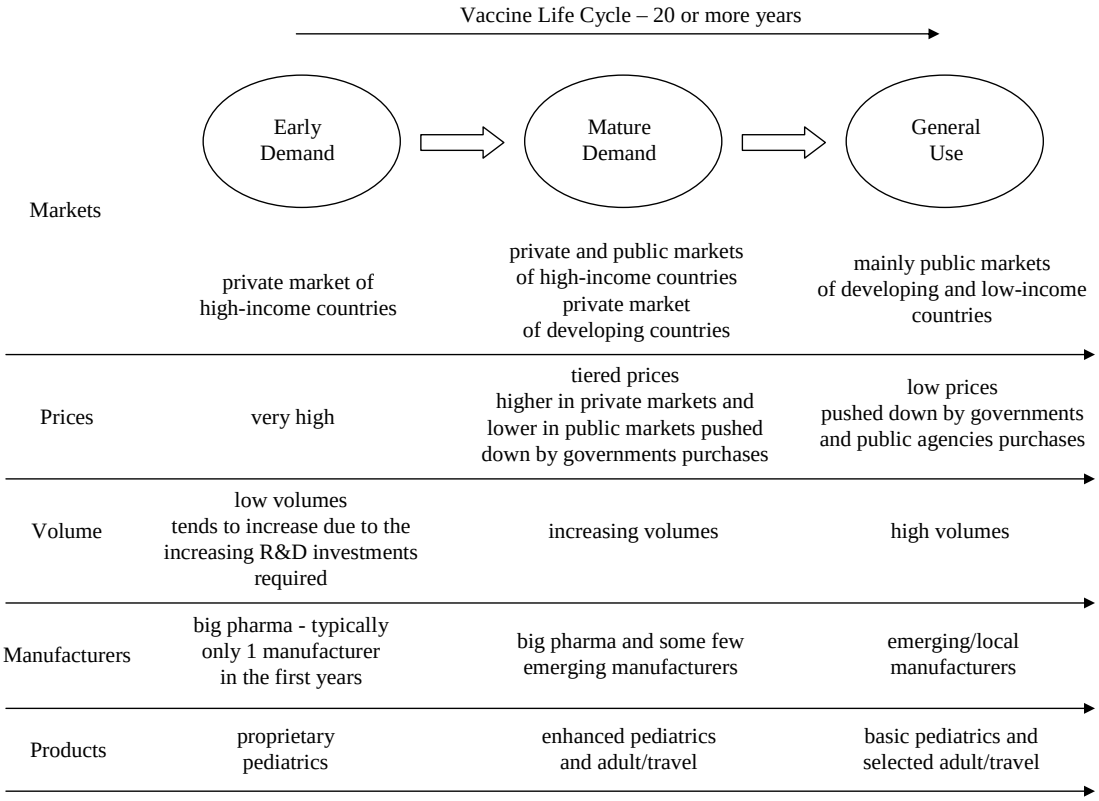


Source: Adapted from Boston Consulting Group (2005)

Figure 6.4: International Market Segmentation

[204] This growth excludes the worldwide effort to eradicate poliomyelitis.
[205] In a comparison between the six biggest MNCs (see Footnote 183 in this chapter) and the 18 main emerging manufacturers, the BCG's report (2005) found that the sales of the former represented approx. 92% of the total sales of vaccines of both groups in 2004, but only 42% of the doses supplied.

As also stated before (Sub-sections 6.2.2, 6.2.3 and 6.2.4), smaller and emerging manufacturers, including one Brazilian manufacturer, have been increasing their participation in the international market. However, mainly high volumes of basic and existing vaccines to address public markets of middle and low-income countries have characterized their participation.



Source: Adapted from Vandersmissen (2001), Milstien and Candries (2002) and Mercer Management Consulting (2002).

Figure 6.5: Typical Vaccine Life Cycle

The lifecycle of a vaccine in the market follows a similar pattern to other products in the pharmaceutical sector, but it has some specific characteristics due to the action of governments and public agencies. Vandersmissen (2001) describes the typical stages of this market development. According to him, in its early stage the product is marketed at a high price only in private markets of high-income countries. Due to the high R&D and capital investments required to develop a vaccine, the existence of this segment is of fundamental importance to the innovator to receive acceptable returns.[206]

[206] See Sub-section 5.3.3 of the previous chapter (pg. 109-110) about investments to develop a vaccine.

In the second stage the vaccine begins to be introduced to public markets of industrialized countries and the power of government purchases forces prices down. In the USA the pressures of public purchases have been indicated as an impediment to vaccine development as they dramatically reduce the manufacturers' profits (Hinman et al., 2006). Tiered prices are found in this stage, and some new manufacturers enter in the market, frequently through either their own R&D efforts or licensing from the owner of the technology (Milstien and Candries, 2002).

In the last stage the vaccine is introduced and almost exclusively marketed in public markets of middle and low-income countries, and large purchases of governments and public agencies force prices to the lowest level. At this stage the intellectual property protecting the product is expiring and several new manufacturers are in the market (Milstien and Candries, 2002). The typical life cycle of a vaccine and its specific characteristics are represented in Figure 6.5.

For each of the three stages of market development described by Vandersmissen, it is possible to identify the vaccines currently in the market, according to the product segments found in the Mercer's report and shown in Table 6.7. At one extreme are the "blockbusters" or proprietary products, new technologies sold exclusively in private markets of high-income countries. At the other extreme are the basic vaccines, old technologies manufactured almost exclusively by emerging/local manufacturers and commercialized in middle and low-income countries. In the middle, the relatively mature vaccines, which are manufactured and marketed in both high and middle-income countries but are more likely to be purchased by the former. According to Mercer's report, adult/travel vaccines are purchased exclusively by high-income countries. However, Influenza and Yellow Fever vaccines have been largely used in middle-income countries and/or endemic regions.

In Brazil, a country ranked by the World Bank as an upper-middle income country, the vaccine market seems to follow a different pattern fuelled by a large population, a decreasing but still important birth rate, and a strong and active federal government

presence through its National Immunization Programme (PNI) and other government policies.[207,208]

Little information is available about the Brazilian private market. Temporão (2002) estimated this market to be around US$ 96 million in 2000 and pointed out that it grows within the gaps left by PNI.[209] According to this author, vaccines sold in this market are mainly the proprietary and the enhanced pediatrics (Table 6.7), all of them produced by foreign manufacturers and marketed by private clinics and in doctor's offices.

Table 6.8: Advanced Vaccines Acquired by PNI / Supplied by BVI – starting dates

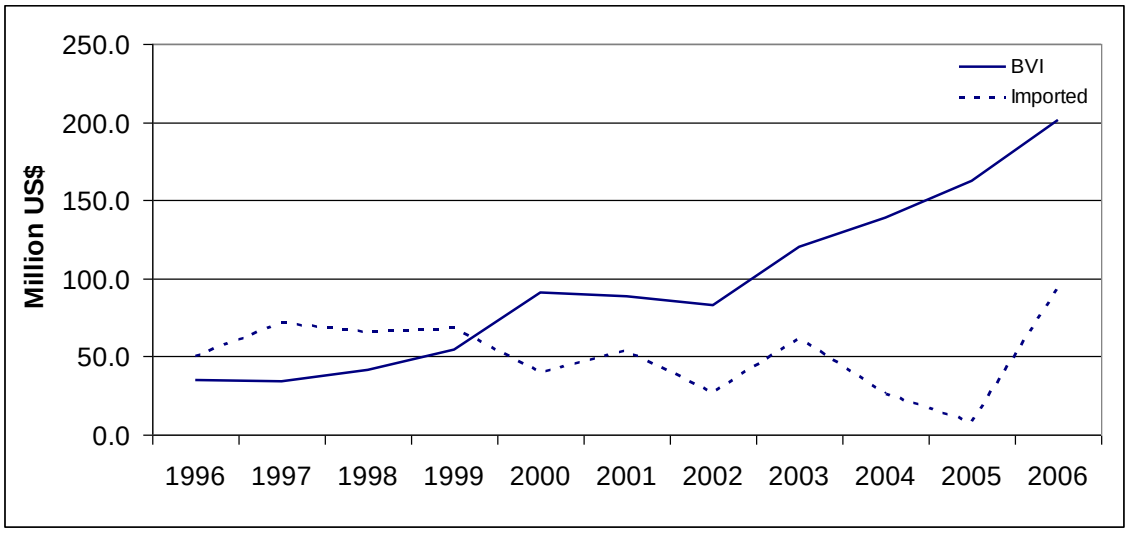
Vaccine	Starting date		Elapsed Time (years)
	PNI Routine or Specific Immunization[1]	Supply by BVI (manufacturer)	
Hepatitis B recombinant	1992	1998 (Butantan)	6
Triple Viral (MMR)	1993	2004 (Bio-Manguinhos)	11
Rubella	1997	-	-
Hib	1999	1999 (Bio-Manguinhos)	0
Influenza	1999	2000 (Butantan)	1
Pneumococcal	1999	-	-
DTaP[2]	1999	-	-
Hepatitis A[2]	1999	-	-
Double Viral (MR)	2000	-	-
Varicella	2001	-	-
Meningococcal Conjugate[2]	2001	-	-
Pentavalent (DTP+Hib+HBV)	2002	registering (Bio-Manguinhos/Butantan)	?
Pneumococcal conjugate	2002	announced for 2010 (Bio-Manguinhos)	8
Tetravalent (DTP+Hib)	2002	2002 (Bio-Manguinhos)	0
Rabies (vero cell) [2]	2002	2002 (Butantan)	0
IPV[2]	2003	-	-
Rotavirus[2]	2006	2007 (Bio-Manguinhos)	1

[1] Some vaccines were introduced by PNI for immunization routine, others for use only in small groups or special communities (e.g. Varicella vaccine has been acquired for immunization of Indian communities). Most of the new generation vaccines were introduced gradually.
Own elaboration. *Source*: Brasil (2003); vaccines with [2] were included from data provided by CGIES/CGPNI (2007).

On the other hand figures for the Brazilian public market are even more impressive than that for the global market. From 1996 to 2006 the public market has grown from

[207] The Brazilian population, the fifth largest in the world, was around 190 million in 2008 according to the Brazilian Institute of Geography and Statistics (IBGE, 2008). The average birth rate in the 1990s was around 2.23%, which represents around 4 million births every year (IBGE, web page, accessed in 11/2009 - data available at http://www.ibge.gov.br/ibgeteen/pesquisas/fecundidade.html#anc3).
[208] The Brazilian institutions and policies are approached in more detail in the next section.
[209] The private market was estimated by the author to be R$ 176 million. It was converted from the Brazilian currency into $US using the average annual exchange rate published by the Central Bank of Brazil (available at www.bcb.gov.br).

US$ 85.2 million to US$ 294.3 million in nominal terms, with an annual growth rate of 13.2%. This growth was basically due to the introduction of more advanced vaccines in the immunization programme by PNI (Temporão and Gadelha, 2007), the coordinator and sole purchaser in this market. The starting dates of regular acquisitions of more advanced vaccines by PNI, as well as of the supply by BVI, are shown in Table 6.8. The purchases from the Brazilian manufacturers were responsible for most of this growth in this period since their annual growth rate was 19.1%, from US$ 35.1 million to US$ 201.3 million. Imports remained fairly steady in the same period (US$ 51.3 million/year in average), with some variations in the years where PNI introduced new generation vaccines in the immunization programme. In 2006, for example, when the recently launched oral rotavirus vaccine was introduced by PNI, the purchase of this vaccine represented 78% of total imports, reaching the highest peak of the analyzed period.[210] Figure 6.6 illustrates the evolution of local and the imported purchases.



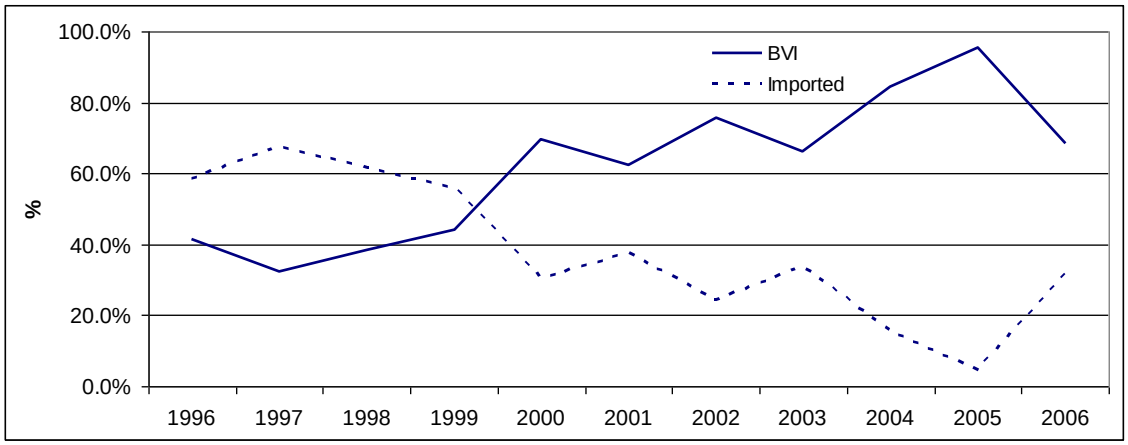
Own elaboration. *Source*: 1996-2004 (Temporão and Gadelha, 2007). 2005 and 2006 (CGIES/CGPNI, 2007).

Figure 6.6: Brazilian Vaccine Public Market – National x Imported purchases (US$ million)

Another aspect to be highlighted in the evolution shown in Figure 6.6, is the shift in the profile of government purchases in late 1999 and early 2000 when local purchases of vaccines overtook imported vaccines. It was at that time that Brazilian manufacturers started supplying more technologically advanced, and consequently more expensive,

[210] In 2007, however, one Brazilian manufacturer started supplying the PNI with this vaccine ending the need for importing it (see Table 6.8). This quick response is explored in more detail in the next chapter.

vaccines – e.g. Hib, Hepatitis B and Influenza (Limonta, 2005; Temporão and Gadelha, 2007), after expanding their portfolio in qualitative terms. Figure 6.7 shows the percentage of participation of each segment in the evolution of government purchases.



Own elaboration. *Source*: *Idem* Figure 6.6.

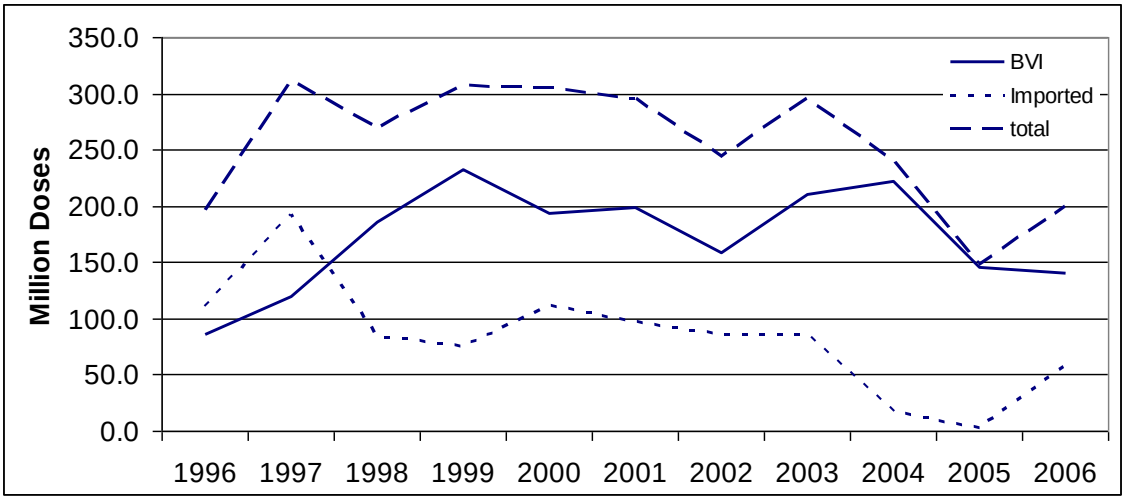
Figure 6.7: Brazilian Vaccine Public Market – National x Imported purchases (%)

The analysis of the number of doses acquired by the Brazilian government in the same period, as shown in Figure 6.8, also reveals the development of the BVI. While the extremes of this period can show a null growth of the total doses acquired (traced line) it is explained by the introduction and growing supply of combined vaccines by the local manufacturers – e.g. DTP+Hib and MMR vaccines – in the early 2000s.[211] The middle of the graphic, however, once more shows a shift in the profile of doses acquired from local and imported segments in the 1990s (dotted and continuous line). In this regard, the impressive growth noted in the supply by local manufacturers to 1999 is attributed to the modernization and expansion of their installed capacity provided by the PASNI investments (Temporão and Gadelha, 2007).

In summary, the above data about the Brazilian vaccine market show some of its specific characteristics. Firstly, the Brazilian government has introduced in its immunization programme some proprietary and enhanced vaccines that are commonly purchased only by high-income countries. Currently, the Brazilian vaccination coverage

[211] The number of doses of a vaccine decreases as multiple antigens are combined into a single product. One example is the MMR vaccine, which production steps are represented in Figure 5.2 on pg. 117. Each single dose of this vaccine protects against three different pathogens – measles, mumps and rubella – avoiding, therefore, the need for three separate doses (see also item f of Sub-section 5.3.1 on pg. 105).

encompasses about 90% of all antigens (Milstien, 2005). Secondly, due to this policy, the Brazilian government has created a huge and attractive, but protected, public market. Thirdly, this huge and protected market has been the platform for the growth of the BVI in the last 13 years or so, in both quantitative and qualitative terms. Some Brazilian manufacturers have been able to introduce more advanced vaccines to this market, drastically reducing government dependence on imported vaccines. The influence and importance of government institutions and policies in the growth and sedimentation of this market are issues for the next section. The strategies of the main Brazilian manufacturers to develop their technological capabilities and introduce the new vaccines needed by the PNI are approached in the next chapter.



Own elaboration. *Source*: *Idem* Figure 6.6.

Figure 6.8: Brazilian Vaccine Public Market – Doses Purchased

6.4 The Role of Government and Institutions

Different from most sectors and industries, the importance and influence of government and institutions to the development of the vaccine industry, in both private and public sectors and in either international or national contexts, have been remarkable. The important achievements and concerns about vaccination and vaccine development and manufacture, as stressed in Chapter 5, have triggered a constant deployment of an array of initiatives that may be considered as unique.

Post WWII was the stage for the appearance of most of these institutions and initiatives. As there is no room in this research for a complete appreciation of this issue, some of

the most influential ones are approached below in Sub-sections 6.4.1 (international context) and 6.4.2 (Brazilian context).

6.4.1 – Government, Policies and Institutions – the international context

World Health Organization (WHO): created in 1948 with the objectives of disseminating high levels of health worldwide and of coordinating the fight against infectious diseases, the WHO selected the fight against Smallpox as one of its first targets (Temporão et al., 2005). Less than twenty years later the WHO launched the huge campaign which culminated with the worldwide eradication of the disease in 1977 (Benchimol, 2001).[212] Seventy four vaccine manufacturers were acknowledged by the WHO throughout the world to produce the 200 million doses/year of the vaccine needed for this task, including Fiocruz in Brazil, as noted by this author.

The launching of the Expanded Programme on Immunization (EPI) in 1974 was another remarkable WHO initiative. Aiming to increase the vaccination rates amongst children of the poorest nations and developing countries (Stern and Markel, 2005), the Programme recommended the inclusion of two new diseases – Poliomyelitis and Measles – to the existing list of diseases commonly fought by immunization at that time (WHO, 2002a).[213] The WHO also provided training and technical assistance, and the principle of national immunization programmes was implemented across the world (WHO, 2002a; Temporão et al., 2005). Later on two new vaccines were added to the EPI – Hepatitis B and Yellow Fever – the latter only in endemic areas, and the MMR vaccine substituted the measles vaccine in several, mostly industrialized countries (WHO, 2002a).

Concerns about the quality and safety of pharmaceutical products, including the vaccines increasingly produced and marketed across the world at that time, motivated the development of the regulatory apparatus by the WHO. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, and the Good Manufacturing Practices (GMP) were first recommended in 1969 (WHO,

[212] According to the author, the date of the last known case of smallpox was 1977. The WHO declared smallpox eradicated from the globe in 1979 - see Sub-section 5.2.1 in the previous chapter (pg. 92).
[213] Smallpox, BCG and Diphtheria, Tetanus and Pertussis were the vaccines commonly in use by most countries at that time. Poliomyelitis and Measles were diseases with a high incidence rate and with good and affordable vaccines available (WHO, 2002a).

2003). Since then they have been periodically revised and extended. One relevant aspect to be highlighted is that the products encompassed by the legislation, and their manufacturers, should be licensed and inspected by competent national regulatory authorities. In the last decades the sophistication and complexity of regulatory legislation has been discussed by many authors (e.g. Milstien and Candries, 2002; Plotkin, 2005c; Offit, 2005) as the main pressure for the increasing costs of vaccine R&D, clinical trials and production, and, consequently, for the delay in the development of new vaccines or the disappearance of many manufacturers.

Pan American Health Organization (PAHO): established over 100 years ago, the PAHO became the arm of WHO in the Americas in 1949, and it has been largely linked to the successful implementation of the national immunization programmes in the region (de Quadros, 2004). One very important initiative of the PAHO was the implementation of the Revolving Fund in 1979 to provide access to vaccines to the poorest countries in the Americas and Caribbean. Through the Revolving Fund, which was initially supported by their own resources and donations from UNICEF, the US government and some European countries, the PAHO was able to purchase large quantities of better quality vaccines at lower prices for its countries' members (Benchimol, 2001). Another advantage for its countries' members was the possibility of refunding the Fund only at the time of the arrival of the product and using their own currencies (Temporão, 2002). Currently, every country in the Americas and Caribbean can buy its vaccines through the Revolving Fund, which enhance its purchasing power.

Brazil has not only used the Revolving Fund for some of its imported vaccines, in addition, one of the Brazilian manufacturers has participated in tenders to export some of its vaccines (Bio-Manguinhos, 2009b). Another important aspect is that the PNI have used the prices achieved by the Revolving Fund as a reference price for establishing the prices to be paid for some of the Brazilian manufacturer's products, putting pressure on the manufacturer's efficiency.

UNICEF: the United Nations Children's Fund has been the operational arm of the WHO's policies on immunization to the less favoured countries of other regions. The incomes of UNICEF come from a large range of voluntary donors, especially governments, but also private sector and non-government organizations (UNICEF,

2009b). Its huge purchases of vaccines since early 1980s have pushed down prices to the lowest levels in the international market (Temporão, 2002). After being at a steady rate in the 1990s, from early 2000, UNICEF vaccine procurement has grown from about US$ 100 million/year to US$ 493 million in 2006, partially due to the financing from GAVI Fund (IAVI, 2008). In 2008 vaccines and biologicals procured accounted for US$ 633 million, almost 50% of the total UNICEF procurement, and 2.6 billion doses of vaccines were delivered to 80 countries (UNICEF, 2009a).[214] More than half of the world's children benefit from UNICEF vaccine procurement annually (WHO, 2009a).

One point to be highlighted is the growing participation of emerging suppliers in the UNICEF procurement since the mid-1990s, as shown in Table 6.9. Bio-Manguinhos, the main Brazilian vaccine manufacturer, is currently a UNICEF supplier having supplied US$ 4.4 million in vaccines in 2008 (UNICEF, 2009a).

Table 6.9: Participation of Emerging Manufacturers in UN Vaccine Purchases[1]

Year	Number of vaccines	Number of suppliers …	… of which Emerging Manufacturers %
1986	4	7	0
1996	5	14	50
2001	6	12	58
2008	N/A	16	50

[1] 1986-2001 – refers to UN Agencies procurement. BCG not included. 2008 – refers to UNICEF procurement only. In 2003 there were 23 pre-qualified vaccines in the list of UNICEF (IAVI, 2008).
Source: 1986-2001, Milstien (2005); 2008, UNICEF (2009a).

GAVI Alliance: by the end of the 1990s, when concerns about low expenditures on immunization in developing and low-income countries increased, the GAVI Alliance (formerly called the Global Alliance for Vaccines and Immunization) was formed to revitalize an international coalition in support of immunization initiatives for children in the poorest countries (Muraskin, 2004). The GAVI Alliance is a global health public-private partnership launched in 2000 with a start-up grant of US$ 750 million from Bill and Melinda Gates. It relies on other donors such as governments, multilateral organizations (e.g. WHO, UNICEF, World Bank), the vaccine industry, civil society

[214] In 2006 UNICEF procurement accounted for around 40% of the global volume of vaccine, but only 5% in terms of value (IAVI, 2008).

organizations and independent individuals, to strengthen the immunization programmes of countries with a Gross National Income per capita below US$ 1,000 in 2003 (GAVI Alliance, web page, accessed in 11/2009). US$ 3.8 billion had been received from public and private sector donors as at the end of 2008, of which US$ 2.7 billion had been disbursed to eligible countries (WHO, 2009a).

New innovative sources of funding for immunization programmes have been created recently: the International Finance Facility for Immunization, which sells bonds in international markets and provides cash to be used by the GAVI Alliance (WHO, 2009a), and the Advanced Market Commitment, a pull mechanism to subsidize future purchases and stimulate the development and manufacture of vaccines for developing countries (Batson et al., 2006).

DCVMN: originally created to strengthen the supply of quality vaccines to the local markets of its members, the Developing Countries Vaccine Manufacturers Network expanded its goals, as the manufacturers developed new capabilities and introduced new vaccines in their portfolio, trying to reach the global market (Jadhav et al., 2008). Currently seven of its members are WHO pre-qualified (see Table 6.5 in Sub-section 6.2.3) and supply vaccines to the two major UN procurement agencies (UNICEF and PAHO). Access to new technologies, one of the strategic priorities of the DCVMN, has also been achieved by some members.

Recently the Netherlands Vaccine Institute (NVI) transferred its own technology of a Hib conjugate vaccine to three DCVMN members, in a move that was seen by GAVI as an opportunity to break the monopoly of Hib containing vaccines in the international market (Jadhav et al., 2008). As an acknowledgement of the growing importance of its members in the international scene, the DCVMN now has a seat on the board of GAVI, joining the representatives from multinational industries on this board (Milstien et al., 2008).

In fact, the list of institutions and governments in the international context that have decisively influenced and participated in the vaccine endeavour worldwide is endless, and many of them have played an important role in the development of the BVI as well. Many other important institutions and organizations could be emphasized perfectly here,

such as the National Institutes of Health (NIH), a federal agency leading in vaccine research and development in the US, the Walter Reed Army Institute of Research (WRAIR), the Rockefeller Foundation, and the Sabin Vaccine Institute, to cite only some acknowledged by Jordan (2002). To quote other authors, the list would include the Children's Vaccine Initiative (CVI), the forerunner of GAVI, according to Milstien et al. (2008), the International AIDS Vaccine Initiative (IAVI), the Malaria Vaccine Initiative (MVI), and the Program for Appropriate Technology in Health (PATH), amongst many others. This research now turns to the Brazilian context in order to provide evidence for connections between national policies and institutions, and the strategies and achievements of the BVI.

6.4.2 – Government, Policies and Institutions – the Brazilian context

Brazil is a country with a good and broad scientific foundation, largely acknowledged by the international scientific community and backed by several universities and research institutes (Homma et al., 2003). Its S&T system and policies have been traditionally governed by the Ministry of S&T and the Ministry of Education through their agencies, namely the National Council of Scientific and Technological Development (CNPq), the Financing Agency for Studies and Projects (FINEP), and the Coordinating Body for Upgrading of Higher Level Personnel (CAPES) (Serruya et al., 2008). More significant strides towards denser initiatives to support innovation and overcome the barriers against technological and scientific development, however, became apparent only in the early 2000s with the launching of 14 Sectoral Funds in S&T, the 1st National Conference on Science, Technology and Innovation in 2001, (Brasil, 2002), and with the enacting of the Innovation Law in 2004.

More recently, the Secretariat of Science, Technology and Innovation in Health was created within the structure of the Ministry of Health to strengthen the development of scientific knowledge and technological innovation concerning the Brazilian health system (Serruya et al., 2008). Traditionally, low investments in health R&D and the need for higher coordination of the investments made in this area, have recently driven the changes in S&T policies of the Ministry of Health (Brasil, 2006b).[215] The lack of

[215] In the 1990s, Latin American countries on average spent only 0.5% of GNP on health R&D. In Brazil these investments were 0.76% on average. In 1998 Brazil spent nearly US$ 715 million on health R&D, half the total investment of all Latin American countries in the same area. By 2001 Brazil invested around

articulation amongst policies in ST&I in Brazil have delayed the development of the BVI, and have recently been the object of criticism by some authors (e.g. Gadelha and Azevedo, 2003; Gadelha, 2005; Temporão and Gadelha, 2007). This is one of the issues addressed below along with the description of the main institutions that have supported the development of the BVI in the last decades.

One further point that deserves to be mentioned relates to the country's general industrial policy context in the last decades. As shown by Figueiredo (2009), this policy has been marked by discontinuities. The import substitution policy of the 1970s and 1980s gave place to the open economy and global competition of the 1990s and 2000s, with little intervention of the government. The author also emphasizes that the new government from 2003 sought to re-establish the role of the government in supporting economic development (*ibid.* p.34), reflecting what was described in the two previous paragraphs.

PNI: The Brazilian National Immunization Programme was created in 1973 aiming to keep Smallpox eradicated and Measles, Tuberculosis, Tetanus, Diphtheria, Whooping Cough and Poliomyelitis under control (Benchimol, 2001). [216] Its remarkable achievements in its first 30 years of existence made it respected by public health experts worldwide and acknowledged as a world reference programme by the WHO and the PAHO (Brasil, 2003). [217] The PNI itself, and the set of institutions and initiatives established by the Ministry of Heath to assure its success, have dramatically influenced the changes and development of the BVI. For this reason the creation of the PNI was set up in this research as the threshold for the analysis of the technological development of this industry.

2% of the public heath expenditure in health R&D, reaching the recommendation of the WHO. For these and other data on this issue, see Brasil (2006b).

[216] The last case of smallpox in Brazil was in 1973 (Brasil, 2003). The objectives of the PNI preceded the launching of the EPI by the WHO (Benchimol, 2001). See more information about the EPI in Sub-section 6.4.1.

[217] Amongst its achievements are the eradication of polio in 1989 and the control and drastic reduction in the mortality rate by all immunopreventable diseases (Brasil, 2003). According to the same source, the PNI has also organized or helped immunization campaigns in Asia and the Middle –East, and provided training to Latin American and African countries. Its merits are enhanced when one takes into account the large population, the geographically diverse continental dimensions, and the huge social and economic contrasts found in Brazil (Temporão et al., 2005).

Some aspects of the PNI have already been approached in Sub-section 6.2.4 and Section 6.3. One point to be re-stated here is the first consequence of the implementation of the programme together with the strengthening of the quality control authority. Higher demands for better quality vaccines in the late 1970s met, at the lower end of the market, local manufacturers with precarious facilities and producing vaccines which did not comply with the then new quality requirements (Temporão, 2002). The requirement for the high investment needed to comply with these new requirements in a less attractive business led to the withdrawal of the main and private manufacturer in 1981, increasing the supply crisis and the dependence on imported vaccines (Temporão and Gadelha, 2007).[218,219] Within this context the government put forward a new and ambitious programme of national self-sufficiency in immunobiologicals (PASNI), by investing in the modernization of the public manufacturers' facilities, and trying to reverse the obsolescence of the national production of immunobiologicals. The characteristics of this programme are approached in the next item.

During the 1980s the PNI's great achievement was the eradication of Poliomyelitis in 1989, but the incidence of other diseases did not decline as expected. In addition, new diseases were reported in some regions of the country – e.g. hepatitis B – and most of the vaccines purchased by the PNI were imported (Brasil, 2003). In the 1990s the budget for purchasing vaccines was substantially increased by the government, and the PNI started to introduce new generation vaccines for either routine or special immunization.[220]

Manufacturers were just stabilizing the production of the basic vaccines in their modernized facilities when they faced new challenges posed by the PNI. Only in the late 1990s did some Brazilian manufacturers manage to start supplying the PNI with these new vaccines (see Table 6.8 in the previous section). Since then the PNI has kept a

[218] Low quality standards led other smaller manufacturers to interrupt vaccine production (Benchimol, 2001).
[219] The referred supply crisis encompassed not only vaccines but also anti-venom serums. The situation of the latter was still more dramatic for the government as there were no substitutes for these products in the international market since they were made from specific poisons from the Brazilian natural species (Benchimol, 2001).
[220] In 1993 the PNI implemented the first State Reference Centres for Special Immunization (Cries) in five different states of the country, with the objective of providing specific vaccines for special individuals (e.g. immunodepressed individuals, Indian and other specific communities, risk groups and other patients with medical prescriptions). By 2003 there were 36 Cries implemented across all states of the country (Brasil, 2003).

policy of gradually introducing the new generation vaccines, firstly in special programmes (e.g. Cries – see Footnote 220) and later on in routine immunization. This gave public immunization in Brazil different characteristics from most developing countries (Brasil, 2003).

PASNI: The Programme of National Self-sufficiency on Immunobiologicals was launched by the government in 1985. It had the basic purpose of strengthening public manufacturers in order to cease the shortage of immunobiologicals and, more ambitiously, to achieve self-sufficiency in the production of immunobiologicals demanded by the PNI by 1990 (Temporão and Gadelha, 2007). Indeed, the crisis generated by the shortage of vaccines and serums forced the government to establish the target of national self-sufficiency in immunobiologicals as an issue of **"national security"**, as noted by Benchimol (2001:359, emphasis added). During its lifetime, between 1985 and 1998, the PASNI invested around US$ 158 million in the modernization of public manufacturer's facilities. Around 84% of these resources were allocated to the four current vaccine manufacturers, with undoubted improvements in terms of quality and installed capacity (Temporão, 2002). Table 6.10 provides the breakdown of the resources invested.

Table 6.10: PASNI – Investments in the Public Manufacturers 1985-1998

Manufacturer	US$ (million)[2]	%	Main Application
Bio-Manguinhos/Fiocruz	66,4	42	New industrial facilities (final processing and production of bacterial concentrate); New facilities for production of test animals;
Butantan	34,8	22	Modernization of production facilities (DTP, BCG, Rabies and serums); Building of a biotechnology centre;
FAP	15,8	10	New industrial facilities for BCG production and quality control;
Tecpar	15,8	10	New facilities for DTP and Rabies production and quality control; Quality assurance.
Others[1]	25,3	16	Quality Control; Serum production.

[1] In this group were five serum manufacturers and the National Quality Control Laboratory (INCQS/Fiocruz), the only non-manufacturer to be awarded with resources from PASNI.
[2] Values updated to July 1998 by the US inflation rate.
Own elaboration. *Source*: Temporão (2002).

In fact, despite the manufacturers having delayed the completion of the new facilities buildings, the PASNI has been acknowledged as one of the most important initiatives in

the development of the BVI.[221,222] However, even though self-sufficiency was amongst its main objectives, it is argued that, in its narrow perspective, it paid little attention to the development of innovative and managerial capabilities (Temporão and Gadelha, 2007).[223] As a result, the introduction of the new generation vaccines for either routine or special immunization by the PNI from the 1990s onwards found no ready answer from the local manufacturers. The manufacturers' strategies for coping with this challenge are emphasized in the next chapter.

National Regulatory Authority: As the quality of the products was one of the main weaknesses of manufacturers in the early 1980s, the government also invested in the strengthening of the institution responsible for the quality control tests, the National Institute of Quality Control in Health (INCQS/Fiocruz). As noted by Temporão and Gadelha (2007), the strengthened INCQS/Fiocruz was of fundamental importance to assure the quality of the products supplied to the PNI. In 2000 the National Health Surveillance Agency (ANVISA) was created as an autonomous governmental agency, incorporating the responsibilities of the national regulatory authority (NRA) and keeping the INCQS/Fiocruz as its technical arm for performing the quality control tests in immunobiologicals and medicines (Miranda and Henriques, 2005). Currently ANVISA has incorporated all activities required by the WHO for an NRA, according to these authors.

Other policies/institutions: More recently some scholars (e.g. Gadelha, 2003, 2005; Gadelha and Romero, 2007) have discussed the fragilities of local manufacturers in terms of technological development and indigenous innovation in a broader perspective, with the vaccine business being part of an integrated complex of productive actors – goods and services – of the health system. The Health-Industrial Complex concept seeks to identify the technological bottlenecks and opportunities shared by the components of

[221] Many reasons were raised for the delay in the completion of the new facilities, amongst them the irregular financial cash flow from the government, the high inflation rate at that time and, more important, the need for developing the new capabilities to comply with GMP requirements by the engineers and contractors (interviews 10 and 21).

[222] Besides the improvements in the quality of the vaccines and the expansion of the installed capacity of production, self-sufficiency in the production of BCG and Rabies vaccines, a large installed capacity for the production of measles and DTP vaccines, and self-sufficiency in the production of anti-poisonous serums are amongst the main achievements of the investments made through PASNI.

[223] The building of the Biotechnology Center by the Instituto Butantan was the sole example of investment in infrastructure for vaccine R&D with resources from PASNI.

this complex, in order to guide the integration of the industrial, ST&I and social policies and stimulate technological strategies towards competitiveness. Included as one of the priorities of the More Health Programme of the Ministry of Health, the Health-Industrial Complex will receive around US$ 1.09 billion between 2008 and 2011 to strengthen the competitiveness of its actors and, consequently, of the health policy (Brasil, 2008).[224,225]

The discussions around the health-industrial complex led to other initiatives. The main one was the Health Innovation Project, coordinated by the Oswaldo Cruz Foundation. As a result, the sub-project vaccines became the National Programme of Competitiveness in Vaccines (INOVACINA), launched by an Act of the Ministry of Health in 2006 to implement the Brazilian Policy on Vaccine. The four areas elected by the programme for investment were: infrastructure and expenditures of R&D in vaccines; the strengthening of GMP by the manufacturers; the strengthening of the NRA; and a public network for pre-clinical and clinical trials (Brasil, 2006a).[226] The programme has not yet been fully implemented, according to some interviewees (interviews 6, 10 and 17).

According to one of the interviewees, despite all of these initiatives Brazil still lacks an institution operating similarly to the NIH/USA, in order to finance, induce and coordinate applied research in the health area, and make possible greater achievements in terms of innovation in vaccines (interview 5).

6.5 Summary

This chapter has described the current situation of the vaccine industry and the main aspects that have characterized its development in the last decades in both international

[224] The value was converted from Brazilian reais into $US using the 2008 average rate of exchange provided by the Federal Reserve.

[225] The More Health Programme is part of the Growth Acceleration Programme (PAC), a large programme launched by the current Brazilian government in 2007 to promote economic growth. As a productive system structuring programme, the More Health Programme will invest around US$ 3.3 billion in several actions such as, amongst others, "the consolidation of a more competitive Brazilian industry (medical equipments, materials, reagents and diagnosis devices, immunobiologicals, active principles and drugs, vegetable extracts for therapeutic purposes); strategic areas of the field of scientific-technologic knowledge; and the self-sufficiency in the production of blood by-products" (Serruya et al., 2008:25), with a substantial part of the funds coming from the Brazilian Development Bank (BNDES), according to these authors.

[226] The Programme set the government vaccine priorities for 3, 5 and 10+ years, in order to guide the R&D pipeline of the Brazilian manufacturers (Carvalheiro et al., 2005).

and Brazilian contexts. The data provided and the aspects highlighted has shown considerable differences in the dynamics, organization and market strategies of the three main groups that represent this industry – the "Big Pharma", the biotech firms and the emerging manufacturers. On the other hand, it is also shown that there are complementarities amongst the three groups that made their coexistence important for the searching of a worldwide equilibrium in terms of technology development and the fulfilment of market needs. Within the market context the growing importance of the Brazilian public market and of the local manufacturers has been emphasized.

Concerning the role of government and institutions, the information gathered confirms that the social implications of vaccines and immunization, and the technological complexities of vaccine development and manufacturing as discussed in the previous chapter, along with the market failures approached in the present chapter, have been determinant to a remarkable performance of governments, UN agencies and other non-governmental organizations in the support, harmonization and regulation of this industry. The role of this intricate network of institutions, rarely found in other sectors and industries, is especially apparent with regards to the strengthening of the BVI since the 1970s. In the Brazilian context the government protection to the public vaccine manufacturers has remained steady across discontinuities in the industrial policy regime in the last decades, and macro-instabilities in the economy in the 1980s and 1990s. However, a stronger integration of the industrial, ST&I and social policies, along with more induction to basic research in the health area, are points still in need of strengthening in order to grant greater benefits to innovation in vaccines.

The issues discussed in this chapter have advanced the overview of the main elements that have exerted important influence on the development of the vaccine industry as addressed in the analytical framework in Chapter 3. The next chapter completes the series of empirical chapters of this research by approaching the sources of technological knowledge and the specificities of the technological capabilities development in BVI since the early 1970s, with an emphasis on the transition period as a result of the government policies, market forces and strategies adopted.

Chapter 7 – Technological Capabilities in the Brazilian Vaccine Industry

7.1 Introduction

This is the final empirical chapter of this research. Its main objective is to approach the process of development of technological capabilities in the Brazilian vaccine industry (BVI). This will be achieved through describing the dynamics of the sources of knowledge exploited in the development of this industry, and the characteristics of its transition phase. One remaining point of the group of the other influencing elements – organizational capabilities – is also approached here as it is related to the internal issues of the firms. Moreover, this chapter presents the results of a survey carried out in the largest firm in the BVI to assess its current level of technological capability, and to show some of its strengths and weaknesses from a different perspective.

As stated before (Sub-section 6.4.2 on pg. 157) the period of observation of this research starts in the early 1970s, the time of the creation of the Brazilian National Immunization Programme (PNI). The reasons for concentrating the focus on the two main manufacturers of the BVI were stated in Chapter 4 (Sub-section 4.2.2 on pg. 81), and restated using facts and figures in Chapter 6 (Sub-section 6.2.4 on pg. 135-143). However, some facts and figures of the two smaller manufacturers are also presented.

In addition to this introduction and the summary of the whole chapter in Section 7.7, this chapter consists of two main parts. In the first the emphasis is on the elements of the development of technological capabilities within the industry. In this regard, Section 7.2 approaches the issues on technology acquisition whilst the development of innovative capabilities, including the issues on internal and external linkages and learning by training, is approached in Section 7.3. Still in the first part, Section 7.4 briefly presents some aspects of the organizational capabilities within the BVI.

The second part is dedicated to the description of the boundaries, characteristics and constraints of the technological capabilities transition phase in the BVI (Section 7.5). It will also present the results of the survey carried out in one of the firms as a complementary tool to assess strengths, weaknesses and the current level of

technological capability, and to support the analysis of the transition phase in this industry (Section 7.6).

7.2 Technology Acquisition

This thesis has argued that technology acquisition (TA) has possibly been the main source of knowledge for the development of the BVI over the last decades, and that the persistence with this strategy has determined a different pattern of technological accumulation within this industry. This section seeks to approach the overall aspects involved in the process of TA in the BVI in order to clarify its determinants, dynamics and the extent of its application (Sub-section 7.2.1). It will also describe the characteristics of the process (Sub-section 7.2.2), some trends in the adoption of this strategy in the future (Sub-section 7.2.3) and, therefore, the implications for the development of the BVI.

7.2.1 Determinants, Dynamics and Extent of the Processes of Technology Acquisition

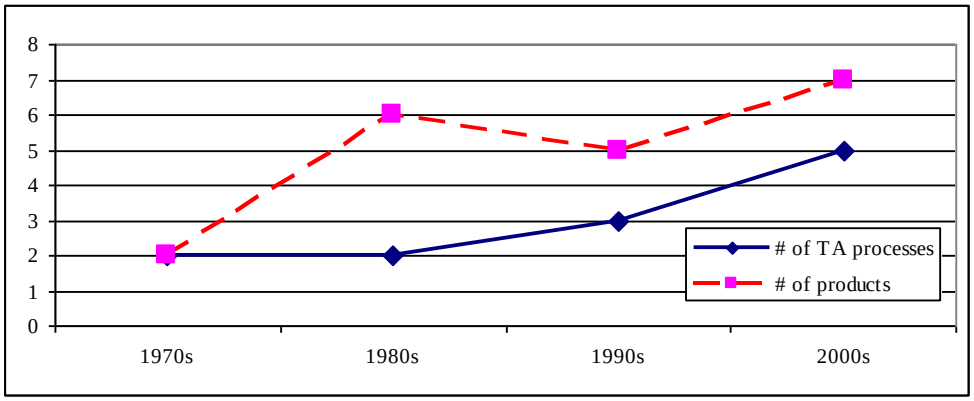
The adoption of TA strategy by the BVI was not a single decision by the firms but the result of a set of combined factors encompassing technological, political, marketing and strategic perspectives. They should be put together here for the whole comprehension of the context. As shown in Chapters 5 and 6 the BVI lagged far behind the technological frontier in this field, especially after WWII, whilst the initiatives of immunization in Brazil were dispersed and limited until the early 1970s. The creation of the PNI in 1973, and the health and social policies backing it, opened the perspective of a growing internal market on the one hand but ran into the fragility of the local industry on the other. The situation became harder after the withdrawal of the main manufacturer – a private company – due to tighter quality requirements imposed on this industry by the government in the late 1970s. Moreover, the delicate situation of the Brazilian balance of payments hindered the importation of vaccines to fulfil the demands generated by the PNI. This context urged the government to set up the vaccine sector as being of strategic interest and to deploy governmental measures to strengthen the public manufacturers (interviews 7 and 15). Since then, the quickest and cheapest way and the only option left to this industry to realize the expansion of the PNI in most cases, has been the acquisition of foreign technology (interviews 7 and 10). The magnitude of the adoption of the TA strategy by the BVI may be observed in Table 7.1 and is emphasized in more detail afterwards.

Table 7.1: Vaccines Introduced by the BVI post-PNI and Sources of Knowledge

Year[1]	Vaccine[2]	Institution	Source of Knowledge In-house x Tech Transfer (technology transferor)
1976 (1974/75)	Meningococcal C, A+C	Bio-Manguinhos	Tech Acquisition[6] by cooperation agreement (Mérieux Institute)
1979 (1963)	*Measles*[3]	Butantan	Tech Acquisition not concluded/interrupted (Merck)
1983 (N/A)	*Measles*	Bio-Manguinhos	Tech Acquisition by cooperation agreement (Biken Institute)
1984 (N/A)	Oral Polio Vaccine	Bio-Manguinhos	Tech Acquisition by cooperation agreement (Japan Poliomyelitis Institute)
1986	*Human Rabies*	Tecpar	In-house
1987	*TT*, DT, DTPw	Butantan	In-house
1996 (N/A)	*DTPw, dT*	Tecpar	Tech Acquisition[6] not concluded/interrupted (Pasteur Mérieux)
1998	Hepatitis B recombinant	Butantan	In-house/consultancy
1999	dT	Butantan	In-house
1999 (1993)	Hib	Bio-Manguinhos	Tech Acquisition by licensing (SmithKline Biologicals)
2000 (1968)	Influenza	Butantan	Tech Acquisition by licensing (Aventis Pasteur)
2002 (1985)	*Human Rabies (Vero cell)*	Butantan	Tech Acquisition not concluded (Aventis Pasteur)
2002	DTPw+Hib	Bio-Manguinhos	In-house/cooperation
2004 (1997)	Triple Viral (MMR)[4]	Bio-Manguinhos	Tech Acquisition by licensing (GSK)
2006	Human Rabies (Vero cell)	Butantan	In-house
2007 (2006)	Rotavirus[4]	Bio-Manguinhos	Tech Acquisition by licensing (GSK)
2010 (2009)	10-Valent Pneumococcal Conjugate[5]	Bio-Manguinhos	Tech Acquisition by licensing (GSK)

[1] Between parentheses the year of introduction of the vaccine in the international market by the technology transferor. [2] In italic are the vaccines withdrawn from the market. [3] Vaccine not even introduced in the market. [4] Technology transfer still in process. [5] Production not started by the time of the elaboration of this table. [6] The process involved 2 different products.
Source: Own elaboration from data gathered during the fieldwork.

As can be seen from Table 7.1 the TA strategy was by far the one preferred in order to introduce new products to the Brazilian public market, especially the new technological generation vaccines.[227] Of the 21 products listed, 13 (62%) were the result of successful or unsuccessful TA processes, and the development of at least one other– DTPw+Hib – was made possible thanks, in part, to the acquisition of the HiB technology.[228,229] One of the firms – Bio-Manguinhos/Fiocruz – was alone responsible for 62% (eight TA processes) of all TA processes undertaken by the BVI. From the beginning of its adoption as the main strategy to supply the PNI the TA strategy has lasted for over 34 years.[230]



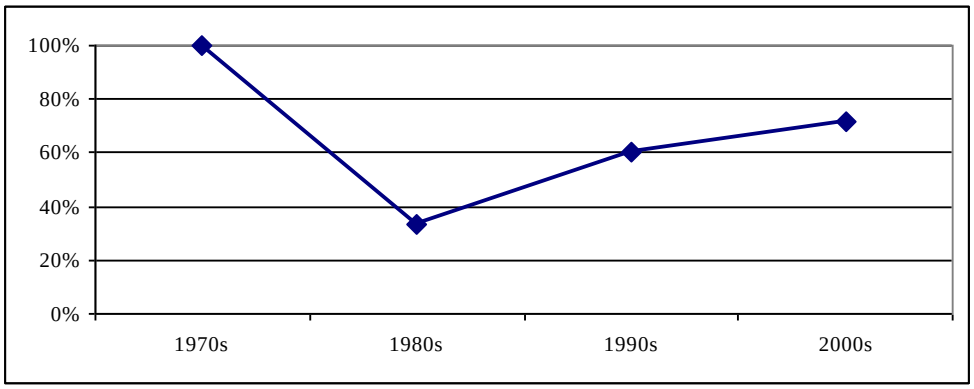
Source: Own elaboration.

Figure 7.1: Technology Acquisition Processes X Products Introduced

Another aspect that strengthens the argument raised in this research is the intensity of the TA processes in the four decades described in Table 7.1. In absolute terms the number of TA processes has increased from two in the 1970s and 1980s to three in the 1990s and five more recently, as represented in Figure 7.1. This figure also shows the total number of products introduced through the decades, some of them developed in-house, which is an issue to be analyzed in the next section.

[227] Table 7.1 lists the products introduced after the creation of the PNI. Therefore, three products currently purchased by the PNI from the BVI were not included in the table. The first is the yellow fever vaccine, produced by Bio-Manguinhos/Fiocruz since 1938 (see footnote 230). The other two are the intradermal BCG vaccines produced by Instituto Butantan since 1971 and by Fundação Ataulfo de Paiva since 1972, both similar and old technologies developed in-house.
[228] The aspects of the vaccines developed in-house will be approached in Section 7.3.
[229] As stated in footnote 6 of Table 7.1, some TA processes included more than one product. As this research is focusing on the products introduced, the same TA process was counted twice in these cases.
[230] Technology acquisition is not new to the BVI, however. In 1938 the technology of the, then, recently developed yellow fever vaccine was transferred to Fiocruz by the Rockefeller Foundation/USA.

The figures increase and are more revealing in percentage terms, as shown in Figure 7.2. In this figure, apart from the first decade when the two products introduced to the market were the results of TA, there was an increase in the number of TA processes related to the number of products introduced to the public market from 33% in the 1980s, to 60% in the 1990s, and 71% in the 2000s.[231]



Source: Own elaboration.

Figure 7.2: Technology Acquisition Processes as % of Products Introduced

7.2.2 The Characteristics of the Process of Technology Acquisition in BVI

The processes of technology acquisition by the BVI firms can be approached from other perspectives. At the beginning the mechanisms were mostly of cooperation with no economic interest involved, and the technologies transferred were mature and of general use in the market.[232,233] Some of the agreements benefited from broader cooperation agreements between the nations involved (interviews 2, 11 and 19).[234] Strong quality control capabilities were developed within the successful agreements but Good

[231] In both Figures 7.1 and 7.2 the TA process of the measles vaccine carried out by Instituto Butantan in 1979 was omitted since the process was interrupted before the vaccine was introduced to the market, as revealed in interview 6.

[232] The first technology acquisition approached in Table 7.1 is an exception to this rule and is described in detail by Barbosa (2009:106-115): following an epidemic of meningitis in the country, the Brazilian government decided to immunize the entire population and 80 million doses of the vaccine were bought from the Mérieux Institute in France. As the technology had been recently developed the manufacturer did not have installed capacity to produce all the doses required and decided to build a pilot plant in Brazil. At the end of the business the pilot plant was donated to Oswaldo Cruz Foundation along with the technology, personnel training and technical assistance.

[233] See Figure 6.5 in the previous chapter for a typology of the vaccine life cycle in the markets.

[234] The agreements for the technology transfer of the measles and polio vaccines to Bio-Manguinhos/Fiocruz took place under a broader cooperation agreement between Brazil and Japan. This was coordinated by the Japan International Cooperation Agency (JICA) and involved the donation of equipment and personnel training (Barbosa, 2009 and interview 11).

Manufacturing Practices (GMP) were not required by the transferors and were not implemented by the BVI at that time (interviews 6 and 11).[235]

The second phase of the technology acquisition was inaugurated in 1998 with the agreement for the technology transfer of the Hib vaccine, and it remains up to the present time.[236] From that time on, a new mechanism was used for the agreements – licensing – since the vaccines were mostly proprietary products (interview 15).[237] The technologies transferred became increasingly more complex, and the elapsed time between the launch of the vaccine on to the international market by the transferor, and the starting of the technology transfer to the firms of the BVI became surprisingly short.[238] As shown in the first column of Table 7.1, from 1999 most of the technologies transferred were in their early product phase and, more recently, the elapsed time of the last two technology transfer agreements was around 1 year; this is the exact opposite of the pattern described in literature about technology transfer to catch-up countries and industries.[239] According to several interviewees the huge Brazilian public market created by the PNI, along with government purchasing power and preference for vaccines produced by the local manufacturers, have been determinant in persuading some "Big Pharma" firms to adopt this different strategy (interviews 3, 7, 9, 10, 13, 15 and 19).

The technologies transferred during this second phase resulted in another important impact on the two main BVI firms. As new technologies were introduced, the price profile of the vaccines marketed has risen from cents to dollars and therefore the income of the firms has grown dramatically, bringing the firms to a new economic reality.[240]

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[235] Later on Bio-Manguinhos/Fiocruz became the representative of the JICA and hosted annual training programmes on quality control techniques for measles and poliomyelitis vaccines for third world countries (Barbosa, 2009).

[236] The agreement was signed in 1998 and production started in 1999 (interview 11).

[237] As there were patents involved, the agreement had to be approved by the Brazilian intellectual property authority – the National Institute of Industrial Property – INPI (interview 15).

[238] It is worth clarifying that the adoption of the launch date of the vaccines to the market by the transferor in Table 7.1 instead of the date of the first introduction of the vaccine to the world market in some cases (as presented in Table 5.4 of Chapter 5 on pg. 104), is because the former constitutes newly and improved technologies partially or totally protected by patents.

[239] The issues about technology transfer of mature products to catch-up countries and about the specificities of the vaccine life cycle are approached in Sub-section 3.4.2 of Chapter 3 (pg. 54 and footnote 82) and Figure 6.5 of Chapter 6 (pg. 146) respectively.

[240] Figures about the BVI are presented in Sub-section 6.2.4 (pg. 135-143) and Section 6.3 (pg. 147-151) of the previous chapter.

The high complexity of the manufacturing process of vaccine, already described and illustrated in Section 5.4 of Chapter 5 (pg. 115-118), was a critical issue in the processes of technology transfer listed in Table 7.1. This was central to the specific and "reverse" way the technologies have been transferred (interview 11). In the first stage the firm acquires the "bulk" of the vaccine from the transferor and carries out the final processing steps, including quality controls. In addition to being less technologically complex, the capabilities for final processing are normally already developed and used for other vaccines manufactured by the firms.[241] The same is often true for the facilities that can normally be used for the final processing of different types of vaccines. This stage can last several years whilst the firm learns the upstream stage – the production of the concentrate(s) – and adapts or builds the proper facilities for this second stage of the manufacturing process.[242] The implementation of the second stage can also last several years, depending on the level of complexity of the technology and on the technical conditions of the transferee to receive and even to adapt the technology to the local conditions.[243,244]

Amongst the interviewees approached about the subject of operating capabilities, it was unanimous that previous knowledge was key for the accomplishment of the processes (interviews 2, 6, 8 and 11). Furthermore, several capabilities developed during the first TA processes have made the more recent processes easier and quicker (interviews 2 and

[241] It does not mean that knowledge acquisition is not intense in this stage. On the contrary, there are many things to learn about the new technology, especially about the steps of formulation, freeze-drying and about the quality control tests required. Furthermore, the second stage is planned and the facilities begin to be adapted and/or built during this stage (interview 11).

[242] In some cases this reverse process can start more downstream, that is, the first stage starts with the acquisition of the vaccine already in the vials and the transferee carries out only the labelling and packaging steps of the final processing. Amongst the possible reasons are the very special characteristics of the technology transferred, the need to speed up the introduction of the vaccine in the market and the need to adapt or expand the final processing facilities (interview 11). Delays in adapting or building the new facilities have often postponed the conclusion of the processes (Barbosa, 2009 and interview 6).

[243] This reverse way of transferring the technologies is convenient for all the actors involved. For the transferee it allows enough time to absorb the technology, develop the capabilities needed and implement the production process safely at the same time it starts selling the product to the government. For the government it allows a quicker introduction of the product to the immunization programme and enables the supply of the product on a regular basis. For the transferor the quick introduction of the vaccine to the market and bulk selling for several years normally provides high financial returns and a guaranteed market (interview 7).

[244] The most recent technology transfer agreement is a revealing example. Although the production start-up of the 10-valent pneumococcal conjugate vaccine is planned for 2010, less than one year after the contract signature, the entire process of technology transfer is predicted to last at least eight years (interview 10). The reasons presented by the interviewee are the high complexity of the technology, which consists in ten vaccines in one, and the need for new and dedicated facilities for the concentrate production.

11). Indeed, the benefits to the development of technological capabilities within the two main firms have been countless. Not only the specific capabilities directly involved in the manufacture of the vaccines but also others that could be exploited in the business in general.

One good example is the quality assurance capability – including metrology and validation – that was highly improved by Bio-Manguinhos/Fiocruz during the technology transfer of the Hib vaccine. The process was extended not only to all vaccine manufacturing lines but also to the management of the production processes. It allowed the firm to apply and obtain pre-qualification from WHO to supply the international market with some of its vaccines (Benedetti, 2008 and interviews 2 and 11). Instituto Butantan also had its quality assurance capabilities strengthened along with the technology transfer of the influenza vaccine even though these capabilities are to be further improved by the Institute (interview 6).

Other important capabilities developed by both firms were in the area of engineering. As mentioned before, to receive the transferred technologies the firms often need to adapt or even build new facilities that require a type of capability seldom found in the country due to the specificities of the vaccine sector. Therefore the transfer agreements always involved some technical assistance to support the local engineers with the design of the facilities, and with equipment and materials specifications (interviews 6 and 21).[245] In summary, what is evident is that the technology transfer agreements have helped the two main firms of the BVI to develop world class operating capabilities and to grow in the international scenario (interviews 7, 10, 11 and 20).[246]

Notwithstanding, one point of great interest for the BVI and for this research remains highly controversial, as has been raised during the interviews. It relates to the supposedly intended benefits of the technology transfer processes to the development of

[245] According to one interviewee the agreement for the technology transfer of the influenza vaccine also included equipment specifications that were passed to the local equipment industry making possible the acquisition of several equipments locally (interview 6).

[246] The processes of technology acquisition have benefited other firms of the BVI directly or indirectly. One example is the outsourcing of part of the production process of the Hib vaccine to Tecpar. Within this strategic alliance, Tecpar is producing the monomeric tetanic protein for Bio-Manguinhos/Fiocruz to be used in the conjugation of the Hib vaccine. Besides the specifications for the production of this component, Bio-Manguinhos/Fiocruz also helped Tecpar with the development of its quality assurance system to ensure that the production complies with GMP requirements (Barbosa, 2009).

innovative capabilities. For most of the interviewees approached about the subjects of policies, corporate strategies and operating capabilities, the TA processes have been important and directly or indirectly helped the development of internal innovative capabilities or somewhat accelerated it (interviews 2, 3, 10, 11, 13, 15 and 19). As technologies transferred invariably need to be adapted to local needs, the R&D areas are constantly developing to support the ideal establishment of the processes (interview 11).

For most of those interviewees who work with technological development, however, the knowledge spillover from these agreements to R&D areas is limited, sometimes localized but not that useful in terms of development of the capabilities needed to innovate (interviews 1, 4, 6, 12 and 14). In this sense the TA processes are seen as a means of postponing the pressures and needs for quick answers from the R&D areas rather than to help to develop them. Moreover, within these agreements the transferors are keen to control the capabilities they do not wish to transfer (interview 1). For some interviewees the TA processes can eventually hinder the development of innovative capabilities since projects are cancelled due to the lack of practical necessity of their results (interviews 1 and 12).

However, other interviewees point out the importance of the proximity between production and R&D areas, stating that these interactions have been increasingly important to the development of some innovative capabilities (interviews 5 and 18). As an example, several improvements to the old yellow fever vaccine and to its production process were made possible from the knowledge acquired in the TA process of the measles vaccine (interview 18). The same interviewee points out that some capabilities developed within the TA process of the MMR vaccine might help the in-house development of a Hepatitis A vaccine. The domain of new technological platforms has also been possible with some of the agreements and is of interest to the firms for the development of innovative capabilities (interviews 5 and 18). The issue is, therefore, far from an agreement.

One last point about the TA agreements relates to the contracts themselves and their implications to the firms. There are some restrictions imposed by the transferors and the most important relates to the markets where the firms can sell the technologies

transferred.[247] Normally, by contract, they are allowed to supply the Brazilian public market only, which restricts important international markets such as UNICEF and PAHO (interview 7).[248]

7.2.3 Trends to the Technology Acquisition Strategy

One of the concerns of this research was to try to capture future trends in the adoption of TA strategy. In an article about the Brazilian and Indian vaccine industries Milstien et al (2007) pointed out that, despite the increasing development of their innovative capabilities, these emerging manufacturers are expected to resort more often to technology transfer agreements. This is due to the implications of the implementation of the TRIPS Agreement in these countries. One of the interviewees, the former general director and founder of one of the firms and responsible for the firm's TA strategy since the 1980s, believes that TA will still remain important for 10 or more years whilst the firm develops and strengthens its innovative capabilities. After that period, the TA strategy might continue but it would decrease in importance (interview 19). In a similar direction other interviewees see the BVI links to the TA strategy tightened in the short term, but point out that the industry and government should be aware of the risks of relying excessively on this strategy (interviews 7, 13, 15 and 16).

From a more critical view and based in some indicators, another interviewee recognizes that the TA strategy was very important for the first phase of the BVI's development. The strategy helped the two main firms to become larger, with significant income and best practice in the production area.[249] However, the role of this strategy has now been fulfilled and the firms should concentrate their efforts on developing their innovative capabilities, taking advantage of several of the innovation policies and funds made available more recently by the Brazilian government and governmental institutions (interview 20).

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[247] Another restriction is the limit of freedom to modify the technology transferred. Any improvement or change to the technical specifications of the product should be previously submitted to and approved by the transferor (interview 11). However, this restriction has not hindered the improvement of the products especially in adapting them to local circumstances. This issue is approached in Section 7.3.

[248] Some aspects of the UNICEF and PAHO markets are presented in Sub-section 6.4.1 of Chapter 6 (pg. 153-154).

[249] The interviewee pointed out that, before the second phase of the TA agreements, the incomes of the firms were tiny and did not justify high investment in R&D. With the incomes now in the hundreds of millions of dollars there is room for more significant investment in R&D.

In his view, to speed up the process, the firms should use the government purchasing power to force the "Big Pharma" to transfer innovative capabilities. In fact, less than one year after this interview the first TA agreement signed by one of the firms – to transfer the technology of the 10-valent pneumococcal conjugate vaccine – encompassed cooperation for the development of new vaccines and investments of about US$ 30 million from the transferor to this cooperation (interview 10).[250] According to the same interviewee, this unprecedented type of TA agreement is certainly a distinguishing initiative of the firm, and it may constitute the beginning of a new phase in the BVI's development.

Notwithstanding, there are other signals that the level of importance of TA will remain high in the BVI. One example is its suitability to the Ministry of Health's short-term policies. As new and improved vaccines have been introduced in the international market, there is pressure from the society for their quick introduction to the Brazilian market; this would not be possible through in-house development (interview 16). In a book celebrating 30 years since the creation of the PNI, TA agreements are acknowledged today as a shortcut, a more rational and more suitable strategy to enable the access to new technologies (Brasil, 2003:32). Moreover, even though the firms, together with the Ministry of Health, have produced a list of priority vaccines within the scope of the INOVACINA Programme, looking for strengthening R&D and innovation inside the BVI (Carvalheiro et al., 2005), of the first three vaccines already introduced two were a result of TA agreements (rotavirus and pneumococcal), and the third (human rabies in vero cell) was first introduced through a TA agreement and later substituted by the same technology developed in-house.[251,252]

7.3 Development of Innovative Capabilities

In this section this research turns to those sources of knowledge that are increasingly important in a common pattern of technological capabilities development in catching-up industries, as argued in the conceptual framework in Chapter 3. In the model developed, the transition from advanced to competitive levels of technological capabilities is based

[250] The collaboration for the development of the dengue, inactivated polio and malaria vaccines are included in the agreement (Bio-Manguinhos, 2009a and interview 10).
[251] The INOVACINA Programme was briefly approached in Sub-section 6.4.2 of the previous chapter (pg. 161).
[252] There are 31 vaccines listed as being of priority interest for Brazilian health policies, 16 of which were still not available worldwide by the time the list had been prepared (Carvalheiro et al., 2005:276-279).

on increasing levels of innovative capabilities. This includes other channels of exploiting sources of technological knowledge, such as internal and external linkages and training, rather than on TA.

The extent of the adoption of the TA strategy, especially in recent years as stressed in the previous section, may lead to a perception that the BVI firms have been either passive or are still in the early stages in terms of innovative capability development. However, data gathered from the two main firms during the fieldwork show that this perception may be misleading.

This research has tracked the development of internal innovative capabilities, and of internal and external linkages, by these main BVI firms seeking to disclose its real extension, its current level and possible constraints to the completion of the transition phase. This was done in order to enable the examination of the real pattern of technological development and the characteristics of the transition phase of this industry. With the same objective the existence of initiatives of training by the firms was investigated. In this sense, Sub-section 7.3.1 presents the trajectory and main achievements in the process of internal innovative capability development, including in-house R&D and clinical trials. The strengthening of internal and external linkages is examined in Sub-section 7.3.2, and finally the importance of learning by training within the BVI as a source of knowledge is briefly approached in Sub-section 7.3.3.

7.3.1 Internal Innovative Capabilities: Own R&D, Clinical Trials, Design and Engineering

Own R&D – Even though the period studied in this research starts in the 1970s it is worth remembering that the two main firms of the BVI have their origins in the early 20th century when they had the task of developing and producing serum for bubonic plague. After doing that successfully, several other vaccines were developed and produced by both institutions before the period focused on in this thesis.[253] Therefore, although there had been great transformations in the scientific and technological vaccine knowledge base in the international scenario, especially after WWII, one can suppose

[253] See Sub-section 5.2.3 on pg. 98-100).

that in the early 1970s those BVI firms had inherited some technological capabilities from the past.

Notwithstanding, during the 1970s and first half of the 1980s what can be observed in the BVI is basic and intermediate levels of innovative capabilities. These were mostly informal and directed towards adapting foreign technologies and/or improving the production process of old ones. This notion was captured from two interviews and some additional data. In one of the firms, minor adaptations to old technologies, such as the introduction of fermentation processes to the production of the pertussis vaccine, other adaptations to the production of diphtheria and tetanus vaccines and the improvement of the water used in the production process, were carried out basically by the production team in order to improve product quality (Instituto Butantan, 2000 and interview 6). According to the interviewee, at that time production was very small and addressed São Paulo state's needs only. In the other firm a series of improvements to the yellow fever vaccine and its production process were carried out mainly in the 1980s by a sole technician in conjunction with the production and quality control teams (Leal, 2004 and interview 11).

Although both firms were part of research institutions, they did not count on formal R&D areas to support technological innovation at that time. Eventually, however, there were significant achievements. The most important was the adaptation of the poliomyelitis vaccine during the process of technology transfer and the implementation of its production. In collaboration with a research institute of Fiocruz, Bio-Manguinhos/Fiocruz developed a new formulation to the vaccine to adapt it to the characteristics of the country. The WHO then recommended that the new formulation be adopted in all tropical countries (interview 11).[254] Prior knowledge in vaccine production was a very important asset at this phase, as emphasized by the interviewees.

From the mid-1980s this situation started changing. The firms realized that building new production facilities would not be enough either to cope with the tighter quality requirements imposed by the government or to keep up with the technological advances

[254] The original formulation of the vaccine did not give protection against one of the prevalent virus of the disease in the country. With the change in the formulation the vaccine became fully protective and the last case of poliomyelitis in Brazil was registered a few years later, in 1989 (Brasil, 2003).

in the vaccine area in the international scenario. The precursory fact of this new phase took place in 1985 with the inauguration of the Biotechnology Centre by the Instituto Butantan (Gadelha and Azevedo, 2003). A short time later Bio-Manguinhos/Fiocruz implemented the first two laboratories dedicated to technological development of viral and bacterial vaccines (Leal, 2004). The importance of both initiatives, and the new approach to technology, can be recognized as a landmark in the development of innovative capabilities within this industry. The events that unfolded since then are described below.

The results of the initiatives of both firms described above came shortly after. In 1987 the Instituto Butantan concluded the development of DTP and DT vaccines, as shown in Table 7.1.[255] The most important and visible result of the creation of the Biotechnology Centre, however, was the development of a recombinant hepatitis B vaccine, concluded in 1998 (interviews 5 and 6).[256,257] As noted by Gadelha and Azevedo (2003), in addition to consolidating the importance of the Biotechnology Centre within the institution, this achievement also represented to the BVI an advance in terms of technological management. This was because its pioneering managed to integrate biomedical research, technological development and industrial scale-up, a phenomenon hardly seen in most Brazilian industries.[258] Other achievements of the Biotechnology Centre in terms of product development that evidence the development of innovative capabilities within the firm were the development of a dT vaccine and, more recently, of a rabies vaccine in vero cell (see Table 7.1 on pg. 165).[259]

[255] Since the 1970s, the Instituto Butantan had already produced the components of the DTP vaccine as single vaccines. In addition to the studies for combining the components into a triple vaccine, they also established a new process for producing each of the components in "closed systems". This avoided contaminations and guaranteed the quality of the product (interview 6). The interviewee also emphasized that there were manuals in the public domain on how to produce the old vaccine but, in practice, establishing the parameters and developing tacit knowledge was a painstaking process.

[256] It is worth noting that the hepatitis B vaccine was the first vaccine developed using genetic engineering techniques and that it had been launched in the international market by Merck only 12 years before (see Sub-section 5.3.1 on pg. 105 and Table 5.4 on pg. 104).

[257] According to one interviewee the development of the vaccine started in 1993 after the hiring of two Russian researchers who owned the strain of the virus. They were then provided with a team, facilities in the Biotechnology Centre, and material resources to develop the vaccine (interview 6). Although the product had been launched in 1998, the clinical trials had to be carried out again as they did not meet with the regulatory authority's requirements and the use of the vaccine by the PNI was postponed till 2001 (Gadelha and Azevedo, 2003).

[258] The gap between basic research and technological development is one of the bottlenecks that the BVI is still struggling to overcome (interview 19)

[259] With the development of the rabies vaccine in vero cell, the firm could interrupt the process of technology transfer started four years earlier (interview 6). The interviewee stated that the vaccine was developed entirely in-house, not benefiting from the technology partially transferred from Aventis Pasteur.

In Bio-Manguinhos/Fiocruz the two R&D laboratories implemented were responsible for several incremental innovations to the vaccines produced by the firm and to their production processes during the 1990s, up to the point that the original technology of some of these products was completely transformed (Leal, 2004 and interview 11). The R&D area was then expanded with the creation of the Department of Technological Development in the early 1990s, with the introduction of studies on DNA recombinant technology in 1994, and with the implementation of the Recombinant Technology Laboratory in 1998 to start the development of new DNA recombinant vaccines (Leal, 2004). More recently the R&D structure was reformed with the creation of the Directory of Technological Development (Barbosa, 2009).[260] In terms of new products the most important achievement of the firm so far was the introduction of the DTP+Hib vaccine in 2002 (see Table 7.1 on pg. 165).[261,262]

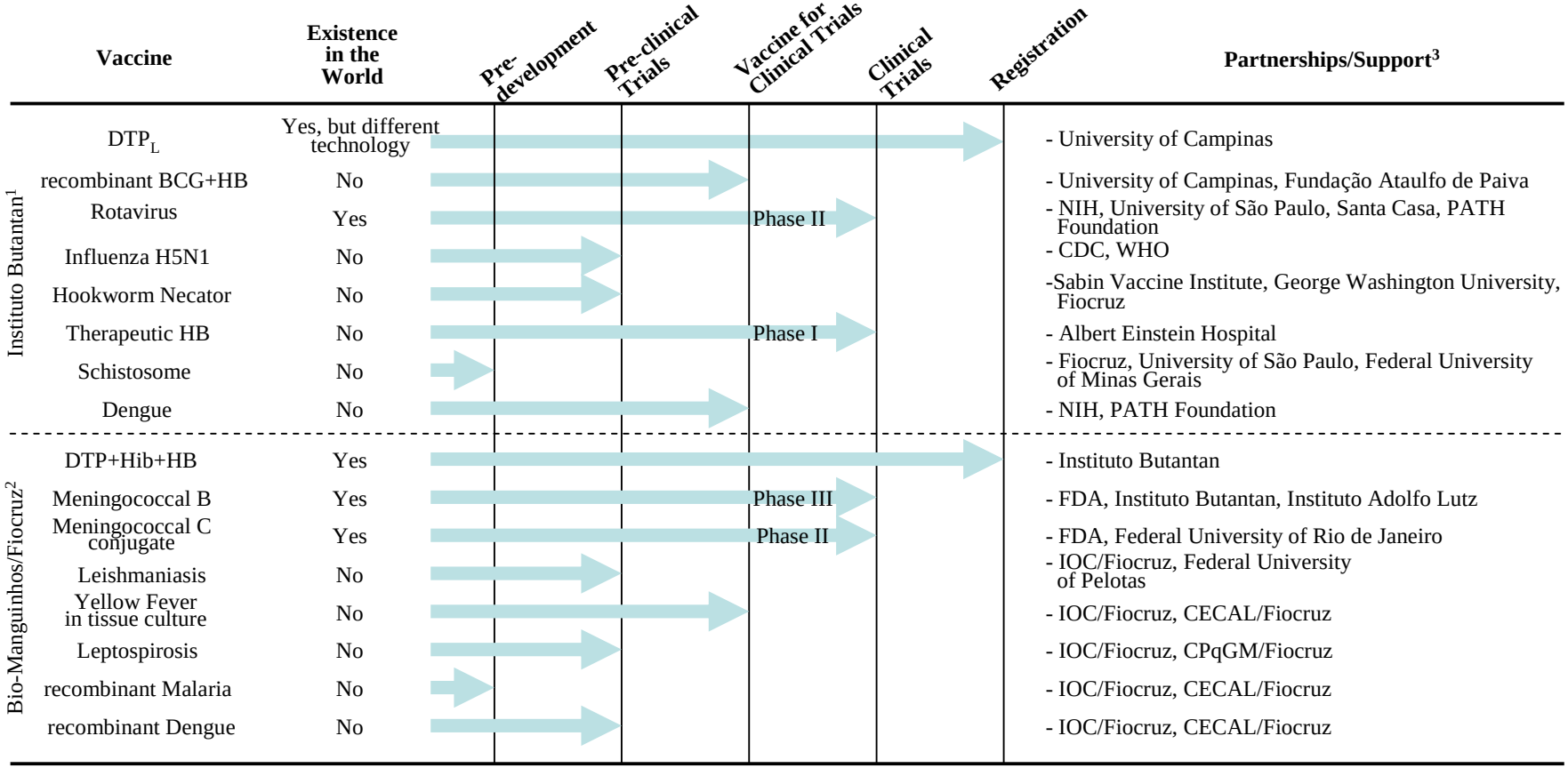
Notwithstanding, if we look at the R&D pipeline of both firms greater achievements seem to be on the way, strengthening the notion that they have already developed advanced innovative capabilities. According to the data gathered from the firms there are currently 29 new vaccines under development. Figure 7.3 shows some selected projects being developed by each firm, their current stage, the availability of the product worldwide and the partnerships established during their development.

[260] Two other more recent initiatives, currently in the final stages of construction, have been pointed out as being of key importance to the strengthening of vaccine innovation: the first is the construction by Fiocruz of the Centre of Technological Development in Health (CDTS), a new institute aiming to fill the gap between basic research, carried out by its research institutes, and technological development, carried out by its production institutes, and to comply with the legal requirements (Good Laboratories Practices – GLP) to develop a vaccine. The second is the construction of a pilot plant by Bio-Manguinhos/Fiocruz, aiming to provide modern and dedicated facilities to the scale-up and production of vaccines for the clinical trial (phases I and II) phase of the vaccines technological development (Leal, 2004; Moreira, 2005).

[261] The development of this tetravalent vaccine was extremely important to both Bio-Manguinhos/Fiocruz and Instituto Butantan, as the PNI intended to introduce it to the immunization routine; the importation of the vaccine would dramatically affect both firms (interview 11). The quick response of Bio-Manguinhos/Fiocruz in combining its Hib vaccine with the DTP vaccine produced by Butantan, carrying out the clinical trials required, registering the product, organizing the production process and launching the new vaccine, is the main aspect to be highlighted about this achievement. According to the interviewee, the firm counted on the collaboration of GSK and Instituto Butantan in this project,.

[262] Incremental innovations during the absorption of foreign technologies have remained important and effective in recent years. One example relates to the MMR vaccine. During the absorption of the technology the firm needed to develop a new freeze-drying process to obtain better results than the original technology. This new process is now under final tests in order to be implemented and has awakened the interest of the transferor of the technology (interview 11).

As can be seen in Figure 7.3, there is a big diversity amongst the projects in the firms' pipeline. Some are in the earlier stages of development, others are in later stages or even in the process of being registered. Some address existing products but several projects address products that are new to the world market. All the projects, however, address Brazilian needs, some of them addressing diseases only found in developing countries and, therefore, not of interest of the "Big Pharma" – e.g. leishmaniasis and leptospirosis (interview 19).



[1] In 2007.
[2] In 2009.
[3] NIH (National Institutes of Health/USA); CDC (Centers for Disease Control and Prevention/USA); WHO (World Health Organization); FDA (Food and Drug Administration/USA); Fiocruz (Oswaldo Cruz Foundation); IOC (Oswaldo Cruz Institute); CECAL (Animal Breeding Centre); CPqGM (Gonçalo Moniz Research Centre).

Source: Own elaboration from data gathered during the fieldwork.

Figure 7.3: Selected Projects of the R&D Pipeline of the BVI Firms

Although some projects address existing products they have an innovative approach, as in the case of the DTP_L vaccine – Diphtheria, Tetanus and "low" Pertussis – (interview 6).[263] Even therapeutic vaccines, considered the future of vaccines by vaccine experts (e.g. Plotkin, 2005b), are in the later stages of development by one of the BVI firms.[264]

Another point emphasized by one of the interviewees is the good results that one of the firms is achieving with the development of new adjuvants (interview 6). Adjuvants are important components of vaccines, as already stressed in Sub-section 5.3.1 of Chapter 5 (pg. 106).

Table 7.2: R&D Personnel x Employee Total in Bio-Manguinhos/Fiocruz

Year / Growth	Employee Total (A)	R&D Personnel[1] (B)	B/A	PhD (R&D) (C)	C/A	C/B
1999	411	58	14.1%	8	1.9%	13.8%
2008	1102	162	14.7%	31	2.8%	19.1%
Growth	168.1%	179.3%	-	287.5%	-	-
Annual Average Growth	11.7%	14.2%	-	17.8%	-	-

[1] Include personnel engaged in R&D of diagnostic reagents and biopharmaceuticals and in clinical trials.
Source: Own elaboration from data gathered during the field work.

Other data and figures were gathered to help the examination of the strengthening of innovative capabilities in the BVI. The evolution of the personnel engaged in R&D is one of them. In Bio-Manguinhos/Fiocruz detailed data of the last 10 years (i.e., when the firm experienced rapid growth due to the new vaccines introduced by technology transfer) show that the R&D area was not neglected in terms of R&D personnel and their qualifications. As shown in Table 7.2 above the rise in the numbers of R&D personnel from 1999 to 2008 has indeed overcome the rise in the total number of employees. Whilst the former has grown at an annual average rate of 14.2%, the latter has grown at 11.7%. The ratio of R&D personnel to total employee, therefore, rose from 14.1% to 14.7%. As a matter of comparison the same ratio in the "Big Pharma" Sanofi-

[263] The interviewee explained that the (whole) pertussis component of the traditional DTP vaccine is very reactogenic, and the substitute vaccine available worldwide using acellular pertussis is very expensive as its production yield is very low. Instituto Butantan managed to develop a new process to obtain a less reactogenic pertussis component at a much lower cost and with similar or better immunogenicity.
[264] The firm is developing two therapeutic vaccines according to institutional material released (Instituto Butantan, 2007).

Aventis has remained stable at around 19.2% during the period 2006-2008 (Sanofi-Aventis, 2009).

Another important figure shown in the table relates to qualifications of R&D personnel; this was because the rise in the numbers of PhDs engaged in R&D was still more impressive in the period studied. With an annual average growth rate of 17.8% the ratio of PhDs to other personnel within the R&D area has decreased from 1:6 to 1:4 approximately.

The achievements of the Biotechnology Centre are undoubtedly linked to the strengthening of its personnel. The hiring of some retired scientific leaders just before the inauguration of the centre was a strategy used to attract skilled researchers and students from universities and research institutes (interview 5).[265] Figures gathered during the fieldwork show a fair increase of skilled people in recent years. In 1998 the Biotechnology Centre employed 15 PhDs (Mello, 2000). By 2009 the number of PhDs allocated to the centre had reached 21 (Chaimovich, 2010), a growth of 40% in the period. However, according to the manager of the centre, more skilled people should be hired to speed up the results, but it has been a very difficult process. Moreover, the facilities must be expanded before it is possible to offer more adequate conditions (interview 5).

It is also useful to look at the R&D expenditures of the firms. As noted by Milstien et al. (2007) both firms have significantly increased their R&D expenditure in recent years, however this was not quantified. Table 7.3 presents these figures from one of the firms to exemplify the growth mentioned by the authors and provide a quantitative picture of the situation.[266] As can be seen from the table the growth figures are really impressive, especially the R&D intensity that has more than tripled in six years, denoting an awareness of the importance of this area to the development of the firm as well as a conscious effort toward its strengthening. However, in a broader context the situation is

[265] More information about this issue can be found in Sub-section 7.3.2 of this chapter.

[266] The values of R&D investments and total revenues were converted into dollars because this is the currency used in this research; it also allowed a comparison with figures of the international scenario. However it is worth noting that the Brazilian currency – the Real – has sharply appreciated to the US dollar in the last decade, and the same figures present a different growth and annual average growth when expressed in the Brazilian currency, even adjusted by the Brazilian inflation. In this case the R&D investments and the total revenues have grown by 660.3% and 107.9% in the period studied at a 44.3% and 18.3% annual average rate respectively.

still far from being significant. Not only were R&D investments in 2008 tiny when compared to those of the four "Big Pharma" – over US$ 500 million on average – but the same is also true of the R&D intensity indicator. This varied from 14.9% to 20.5% on average during the period 2006-2008 for the same companies (see Table 6.1 in the previous chapter on pg. 125).

Table 7.3: R&D Intensity and Investment Growth in Bio-Manguinhos/Fiocruz

Year/Growth	R&D Investments (US$)[1] (A)	Total Revenues (US$)[1] (B)	R&D Intensity (A/B)
2002	1,252,103	80,764,699	1.6%
2008	17,964,653	316,808,419	5.7%
Growth	1,334.8%	292.3%	-
Average Annual Growth	62.5%	31.7%	-

[1] Values encompass all the businesses of the firm. They were converted into US$ by the average rate of exchange provided by the Brazilian Central Bank. The values of 2002 were then adjusted to 2008 by the US inflation rate (CPI) provided by the US Bureau of Labor Statistics.
Own elaboration. *Source:* Bio-Manguinhos (2008, 2009b)

However, the responses of the interviewees who work in the R&D area show that the amount of resources currently invested in R&D is only part of the problem relating to the development of technological capabilities within the firms (interviews 1, 4, 5, 12, 14 and 18). Although they unanimously recognize that more resources should be invested in more adequate facilities, in the domains of new technological platforms, strengthening of specific technological capabilities, increasing the number of skilled people and training activities to speed up the results of the projects, there is a common sense amongst them that the lack of efficient R&D management and the bureaucracy of the public sector are important hindrances that, if not solved, will postpone or even invalidate any increase of resources invested.

Clinical trials – due to several reasons already discussed in Sub-sections 3.5.1 (Chapter 3 on pg. 69-70) and 5.3.3 (Chapter 5 on pg. 109-114), special attention is given in this research to the process of vaccine development in order to help the examination of the strengthening of innovative capabilities within the BVI. From one perspective, in spite of the fact that most projects fail during the clinical trials phase, the existence of several vaccine projects in the clinical trials phase of development, as shown in Figure 7.3,

itself suggests that the BVI firms have reached a significant level of innovative capabilities, as several complex steps have to be accomplished before this important stage. On the other hand, as the regulatory authorities have tightened the requirements for clinical trials, aiming at the safety and efficacy of the vaccines, the domain of clinical trials capabilities have become essential and limited to only a few firms, as noted by the WHO (2002b).[267] The vaccine manufacturers have increasingly outsourced the clinical trials to specialized institutions (the Contract Research Organizations (CROs)); this is also done by some "Big Pharma" firms.[268]

In Brazil there are only a few CROs, all of them dedicated to carrying out clinical trials for multinational firms (interview 22). An initiative of developing a network of clinical research in the country was launched some years ago by the MOH but no concrete results have been achieved so far (interview 17). In the BVI both firms have followed a different strategy. The Instituto Butantan, the first to develop vaccines in recent times, has relied on partnerships with universities and public hospitals to carry out clinical trials. However, not to own any clinical trials capabilities is risky, and sometimes the result may be frustrating as happened with the development of the hepatitis B vaccine, where clinical trials were considered not to have complied with the requirements (see footnote 257). New clinical trials for the vaccine were then financed and coordinated by the PNI (interview 22). More recently the firm recognized the need to develop its own clinical trials capabilities (interview 6). An epidemiologist was then hired with the objective of structuring this activity within the firm (interview 3).

The other firm, however, has been more successful in this purpose. By hiring the expert who had coordinated the clinical trials of the hepatitis B vaccine for the PNI, the firm started structuring this new area in 2002 and have achieved important results since then (interview 16). Amongst these results are the successful conclusions of the clinical trials of the tetravalent vaccine (DTP+Hib), and, more recently, of the pentavalent vaccine (DTP+Hib+HB). In addition, important vaccines are currently in the clinical trials phase, as shown in Figure 7.3 (interview 22).[269] With a rapid expansion the firm employed 32

[267] See Sub-section 6.2.1 (pg. 122-123) on the importance of clinical trials capabilities for the "Big Pharma".
[268] See Sub-section 5.3.3 (pg. 109-114) and Table 5.6 (pg. 110) in Chapter 5 for these and other general aspects of clinical trials.
[269] According to the interviewee, some existing vaccines were also successfully tested through clinical trials in order to obtain new registration due to incremental innovations.

personnel in this area in 2008, but according to the same interviewee there is still a long way ahead to reach international standards, especially with regards to the infrastructure needed. The development of the protocols for the studies was mentioned as one important capability developed. Moreover, the studies are monitored by an external committee, which confers credibility to the results achieved.[270] The interviewee also pointed out two important advantages of carrying out clinical trials in-house for the development of innovative capabilities: there is a flow of important technical information from the clinical trials to the laboratories that carry out the previous phases of the vaccine development, especially to the immunology laboratory. At the same time, the close interaction with these laboratories during the development of the vaccine helps the design of the protocols and the conduction of the clinical trials later on.

Design and Engineering – Vaccine design is inherent to the process of developing vaccine, beginning with the discovery up to the definition of the production process of a vaccine for clinical trials (interview 18).[271] The background of the professionals for these steps is broad and varied, depending on the step and the type of vaccine being developed. The main source of technological knowledge in this industry, however, is commonly concentrated in the biomedical, biological and chemical sciences. Some specific engineering knowledge may be required only during the development of the downstream process, according to the same interviewee.

The type of design and engineering capabilities more visible and important in this industry, therefore, are those directed towards the design and building of facilities to comply with biosafety, GMP and GLP requirements, as already discussed in Sub-section 7.2.2 of this chapter. Although important for the vaccine industry, this type of capability does not warrant a deeper discussion within the scope of this research.

7.3.2 Other Sources of Knowledge – Internal and External Linkages

The importance of interactivity and networking in the process of innovation was stressed in Sub-section 2.2.2 of Chapter 2 (pg. 15-16). In the present sub-section the existence, evolution and results of specific interactions developed by the BVI in order to

[270] That is, external to the firm.
[271] The development of a vaccine was already discussed in Sub-section 5.3.3 of Chapter 5 (pg. 109-114) and therefore not much attention will be given to this issue here.

acquire technological knowledge, as defined in Sub-section 3.5.2 of Chapter 3 (pg. 70), will be examined. This type of interaction has been decisive to the manufacture of vaccine, especially to the "Big Pharma", as discussed throughout Section 6.2 of Chapter 6 (pg. 121-143).

In the BVI, links with universities and research institutes were common until the mid-1980s due to the location of the firms inside research centres, but the results in terms of innovation in vaccines were limited, with few exceptions.[272] In the mid-1980s, just before the inauguration of its Biotechnology Centre, Instituto Butantan took an important initiative that strengthens the notion that this was the beginning of new times in the BVI. By hiring 10 scientific leaders from the universities and research institutes of São Paulo state, most of them recently retired, the Institute Butantan not only established closer connections with the academic and research communities but also benefited from a rich interchange of students from those institutions (interviews 3, 4 and 5).

In the 1990s the links and collaborations were intensified by both firms and provided several concrete results. Amongst the most important are a collaboration with the FDA, which provided a consultant to participate in the development of a meningococcal B vaccine (Leal, 2004), the hiring of the two Russian researchers who developed the hepatitis B vaccine for Instituto Butantan (see footnote 257 on pg. 176), and the hiring of a British vaccine expert who was the responsible for several incremental innovations of the measles and yellow fever vaccines of Bio-Manguinhos/Fiocruz.[273,274]

In fact, the network of collaborations has been increasingly broadened and strengthened in the last decade, both in the national and international contexts, as the firms realized that this is an essential strategy to achieve quicker and better results. Some interviewees

[272] See paragraph complemented by footnote 254 in Sub-section 7.3.1 of this chapter (pg. 175).
[273] According to Leal (2004:94), the development of the meningococcal B vaccine, which is currently in clinical trials (see Figure 7.3), also involved collaboration between Bio-Manguinhos/Fiocruz and Instituto Butantan and with Instituto Adolfo Lutz, another São Paulo state research institute .
[274] In the late 1990s, Bio-Manguinhos/Fiocruz inaugurated a new instrument – the "Letters of Commitment" – in order to strengthen the links with the research institutes of the Fiocruz and induce research within its areas of interest. By this instrument Bio-Manguinhos/Fiocruz committed to fund projects intended to improve or develop new immunobiologicals. A total of 38 letters were signed with Fiocruz institutes. Later on the initiative was extended to external research institutions and universities (Moreira, 2005). According to Leal (2004), the first results have been achieved in the area of diagnostic reagents.

who work directly within R&D emphasized this point (interviews 1, 4, 14 and 18).[275] Figure 7.3 shows that most of the products in the firms' R&D pipeline are being developed with some kind of collaboration. One interviewee from Bio-Manguinhos/Fiocruz, however, pointed out that, although collaboration with the public sector has been running increasingly well, there is a need to strengthen collaboration with the private sector; this has been more difficult due to the bureaucracy faced by the BVI firms (interview 1). [276] Despite being hampered by the same problem of bureaucracy, Instituto Butantan has already started an interesting type of partnership with a private company with the inauguration in 2006 of a joint research centre with the firm Ouro Fino Animal Health.[277] The objective of this research centre is the research and development of veterinary immunobiologicals to be commercialized by the private company, and with the eventual profits to be invested in human immunobiologicals (Instituto Butantan, 2006).

Linkages with suppliers – both national and international – have also been established by the BVI, although they need to be further strengthened (interviews 6, 10 and 11). These linkages, however, have mainly addressed specific production requirements such as the adequate specification of materials and the certification of the quality of suppliers to ensure the product quality, and to comply with the GMP requirements.

7.3.3 Other Sources of Knowledge – Learning by Training

The focus now turns to a specific way of acquiring technological knowledge – learning by training. Learning by training seems to be especially important in the vaccine industry as several of its specificities are not even found in other segments of the pharmaceutical industry, as already discussed in Chapters 5 and 6, and emphasized by several interviewees (interviews 1, 5, 6, 8, 11, 18 and 22). This means that much of the

[275] The Developing Countries Vaccine Manufacturers Network (DCVMN), outlined in Sub-section 6.4.1 of Chapter 6 (pg. 155), is one recent and original initiative in which the main firms of the BVI are participating, in an attempt to strengthen international collaborations.

[276] The interviewee cited one recent case as an example of the problem of rigidity in establishing agreements with the private sector: after identifying a technology of interest to Bio-Manguinhos/Fiocruz for the development of a new yellow fever vaccine being developed by an international biotech firm, the firm saw the technology being licensed to Acambis during the negotiations. Acambis was one of the most prominent biotech firms in the field of vaccines, which was later acquired by Sanofi-Pasteur, the main competitor of Bio-Manguinhos/Fiocruz in the international market of yellow fever vaccine. The problem rigidity/administrative inflexibility within the BVI is discussed in Section 7.4 (see Figure 6.1 and Table 6.2 in the previous chapter on pg. 123 and 128, respectively, for some information about Acambis).

[277] The research centre was built inside the Instituto Butantan campus from the resources of both firms and from other funds from two governmental financing agencies.

specific capabilities of this industry must be developed in-house as they are difficult to find ready-made in the market (interviews 6 and 11). In addition, the firms have to deal with the deficiencies of the formal education provided by the still developing Brazilian educational system.[278] According to the same interviewees, this, in turn, gives firms a further problem: after extensively training biotechnologists, engineers and technicians to carry out their activities, the firms see some highly skilled people absorbed by private companies that can afford higher salaries than the public sector.

Some evidence of the firms' efforts and strategies, as well as the hindrances they are faced with in terms of providing training as an important source of knowledge, was gathered from interviews, annual reports and theses, and shows both some interesting initiatives and imbalances within the BVI. Despite the high awareness of the need to continuously improve the qualifications of its researchers, biotechnologists and technicians, the Instituto Butantan did not rely on any formal training policy in the 1990s (Mello, 2000). According to Mello, the responsibility of defining the needs and raising funds for training were delegated to each research team at the time of applying to financing agencies for project funds, whilst the firm provided the facilities for the training events. The main reason was the lack of freedom to establish its own training policy due to restrictions of state government bureaucracy (*ibid.* p.219).

Today the situation does not seem to be very different. According to one interviewee, government restrictions still hinder the possibility of training the firm's researchers abroad for periods over three months, and this has been a serious drawback to the qualifications of R&D personnel (interview 5). Providing training for operating capabilities, however, has been easier as there is a need to comply with GMP requirements. Moreover, the technology transfer agreements already encompass personnel training, which are carried out both in Brazil and in the transferors' facilities (interview 6).

[278] As indicated by one interviewee, the existence of several outstanding universities and technical schools in the country is recognized (interview 5).

In the other firm a much more formal commitment to training was found, although being part of the federal government structure also implies certain restrictions.[279] The firm explicitly invested in a Training Programme and the growth of this type of investment has overtaken the growth of the total revenues of the firm. In 2008 the firm invested over US$ 660k in training.[280] The figures, however, seem insignificant when compared with the average annual expenditure per employee in a sample of large organizations in the US; this was in a survey undertaken by The American Society of Training & Development (ASTD). These figures are shown in Table 7.4.[281]

Table 7.4: Training Investment in Bio-Manguinhos/Fiocruz

Year / Growth	Training Investments[1] US$ (A)	Total Revenues[1] US$ (B)	(A/B)	Employee Total	Expenditure per Employee	ASTD Benchmarking US$
2002	134,714	80,764,699	0.17%	560	201	826
2008	669,284	316,808,419	0.21%	1102	607	1,435[2]
Growth	396.8%	292.3%	-	-	-	-
Average Annual Growth	68.2%	31.7%	-	-	-	-

[1] Values encompassing all the firm's businesses. They were converted into US$ by the average rate of exchange provided by the Brazilian Central Bank. The values of 2002 were then adjusted to 2008 by the US inflation rate (CPI) provided by the US Bureau of Labor Statistics. [2] In 2006.
Own elaboration. *Source:* Bio-Manguinhos (2008, 2009b), ASTD (ASTD, web page, accessed in 01/2009).

The firm has had three creative initiatives in recent years that have enhanced the results of those investments. The first was the creation of a "professional" masters degree in technology on immunobiologicals, within the structure of the firm and in partnership with a research institute of Fiocruz (Bio-Manguinhos, 2009b). As noted by Moreira (2005), an interesting characteristic of this degree is that the students are encouraged to present a dissertation representing a concrete contribution to their technical activities. The students have, therefore, generated innovations to the firm's production processes (interview 19).[282] The second was the creation in 2004 of a technical course on

[279] Recently the firm had to stop financing external training to outsourced personnel for legal reasons. As the firm relied heavily on personnel outsourcing as an alternative to the limitations in hiring public workers, this legal restriction caused an important impact to the firm's training programme (Barbosa, 2009).
[280] These investments include training abroad provided by the transferors of technologies (Barbosa, 2009).
[281] The firm does not calculate the return on investment (ROI) for their activities on training.
[282] Three cohorts have finished the two year degree since then, and the last two cohorts have relied on workers from other institutions of the field of immunobiologicals (interview 10).

biotechnology in health. This course is a partnership with an education institute of Fiocruz and is directed at technicians with no graduate background (Barbosa, 2009). The third was the creation in 2005 of a specialization course in industrial management on immunobiologicals, in partnership with an Institute of Engineering of the Federal University of Rio de Janeiro – COPPE/UFRJ (Bio-Manguinhos, 2009b).

7.4 Organizational Capabilities

As this research considers, by definition, that technological capabilities encompass both the firm's technical and organizational efforts in dealing with technology, this section briefly approaches some of those types of competencies concerning the governance of the organizations as a whole, in the sense distinguished by Dosi et al. (2008).[283] In this regard, and more specifically, two key issues of a managerial and strategic nature were identified as of interest to this research:

a) the public nature of the BVI firms in the context of a country where public companies are popularly regarded as less efficient than private ones. This is because of the limited freedom to the management of their structure, people, finances and procurement and, therefore, of their decision process (Castanhar et al., 2005); and,[284]
b) the high dependence of a sole purchaser – the PNI – as a strategic weakness the BVI firms have been faced with, as indicated by these same authors (*ibid.* p.246).

How the firms have been dealing with these issues is the point approached here.

The limitations mentioned above have posed a huge challenge to BVI firms. The same government arrangements that have made their growth possible, and enabled the development of important technological capabilities so far in a sector dominated by few oligopolistic multinationals, have apparently imprisoned the firms within a managerial

[283] Technological capabilities were defined, for the purpose of this research, in Sub-section 3.4.1 on pg. 52. The approach of this research to organizational capabilities is discussed in Sub-section 3.5.2 on pg. 71-72.

[284] One example given by one interviewee was the case of Petrobrás, the biggest Brazilian company that runs businesses in the energy sector. The company is public: it is, however, a different and more flexible type of public company than the BVI firms. To become more efficient and competitive in the international market, however, the company needed more organizational flexibility that was gained a decade ago by the approval by the Brazilian Congress of a specific law, known as the Petroleum Law (interview 10).

system that seems to hamper the further developments needed to make them competitive in an international context and even in the local market.

Amongst the firms' managers interviewed there is a great awareness and consensus about the need of the firms to become efficient and competitive. This is in order to keep on developing and strengthening their main vocation – to fulfil public demands (interviews 3, 9, 10 and 19). Worrying, however, is the consensus amongst the same managers, and among other managers outside the BVI who were interviewed about the subject of Policies, that BVI firms would not be able to survive without the current government protection (previous interviews plus interviews 7, 13, 15 and 16). In addition, according to one interviewee, as the public market grows and the PNI introduces more sophisticated vaccines in the routine, there is a high probability that this market will again draw the attention of private companies, especially of the "Big Pharma" firms that have not been benefiting from this market through the licensing of their technologies (interview 9).[285]

Despite the growth of the Brazilian public market, what the main firms of the BVI seem to be relatively aware of today is that they have reached a size whereby providing vaccines only to this protected market is not enough to ensure their growth, technological development and survival in the long term. One of the interviewees, with great international experience in vaccines, stated emphatically that technological development of vaccines does not take place if not backed by a solid productive base (interview 19). This implies the need to keep on expanding the horizons of the firms.

Yet, most of the firms' initiatives to strengthen their managerial capacity and reach new markets have so far been limited. There seems to be the same lack of strategic mindset in the way described by Hobday et al. (2004:1454). The main alternative explored by the firms to gain administrative flexibility has been to resort to non-profit private organizations created specifically to support them.[286]

[285] In fact Novartis is currently building facilities for vaccine production in Brazil, as already mentioned in footnote 190 in Chapter 6 (pg. 136).
[286] Already mentioned in Sub-section 6.2.4 of the previous chapter (pg. 138 and 140).

Although this initiative has indeed provided some more flexibility and efficiency to the firms (interview10), and is being considered by some as a complete solution to their constraints (interview 3), it is actually far from being the appropriate model to deal with the legal restrictions imposed by public sector legislation in the long term. As noted by Castanhar et al. (2005), the use of this mechanism to bypass the law is constantly objected to by public auditors and solicitors.

Another fragility of the managerial system relates to the hiring of personnel. In order to grow amid the restrictions of hiring public workers, firms use the alternative of outsourcing human resources, including to the production and R&D areas. In other words, the kind of personnel who own valuable technical information and tacit knowledge. While the Instituto Butantan relied on around 20% of outsourced personnel in 2004, the percentage of these workers performing technical and administrative activities in Bio-Manguinhos/Fiocruz was over 79%, according to figures presented by the same authors.[287]

On the other hand some more consistent initiatives that were intended to strengthen the efficiency of the firms were found amongst the data gathered. The start-up to the implementation of a quality assurance system in the Instituto Butantan is one of them (interview 6).[288] In Bio-Manguinhos/Fiocruz, in addition to the creation of a project management team in 2003, aimed at the organization and assessment of R&D projects (Moreira, 2005), a partnership with COPPE/UFRJ, an Institute of Engineering of the Federal University of Rio de Janeiro, provided the development of capabilities and routines to production management, and the design and implementation of an ERP system (Bio-Manguinhos, 2008).

With regard to the firms' strategies to the market, there has been a mix of successful and unsuccessful achievements so far. Both firms have succeeded in diversifying their businesses, with Bio-Manguinhos implementing the production and R&D of biopharmaceuticals in 2004 (Bio-Manguinhos, 2008), and the Instituto Butantan

[287] Data gathered during the fieldwork show that the situation has not changed in Bio-Manguinhos/Fiocruz as the firm relied on 77% of outsourced personnel in 2008.

[288] Bio-Manguinhos/Fiocruz, which already has a full quality system implemented, has helped the Instituto Butantan in this initiative (interviews 6 and 19). It has also collaborated with Tecpar in the same initiative (interview 9).

expanding its business toward the production and R&D of biopharmaceuticals and, more recently, of blood products (interview 3). The new businesses have been directed, however, exclusively towards the Brazilian public market. Relating to vaccines, Bio-Manguinhos/Fiocruz, which obtained WHO pre-qualification in 2001 (Benedetti, 2008), has been exporting surplus production of two products to the UN. However, expanding the export to other products has been prevented due to restrictions in the technology transfer agreements.[289,290]

Instituto Butantan, which has been exporting its serums to several countries (Instituto Butantan, 2007), has applied for pre-qualification but it has not so far been inspected by the WHO and, therefore, its human vaccines have been directed only to the local public market (interviews 3 and 6). According to these interviewees, after obtaining the WHO pre-qualification the Institute will quickly be able to export several of its products through the UN agencies.

With regard to the formulation of the technological strategies, the evidence shows different approaches amongst the firms. In this regard, one of the firms has implemented a broad process of discussing and defining its objectives across all managers and by using a specific tool – the Balanced Scorecard (Bio-Manguinhos, 2008, 2009b). In the other firm the responsibility of formulating its technology strategies is restricted to its higher boards or to its main scientific leader (Instituto Butantan, 2007 and interview 5).

7.5 Technological Capabilities and the Unfinished Transition in the BVI

This section draws on the conceptual and analytical aspects of the transition phase as defined in Sub-sections 3.4.3 and 3.5.2 of Chapter 3 (pg. 58-63 and 74-75, respectively). It also draws on all data presented previously in the empirical chapters – Chapters 5 and 6 and Sections 7.2 to 7.4 of this present chapter. This section will describe the boundaries (Sub-section 7.5.1) and characteristics (Sub-section 7.5.2) of the transition phase of the BVI firms., It will also try to identify the main constraints to the development of innovative capabilities of this industry and to the completion of this

[289] According to Benedetti (2008), in 2001 the firm obtained the first WHO pre-qualification for the Yellow Fever vaccine. He noted that the process started in 1992 with training in GMP provided to 66 workers by a WHO expert.
[290] The vaccines being exported are Yellow Fever and Meningococcal C.

transition phase (Sub-section 7.5.3). Table 7.5 summarizes these boundaries, characteristics and constraints at the end the sub-section.

7.5.1 The Boundaries of the Transition Phase

Although establishing the boundaries of the transition phase may appear a somewhat subjective task, it seems there is enough evidence gathered to make a clear distinction between the pre-transition and transition phases of technological capabilities development within the BVI, and to set up when and how it started. At the other extreme, the empirical evidence shows that the upper limit of this transition phase needs to be better qualified due to the different long term objectives of the BVI firms from those approached in the works of Dutrénit (2000, 2007) and Hobday et al. (2004).

To discuss the first point, this research draws on the concepts of the "accumulation of minimum essential knowledge base" and "development of embryonic strategic capabilities" developed by Dutrénit (2000) to distinguish the characteristics of the pre-transition phase and to set up the mid-1980s as the beginning of the transitions phase. As can be noted from the empirical evidence, the minimum essential knowledge base accumulated within the BVI stands for the accumulation of a set of basic and intermediate capabilities. The more visible ones are the production of old vaccines by processes and internal facilities that were not of assured quality, the identification of mature technologies abroad of interest to the public market, and the absorption and implementation of the production of foreign mature technologies. Moreover, some basic to intermediate innovative capabilities can be identified, such as the adaptation of acquired foreign technologies to the context of the country, and the improvement of existing products with a series of incremental innovations.

However, these innovative capabilities were essentially informal as there were no physical structures dedicated specifically to the R&D activities in both firms. During this period the firms started strengthening their capabilities and managed to survive even though most of the vaccines bought by the PNI had been imported. All this evidence is highly indicative of the completion of a pre-transition phase in an analogy with the minimum essential knowledge base described by Dutrénit.

It is also possible to match the overall characteristics of this pre-transition phase with some characteristics of the "Reactive" type of firm as defined by Bessant et al. (2001).[291] In the period up to the mid-1980s, despite a fair awareness of the need to continuously improve technology, the firms clearly had limited internal resources and a lack of key skills in more advanced technologies. Furthermore the approach to technology was still reactive rather than strategic and poor external links had been developed.

On the other hand from the mid-1980s onwards, the firms presented a different approach to technology. This was more strategic, starting with the implementation of R&D facilities, use of international consultants to support R&D activities, growing links with external research institutions, consistent achievements in terms of development of new products (new to the firms), the design of new facilities to comply with the tighter quality requirements, and so on. The transition phase had started, and its characteristics are approached in more detail in the next sub-section.

Relating to the second point – the upper boundaries of this transition phase – there is a need to clarify the BVI firms' strategies *a priori*. According to some interviewees who are in charge of the formulation strategies of those firms (interviews 3, 10 and 19), there are significant differences between the strategies of the oligopolistic firms – the technological and market leaders – and of the BVI firms. They see neither possibility nor need to try to compete with the "Big Pharma" firms in terms of innovation and market strategies, even though it may eventually occur in certain specific circumstances.[292] Indeed, the strategy of the BVI firms can be seen as complimentary to those of the "Big Pharma" firms' ones.

The focus is on the needs of the Brazilian public market and includes vaccines already in the international market (follower strategy), and vaccines new to the world (but for

[291] At this level of technological capability, the firms still do not have the capability of interest for analyzing transition, in the sense employed by Hobday et al. (2004). See also Sub-section 3.4.3 and Table 3.2 on pg. 73-74 and 60, respectively, for more details about the boundaries of these levels as adopted by these authors.

[292] The case of the yellow fever vaccine is one example. As the biggest world manufacturer of this vaccine Bio-Manguinhos/Fiocruz is exhorted by the UN agencies to produce enough to fulfil the needs of the poor countries. In this field the firm competes with Aventis-Pasteur, which is also a large supplier of this vaccine in the international market. In the R&D area there is another example since Bio-Manguinhos is establishing a strategic partnership with GSK for the development of dengue and malaria vaccines.

neglected diseases of epidemiological interest to the country, where there is little or no interest by the "Big Pharma" firms to invest).[293] In a broader perspective, the BVI, as it is currently constituted, seeks to develop technological capabilities in order to dominate the process of technological change and to achieve technological self-sustainability within the strategic field of vaccines.[294] Furthermore, the firms do not intend to try and compete in the private market of both developed and developing countries, which is where the "Big Pharma" firms make most of their revenues. Conversely, their strategies for international markets so far encompass the supply of the production surplus to the UN agencies procurement only.

Therefore, it is clear that the BVI firms' catch-up process does not seek international technological and market leadership at all, but rather seeks to become innovative and competitive in a niche market, eventually contributing to the technological frontier. Consequently, and slightly different from the cases approached by Dutrénit (2000, 2007) and Hobday et al. (2004), the upper limit for the transition phase applies specifically to the case of the BVI; this approach, therefore, seems to be more appropriate.

The assessment of the current level of technological capabilities in the BVI, therefore, takes into account the characteristics of the transition phase as defined in the works of Dutrénit (2000, 2007), Bessant et al. (2001), Hobday et al. (2004) and Rush et al. (2007), with the upper limits defined above.

7.5.2 The Characteristics of the Transition Phase – Unfinished Transition?

In the previous sub-section it was stated that the transition phase of technological capabilities development in the BVI had begun in the mid-1980s, when the firms had already built the minimum essential knowledge base and had started to adopt a strategic approach to technology. This sub-section seeks to identify the overall characteristics of this transition phase amongst all empirical data gathered, and in the light of the characteristics described in previous works already mentioned and summarized in Table 3.3 of Chapter 3 (pg. 62 and 63).

[293] Some examples are presented in Figure 7.3.

[294] Strategic or an issue of national security, as the Brazilian government defined the field of vaccines since the early 1980s. See Sub-sections 7.2.1 in this chapter (pg. 164) and 6.4.2 in the previous chapter (pg. 159) for other details.

The first important characteristic to be highlighted is the intensity of the technology acquisition processes, especially from the late 1990s up to the present time. Although this strategy was expected to be of decreasing importance during the transition phase it has indeed been increasingly adopted, as demonstrated in Figures 7.1 and 7.2 (pg. 166 and 167). Notwithstanding, during this period this strategy enabled the main firms of the BVI to develop world class operating capabilities and strengthen their technological capabilities overall much faster. At the same time it has assured the supply of most needs of the Brazilian public market by these firms. On the other hand, the benefits of this strategy to the development of innovative capabilities are highly controversial, and the current intensity of its adoption seems an unequivocal signal that the transition is still unfinished.

However, there is abundant evidence about the characteristics of the development of innovative capabilities within the BVI and of its growing importance during the transition phase. The first was selected by this research as the starting point of this transition phase and stands for a new and more strategic approach to technology. This characteristic was identified from the establishment of organizational structures and building of facilities especially dedicated to R&D activities, and with the hiring of senior scientists from universities and research institutes in the mid-1980s. The sharp increase in the number of technical personnel and PhDs allocated to R&D activities, and of investments in R&D activities to strengthen in-house capabilities, is another characteristic of this transition phase. These investments have also encompassed training activities, including an important initiative – the creation of a specific Masters degree in the technology of immunobiologicals inside one of the firms. The development of new capabilities, such as genetic engineering and clinical trials, and the domain of some new (to the firms) technological platforms, were other characteristics of strategic importance during this phase.

Another characteristic of the BVI firms' transition phase was the support from international consultants and researchers for improvements to existing products and development of new products. At the same time the firms strengthened their internal and external links through strategic alliances between themselves, and developed links and collaborations with universities and research institutes in both national and international contexts. A partnership with a private company was also started by one of

the firms. Linkages with suppliers have been also developed, although not to address the development of innovative capabilities.

At the organizational level it is explicit from the data gathered that the firms have developed a high awareness of the need to improve organizational capabilities. Some initiatives had already been taken or were in the process of being taken, such as the implementation of a quality system and of a project management system. The search for more administrative autonomy and flexibility through the support of non-profit organizations was an alternative adopted by the firms in an attempt to overcome the legal limitations imposed by their public nature; this alternative obtained limited success. To address the needs of the Ministry of Health, firms have undertaken the successful implementation of new businesses, and the strengthening of existing businesses, in areas other than human vaccine as a strategy of diversification and of decreasing dependence from a sole business, have been other characteristics of the firms during this transition phase.

One very specific characteristic of the BVI's transition phase is the important support of the government for the firms. To begin with, this support addressed the expansion and strengthening of the vaccine manufacturing of the public firms. At the same time it kept these firms protected from the international manufacturers through the use of purchasing power. More recently, besides continuing to use its purchasing power to benefit the BVI firms, the government has launched other initiatives to try and support the strengthening of innovation by the firms.

All in all the overall assessment of the current technological capabilities of the main firms of the BVI can be translated by the results achieved so far in an extremely technologically complex and competitive field such as the human vaccines. In addition to the imitation of mature technologies, the in-house imitation of newer generation technologies, together with the diversity of products in the firms' R&D pipeline (some of which are in the later stages of development), are unequivocal signals that the BVI has achieved high levels of innovative capabilities. Conversely, these results have not been significant enough so far to enable the firms to become competitive, even in the local public market, and to survive without government protection. Hence, and drawing on the upper limits of this transition phase as posed in the previous sub-section, one can

be assured that the transition is still unfinished. The constraints to the completion of this transition phase are approached in the next sub-section.

7.5.3 The Constraints to the Completion of the Transition Phase in the BVI

It was argued in the previous sub-section that the BVI has achieved high levels of technological capabilities but has not yet completed the transition phase, to the extent as defined in this research. The fact that the firms of this industry in Brazil are eminently different due to their public nature and specific long-term objectives, sets up a specific upper limit to this transition phase and poses somewhat different challenges to its completion. This sub-section speculates on some of the main evidence that seems to have been determinant in the BVI not accomplishing this transition phase so far.

An initial point relates to the specificities of the innovation process on vaccines, and the rate of development of technological capabilities in this sector. Due to its high technological complexity and high cost, the process of developing a new vaccine is usually very long, from 10 to 15 years on average, sometimes longer.[295] For the same reasons, failure rates of the projects are also very high.[296] After only 25 years from the start of a more strategic approach to technology – i.e. the beginning of the transition phase and of the development of more advanced technological capabilities, as argued previously – it is no surprise that only a few products have been developed by the firms of the BVI to date.

On the other hand, this slow build up of technological capabilities in the BVI seems to be linked to other reasons, as the evidence shows. Despite great efforts, R&D intensity remains low and incompatible with the levels found in the pharmaceutical sector. In addition, low investment in training and a reduced number of skilled people allocated to R&D activities, seem to be amongst the reasons for the delay in the completion of the transition phase. Some of the reasons cited by the interviewees that have affected the achievements and rate of development of the BVI include:

- the unavailability of some important technological platforms to express antigens;
- the inadequacy of some R&D facilities to BPL and biosafety requirements;

[295] See Sub-section 5.3.3 (pg 109-114) and Figure 5.1 (pg. 114) in Chapter 5 for a discussion of the process of developing vaccines.
[296] See Table 5.6 (pg. 110) in the same sub-section of the previous footnote for more details about market entrance probability in each of the project development phases.

- the lack of a significant induction of applied research on vaccines; and,
- the still existent gap between basic research and technological development in the country.

In the organizational context the lack of firms' administrative flexibility due to the tight legislation of the public sector has been claimed as one of the main weaknesses. It is also an important constraint not only on an adequate management of the business but also in maintaining a steady growth in the future. However, it seems there is still a gap between what the firms can do in the current context and what they have actually done. In this sense there is a need to strengthen some managerial and market capabilities, to expand the WHO pre-qualification to other products and to exploit strategic partnerships more efficiently.

Table 7.5: Technological Capabilities Transition in the Brazilian Vaccine Industry – Boundaries, Characteristics and Constraints

Zuma Medeiros

Boundaries

. From the beginning of a more strategic approach to technology to full domination of the technical change process, becoming competitive in a niche market, eventually contributing to the technological frontier.

Characteristics

. Minimum essential knowledge base already accumulated – 1) basic and intermediate capabilities such as the production of old technologies with no GMP and identification, absorption and implementation of foreign mature technologies; 2) basic and intermediate informal innovative capabilities such as the adaptation of foreign acquired technologies and incremental innovations to existing products;
. Strategic approach to technology;
. Increasing use of technology acquisition strategy for dominating the local public market, developing world class operating capabilities and strengthening overall technological capabilities;
. Strengthening of in-house innovative capabilities through rapid growth of personnel and PhDs allocated to R&D activities, and of investments in R&D activities;
. Development of new strategic capabilities such as genetic engineering and clinical trials;
. Development of some new (to the firms/country) products and several products under development (some new to the world);
. Hiring of international consultants and researchers to support the development of new products and incremental innovations to existing products;
. Domain of some technological platforms;

Characteristics (cont.)

. Strategic alliances amongst BVI firms;
. Increasing internal and external links, and collaborations with universities and research institutes in the national and international contexts;
. Still limited partnerships with private companies and suppliers;
. High awareness of the need to improve organizational capabilities;
. Strong governmental protection and support to the firms;
. Successful diversification of the business (addressing the Brazilian public market only);

Constraints to complete transition

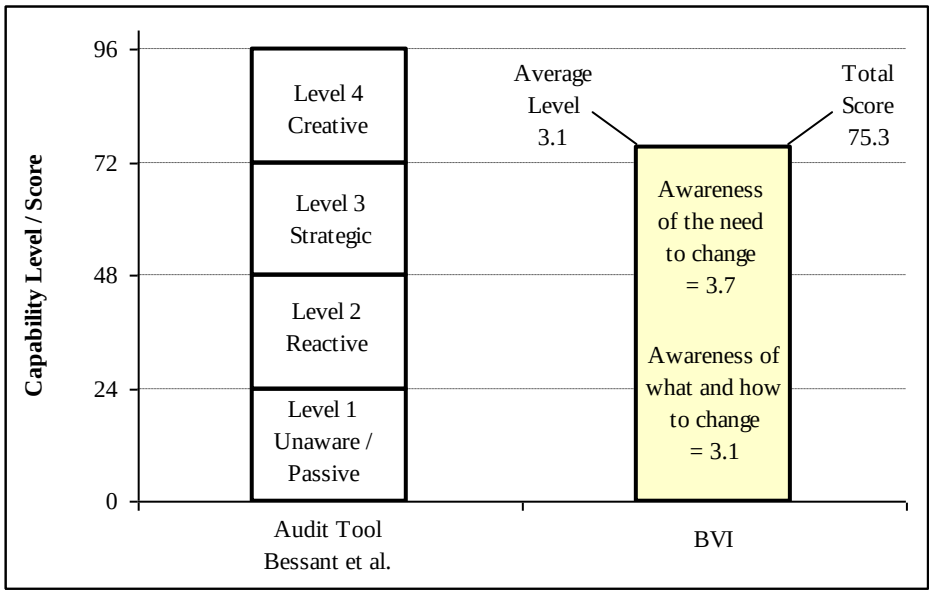
. Slow rate of development of technological capabilities due to:
  . High technological complexity, high cost and length of the process of developing vaccines;
  . Low R&D intensity, low investment in training and need for more skilled people allocated to R&D activities;
  . Unavailability of important technological platforms (e.g. antigen expression);
  . Inadequacy of some R&D facilities to BPL and biosafety requirements;
  . Lack of significant induction of applied research in vaccines, and gap between basic/applied research and technological development in the country;
. Lack of administrative flexibility and strategic mindset;
. Need for strengthening managerial and market capabilities and for expanding WHO pre-qualification to other vaccines;
. Need for exploiting strategic partnerships more efficiently.

Source: Own elaboration, based on empirical findings and following the format of Table 3.3 of Chapter 3 (pg. 62 and 63).

7.6 Assessing the Technological Capabilities – a Survey

Complimentarily to the above approach, this research made use of a survey regarding the assessment of the current level of technological capabilities of the BVI. The survey was based on the tool developed by Bessant et al. (2001), which is also intended to identify strengths and weaknesses in the development of technological capabilities within the firms. It was carried out in the biggest firm of the BVI in August/September 2009.

A few adaptations were made with the inclusion of some information about the respondents in order to make an overview of the results across different areas of work and categories of employees possible. The survey was addressed to employees in posts where graduation was the minimum required background. There were 123 valid responses; this represented 22.9% of the total possible responses and 10.6% of the total employees of the firm.[297]



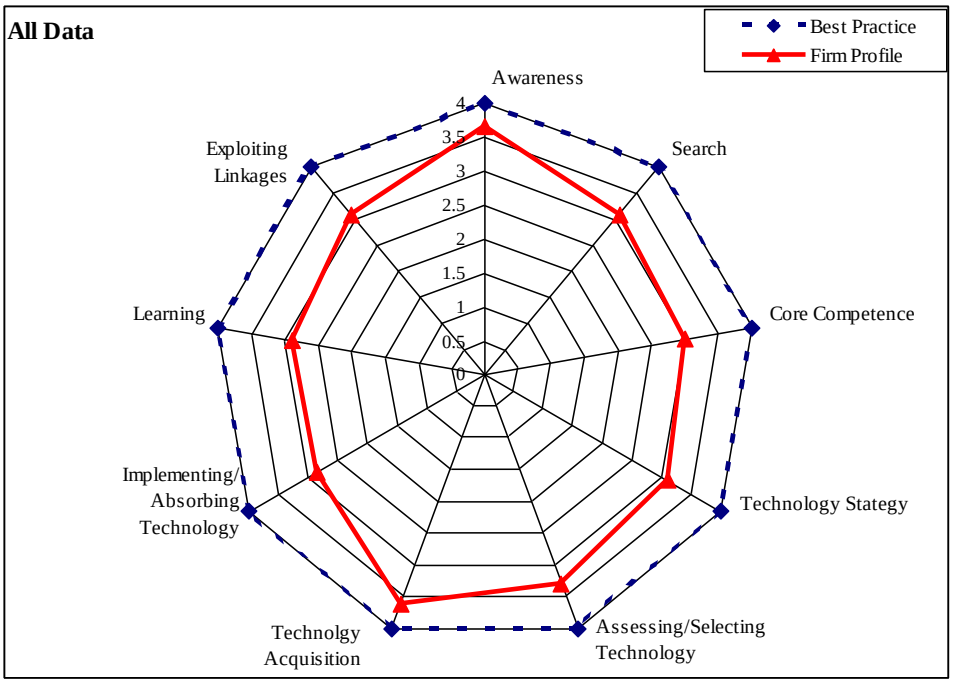
Source: Own elaboration.

Figure 7.4: Capability Level in the BVI – the Overall Results

The results of the survey far exceeded expectations and corroborate the evidence gathered during the fieldwork. As can be seen from Figure 7.4, the current level of

[297] Of the 140 total responses 17 questionnaires were excluded due to poor answers (more than 7 blank answers from 24 questions).

technological capability of the BVI is positioned in the lower band of the highest category of technological capability of the audit tool – the beginning of the creative type of firm level – very close to the limit with the strategic level. In the light of the framework developed by Bessant et al. (2001) it is clear that these results strengthen the overall assessment in Sub-section 7.5.2, that the BVI has achieved high levels of technological capability within the transition phase. They also strengthen the evidence that there is a very high degree of awareness of the need to change in order to accomplish the objectives of this industry. Moreover, they also show that there is a high degree of awareness of what and how to change in order to achieve the results in practice, albeit with the need to develop and/or strengthen some capabilities to become competitive.



Source: Own elaboration from data gathered in the survey.

Figure 7.5: Profile of the Technological Capability of the BVI

The areas where the BVI is strong and where it needs to improve to accomplish its objectives were also identified by the survey. Figure 7.5 shows a graphic representation of the overall results of the survey by each of the technological dimensions compared to the maximum level, the hypothetical best practices. Table 7.6 presents the detailed data arranged across the variables and dimensions of technological capabilities. These figures are examined as follows.

Table 7.6: Survey on Technological Capabilities Level – the Detailed Results

Variables	Dimensions of Technological Capabilities / Average Scores[1]									Total Score[1]	Number of Respondents[2]
	Awareness	Search	Core Competence	Technology Strategy	Assess/Select Technology	Technology Acquisition	Impl/ Absorb Technology	Learning	Exploiting Links		
All Data	92% 3.7	77% 3.1	75% 3.0	77% 3.1	83% 3.3	90% 3.6	71% 2.9	72% 2.9	77% 3.1	75.3	123
Area: R&D	91% 3.7	77% 3.1	73% 2.9	79% 3.2	83% 3.3	87% 3.5	68% 2.7	69% 2.7	74% 3.0	73.9	30
Area: Production	94% 3.8	83% 3.3	78% 3.1	84% 3.4	85% 3.4	94% 3.8	78% 3.1	79% 3.2	75% 3.0	78.6	29
Area: Engineering	89% 3.6	69% 2.8	73% 2.9	67% 2.7	77% 3.1	91% 3.6	63% 2.5	64% 2.6	82% 3.3	72.2	8
Area: Quality	89% 3.6	82% 3.3	80% 3.2	75% 3.0	81% 3.3	90% 3.6	73% 2.9	77% 3.1	82% 3.3	77.4	19
Area: Management	91% 3.7	72% 2.9	72% 2.9	74% 3.0	82% 3.3	87% 3.5	70% 2.8	69% 2.8	76% 3.0	73.5	37
Post: Manager	91% 3.7	77% 3.1	75% 3.0	77% 3.1	83% 3.3	90% 3.6	72% 2.9	70% 2.8	75% 3.0	74.9	65
Post: Non Manager	92% 3.7	77% 3.1	74% 3.0	77% 3.1	83% 3.3	89% 3.5	71% 2.9	74% 3.0	78% 3.1	75.8	55
Years in the Company: Less than 10	91% 3.6	74% 2.9	71% 2.8	74% 3.0	80% 3.2	88% 3.5	70% 2.8	71% 2.8	76% 3.0	73.5	61
Years in the Company: Between 10 and 20	91% 3.6	78% 3.1	77% 3.1	82% 3.3	86% 3.4	92% 3.7	72% 2.9	77% 3.1	79% 3.2	77.7	28
Years in the Company: Over 20	92% 3.7	79% 3.2	77% 3.1	77% 3.1	84% 3.4	89% 3.6	72% 2.9	71% 2.8	76% 3.1	75.5	24
Qualification: Graduation	92% 3.7	73% 2.9	75% 3.0	75% 3.0	88% 3.5	91% 3.6	70% 2.8	81% 3.2	77% 3.1	76.1	8
Qualification: Specialization	93% 3.7	81% 3.2	79% 3.2	82% 3.3	85% 3.4	94% 3.8	78% 3.1	76% 3.0	80% 3.2	79.0	31
Qualification: Masters Degree	91% 3.6	75% 3.0	73% 2.9	76% 3.0	79% 3.2	87% 3.5	67% 2.7	70% 2.8	76% 3.0	73.5	56
Qualification: PhD	89% 3.6	76% 3.1	67% 2.7	76% 3.0	80% 3.2	88% 3.5	71% 2.9	65% 2.6	73% 2.9	72.1	17

Survey carried out in Aug-Sep 2009 – Firm: Bio-Manguinhos/Fiocruz. No. of employees (Aug 2009) = 1,157, of which with graduate background = 536. % of responses = 10.6 and 22.9 respectively. [1] See Annex B for details on how the scores were calculated. [2] The total number of respondents across some variables is less than 123 since some of them did not provide all the information about their profile and therefore those questionnaires were not considered for that specific variable but only for the whole result.
Source: Own elaboration.

The empirical data collected and presented in previous chapters and previous sections of this chapter, as well as the interviews carried out for this research, were used to deepen the interpretation of the results of the survey.

According to the audit tool the degree of "awareness" reflects the ability of the firm to recognize the role of technology to its development and competitiveness: it measures the awareness of the need to change. The very high score achieved in this dimension of technological capability (3.7), highly uniform across all variables, is consistent with several evidences gathered. These include the efforts of the BVI to develop in-house innovative capabilities, its results and prospects, and even with its strategy of keeping updated with the most recent technologies through technology acquisition.

The assessment of the other eight technological capabilities dimensions measures the degree of awareness of the firms in areas that enable them to change what is identified as needed. The average score obtained in the survey for this set of capabilities was high (3.1), but brings to light areas where the firms are strong and where they should improve to complete the transition phase and become competitive. Amongst these dimensions was one distinguished by a very high score (3.6). According to the survey "technology acquisition" (which measures the effectiveness of the firm at acquiring technology from external sources and the existence of good links with important external suppliers of technology), is a very strong capability of this industry. This strengthens the emphasis of this research on the strategy of technology acquisition as one of its main sources of knowledge. Although the results have been fairly uniform across the variables, they were notably higher among production area workers, which is the entrance door of the technologies acquired externally, and amongst the workers with specialization as their highest qualification. In this latter case no apparent reason was identified.

The "Assessing and Selecting" technological capability dimension was another area that received a very high score (3.3). The survey measures the firms' ability to identify the right technology and its best sources for their business. Therefore, this ability is a requirement for the next step in the technological cycle of the firm – technology acquisition. Hence, the result is consistent with the result and comments above about the "Technology Acquisition" dimension.

At the other extreme, two dimensions received the lowest score (2.9) of the survey. “Implementing and absorbing technology” refers to how effective technology activities are organized as well as to the existence of clear processes for carrying out technology projects. “Learning” refers to how effective the firm is in learning from the assessment of technology projects, from post-project reviews, and from one technology project to another. The results suggest the need to improve skills and coordination in areas such as R&D, Engineering, Project Management, Knowledge Management, Marketing and so on. The results for the first dimension were particularly influenced by the responses from workers from the Engineering, R&D and management areas, and from those with a Masters degree as their main background, as shown in Table 7.6. The respondents of the same areas and amongst the PhDs mainly determined the results of the “Learning” dimension.

The result of the “Building Core Competence” dimension (3.0) also fell below the average of these eight dimensions, and it was mainly determined by the workers of the same three areas stated above. This capability refers to the firms’ ability to audit their competencies, and identify and adequately exploit their strengths in order to build up competitive advantages. As empirical data show that the firms of the BVI are well aware of the role of technology to their business, the main needs of this industry in this area seem to be the identification of their advantages, the development of ways of protecting them, and the identification of competencies to be outsourced instead of being developed in-house.

The results of the other three dimensions fell right over the average score for this set of capabilities (3.1), just at the beginning of the creative stage of technological capabilities. “Search”, the ability of firms to assess technological opportunities and threats, was noticeably perceived less favourably by the workers of the Engineering and Management areas, and by those with less than 10 years in the firm or with graduation as main qualification. Conversely, the workers of the production and quality areas assigned the highest degree for this capability. The evidence from interviews and other empirical data suggest, however, that this ability is restricted to some few mature scientific leaders. The development of stronger marketing capabilities and of a broader scientific and technological network through systematic participation in conferences,

seminars and exhibitions abroad are some initiatives to be implemented by the BVI in this area.

The "Technology Strategy" dimension measures how skilled the management is at formulating a technology strategy and defining its priorities to meet business goals. According to the audit tool, to be successful and able to think about technology in a strategic way, firms need a clear understanding of their core competencies and a process for discussing and communicating their technology strategy. Also, choosing whether to conduct technological activities in-house or outsource them to technological partners is a strategic challenge of these firms. Although some formal initiatives about strategy formulation have been detected amid the empirical data, difficulties with the identification and development of core capabilities, and legal restrictions regarding the public nature of the firms, may restrain the formulation of more daring strategies by the firms.

"Exploiting External Linkages and Incentives" refers to how aware the firms are of the existence of government incentives and of external resources to help them to develop technologies and how well they exploit them. The result of the survey in this area also seems very consistent since empirical evidence gathered showed that BVI firms have largely benefited from governmental policies to develop. Moreover, external linkages with universities and research institutes in the national and international contexts, as well as international consultants and researchers, have been increasingly exploited. However, some interviewees pointed out the need to broaden external linkages, especially with private firms and suppliers. Once more, legal impediments can hinder or delay the establishment of some kinds of technological alliances such as joint ventures and public-private partnerships (PPP).

The questionnaire developed by Bessant et al. (2001) and used in the survey is presented in Annex B.

7.7 Summary

This last empirical chapter has approached the development of technological capabilities within the Brazilian Vaccine Industry (BVI) since the early 1970s. The data gathered confirmed that technology acquisition, the acquisition of foreign packaged

technology in the sense defined in Chapter 3, has been an intensive strategy of this industry and an important source of knowledge to develop, even within the transition phase, and has resulted in the development of world class operating capabilities. Evidence has shown that the adoption of this strategy has been mainly pushed by the rapid growth of the Brazilian public market combined with the high complexity of the process of developing vaccines.

On the other hand, data gathered has shown that high levels of innovative capabilities have also been developed by the main firms of the BVI due to a more strategic approach to technology since the mid-1980s. In this sense the strengthening of their own R&D through the hiring of skilled personnel, growing investments in R&D activities and training, and growing linkages with external sources of knowledge, both in the national and international contexts was noticed. In addition, the development of important R&D capabilities especially in the area of clinical trials was also noted. Moreover, some products have been developed by the firms, and several new (to the firms and to the world) products are currently in their R&D pipeline.

The assessment of technological capabilities of the BVI through the use of the transition approach, as defined in Chapter 3, has confirmed that this industry has reached high levels of technological capability but that the transition phase is still unfinished. Furthermore the boundaries and characteristics of this transition phase were identified as well as some of the constraints to its completion.

Finally, the results of a survey carried out in one of the firms were presented. The survey, based on the audit tool developed by Bessant et al. (2001), was used as a complimentary tool to the assessment of the level, strengths and weaknesses of the development of technological capabilities within the BVI. Its results strengthened the assessment made previously from all data presented in the empirical chapters.

The next chapter is dedicated to the analysis and discussion of the whole context of development of technological capabilities in the BVI in the light of the research questions and propositions defined in Chapter 3, and of the interactions represented in the analytical framework developed in the same chapter.

Chapter 8 – Analysis and Discussion

8.1 Introduction

In Chapter 3 the research problem and aims were defined, drawing on the literature reviewed (Chapter 2) and on some assumptions raised about the Brazilian vaccine industry (BVI). The research questions and propositions were then posed and the conceptual and analytical frameworks developed, setting up the elements for investigation. Chapters 5 to 7 provided empirical data gathered in the light of the strategies developed and presented in the Methodology chapter (Chapter 4). The present chapter is dedicated to linking the empirical findings of this research to the objectives of the study, and to interpreting these findings in order to address the research questions and propositions posed.

For convenience, the research questions and propositions are reproduced below:

RQ1 How have technological capabilities in the Brazilian vaccine industry evolved over time?

> *P1* Technological capabilities have been developed in the BVI in a distinct pattern of that represented by the traditional catch-up model identified in the literature on technological accumulation in latecomer firm/industries, influenced by specific circumstances of the context of this industry;
>
> *P2* The strategy of continuous foreign technology acquisition adopted by the BVI has not contributed effectively to the development of local capabilities that could help to narrow the gap to the technological frontier.

RQ2 How far has the Brazilian vaccine industry gone to date in the transition phase, how and why?

> *P3* The BVI has been unable to develop significant innovative capabilities so far within the transition phase;
>
> *P4* The speed of change in the scientific/technological frontier is the most important factor hindering the transition to competitive innovative capabilities;
>
> *P5* The unfinished transition is a by-product of the strategy of continuous foreign technology acquisition adopted by the BVI.

The chapter is thus organized in two sections. Section 8.2 approaches the overall way technological capabilities have been developed within the BVI, with an emphasis on its specific pattern and on the strategy of foreign technology acquisition, in order to address Research Question 1 and its Propositions. The issues on the development of innovative capabilities during the transition phase are approached in Section 8.3 illuminated by Research Question 2 and its Propositions 3 and 4. In order to address the last proposition (Proposition 5) of Research Question 2, the possible existence of a relationship between the strategies adopted by the BVI and the hindrances to the completion of its transition phase is an issue also analyzed in the same section.

8.2 Literature and Development of Technological Capabilities in the BVI

This section is about interpreting the overall way technological capabilities have been developed in the Brazilian vaccine industry over time, as set forth by the Research Question 1. More specifically, it focuses on possible differences and similarities between the specific characteristics of the development of technological capabilities in the BVI, and the common pattern identified in the literature on technological accumulation of catching-up firms/industries of latecomer countries, as proposed in Proposition 1 (Sub-section 8.2.1). Furthermore, this section also discusses the claim that the strategy of technology acquisition has not speeded up the development of the BVI, as asserted in Proposition 2 (Sub-section 8.2.2). Sub-section 8.2.3 presents a summary of the issues discussed in the two previous sub-sections in order to frame the answer of Research Question 1.

8.2.1 The Pattern of Technological Capabilities Development in the BVI – Differences and Similarities

The first concern of this research relates to the possibility of the existence of a distinct pattern of technological accumulation within the BVI due to persistent processes of foreign technology acquisition as the main source of technological knowledge, and as the main strategy to develop and to other specificities in the context of this industry.[298]

The review of the literature on technological accumulation in latecomer countries revealed several approaches to this subject. From the most widespread view (e.g.

[298] Technology acquisition means, for the purpose of this research, the acquisition of foreign packaged technologies (see Chapter 3 on pg. 52).

Dahlman and Fonseca, 1987; Dahlman et al., 1987; Bell and Pavitt, 1993, 1995; Hobday, 1995; Kim, 1997) one can infer, as emphasized in Chapter 2, that the catching-up process of firms/industries in these countries has a common and logical pattern. It starts from a high dependence of the firms on mature technology imported from advanced countries due to the lack of existence of significant innovative capabilities and of local technological infrastructure. To catch-up and become competitive, however, these firms need to develop their internal innovative capabilities and strengthen the capabilities for exploiting other external sources of technological knowledge. Government, institutions and markets play an important role in this process.

In some of these works (Mytelka, 1978; Kim, 1997) the relationships between foreign technology acquisition and the development of innovative capabilities are approached, and present certain situations where the use of the former inhibits the development of the latter. These situations are very close to the case of the BVI and are related to the nature of the firm (state-owned firms, in the case presented by Mytelka), and to the channel of knowledge acquisition (licensing of imported technologies from single sources, in the case observed by Kim).

More recent literature focusing on innovation transition in Korea and Mexico, however, has unveiled in more detail the key issues faced by some firms by the time they attempt to approach the technological frontier and gain competitiveness. One of these key issues refers to the adoption of multiple strategies by the firms towards technology instead of a single corporate strategy (Hobday et al., 2004). The mix of strategies can simultaneously involve leadership, followership and latecomer technology strategies, and depends on the stage of development of each product or product families, according to these authors.

Other works approach the catching-up process in a singular way. They emphasize new directions/paths as an alternative strategy of latecomer firms/industries to overcome their disadvantages and barriers, develop innovative capabilities, take advantage of opportunities and catch-up with the leaders, in line with Gerschenkron's ideas. Among works putting forth this approach are Perez and Soete (1988), Forbes and Wield (2002, 2008), Hobday (2003), Mathews (2006), and Figueiredo (2009).

On the other hand, empirical data gathered within this research has revealed in detail the way and context the main firms of the BVI have developed their technological capabilities in the last 35 years or so. The integration of the approach on innovation transition in the framework proposed in this research has provided the means to focus on the period when those firms have been developing the capabilities to innovate more intensively.

One of the findings of the empirical data on technology acquisition (Chapter 7, Section 7.2, pg. 164-173) was that the introduction of most of the products to the public market by the BVI since the creation of the National Immunization Programme (PNI) in 1973 was originated from technology acquisition processes. Actually, this strategy has been increasingly adopted during the last three decades, as shown in Sub-section 7.2.1 of the same chapter (pg. 164-167). Moreover, technology acquisition is set to continue as an important strategy in the near future, as also shown by empirical data (Sub-section 7.2.3 pg. 172-173).

The persistent strategy of technology acquisition within this industry is the most visible internal element contributing to a supposedly distinct pattern of technological capabilities development. However, as revealed by subsequent parts of the same chapter, the main firms of the BVI have developed important innovative and other technological capabilities. They are now at a point where they are not too far from the threshold of the transition to a competitive level of technological capabilities.[299] In addition, the other empirical chapters (Chapters 5 and 6) have disclosed important particularities of the vaccine industry across the world, as well as of the whole context of this industry in Brazil. These particularities have suggested an active participation of the Brazilian government in support of the development of the industry, and that this industry is very specific, with remarkable differences from other industries, even those of the science-based sector, but also with some differences from other branches of its parent pharmaceutical industry.

At first glance, the data above may suggest some differences between the patterns observed. Nevertheless, looking at the intensity of the strategy of technology acquisition

[299] This issue is addressed in the next section of this chapter.

seems an oversimplification of the analysis, and does not represent the importance of this source of technological knowledge over time. Some other evidence of the context of the main firms of the BVI revealed by empirical data appears to be useful in the attempt to understand the pattern of technological accumulation in the BVI and to identify possible new directions. They are related to the distinct phases of the processes of technology acquisition as described below. The case of multiple corporate strategies toward technology revealed by Hobday et al. (2004) seems to be enlightening to this analysis, although in a different perspective.

In the first phase of the period analyzed in this research, although complying with the demands of the PNI was imperative, the importance of the technology transfers in the development of technical capabilities was undeniable. This situation persisted until the late 1990s and early 2000s with the processes of technology acquisition of the Hib vaccine by Bio-Manguinhos/Fiocruz and the Influenza vaccine by Instituto Butantan respectively. Along with these technology transfer processes the firms were still internalizing important technological capabilities, and this was the time they developed world class operating capabilities. From this time on the objective clearly changed, as quickly fulfilling the public market needs in order to avoid importing became the main explicit objective behind the strategy.

Two facts can be selected from the empirical data to illustrate this situation. The first refers to the introduction of the Human Rabies (vero cell) vaccine. Through a technology transfer agreement with Aventis Pasteur, Instituto Butantan quickly managed to supply the PNI from 2002 whilst its own vaccine was still under development. The agreement was interrupted in 2006, however, when the Brazilian manufacturer managed to conclude the development and license its own vaccine with a similar technology (see Table 6.8 on pg. 148 and Table 7.1 on pg. 165).

The second fact regards the Rotavirus vaccine. When the incidence of this disease rose sharply in 2006 the PNI spent a large amount of money on an imported vaccine it was willing to introduce to its programme's routine (see Figure 6.6 on pg. 149 and its preceding paragraph). Even though a vaccine against this disease was being developed by one of the firms by that time (see Figure 7.3 on pg. 179), it was quickly supplied to PNI from 2007 by the other firm thanks to a technology transfer agreement with GSK

(see Table 6.8 on pg. 148 and Table 7.1 on pg. 165). The development of the Rotavirus vaccine by the Brazilian firm has not yet been concluded, but both examples show that the importance of technology acquisition as a source of technological knowledge has definitely decreased.

Two other examples are also illustrative of the decline of technology acquisition as the main source of technological knowledge in the BVI, along with the strengthening of the innovative capabilities within its main firms. When the PNI announced the intention of adopting the tetravalent vaccine (DTP+Hib) in the early 2000s due to technical and economic reasons, which meant a threat to both BVI's main firms, Bio-Manguinhos/Fiocruz was able to form an alliance with Instituto Butantan, quickly developing a way to combine the antigens, carry out the clinical trials, and supply the PNI from 2002 (see Table 7.1 on pg. 165 and footnote 261 on pg. 177).

A similar situation is happening now with the pentavalent vaccine (DTP+Hib+HB). In this case the vaccine developed by Bio-Manguinhos/Fiocruz in partnership with Instituto Butantan has been already approved in clinical trials and is currently under registration (see Figure 7.3 on pg. 179).

These examples suggest a singular conclusion. On the one hand, taking the linear approach of catching-up they show that the trajectory of the sources of knowledge, in terms of their importance to the process of technological accumulation, appears to have similarities to the common pattern identified in the literature (represented in Figure 3.2 on pg. 53). In this regard they show that the importance of technology acquisition as a source of technological knowledge has decreased at the same time that the importance of innovative capabilities has increased. In addition, they show that technology acquisition did not inhibit the development of innovative capabilities in the case of the BVI.

On the other hand, the analysis of the importance of technology acquisition as a source of technological knowledge shows that it is not related to the intensity of adoption of this strategy since two main distinct objectives behind the strategy were revealed. This may indicate another conclusion. If we think about these distinct objectives, this may suggest new directions. Although the benefits in terms of technological knowledge had

apparently ended in the early 2000s, the strategy was kept in the new phase in order to avoid the re-emergence of imports and the consequent weakening of the policy of protection granted by the government to local manufacturers, while the firms develop more advanced innovative capabilities. What strengthens the notion of a distinguishing path is that this new strategy (or new objective of the strategy) was articulated by the firms together with the government, which used its huge and attractive public market, and its purchasing power, to persuade the "Big Pharma" firms to transfer recently developed technologies to the firms of the BVI.[300] The role of the government and the influence of its local public market are, therefore, clear drivers of this new path/direction.

One further example suggests the existence of new directions in the development path of the BVI. It relates to several projects in the R&D pipeline of the two main firms addressing local/regional neglected diseases (see Figure 7.3 on pg. 179). Many of them were not of interest to the "Big Pharma" firms for economic reasons, as already indicated before. In addition to tackling the special needs of the Brazilian government, developing vaccines for these diseases may open opportunities to exploit export markets in more advantageous conditions.

8.2.2 Technology Acquisition, Local Capabilities and the Gap to the Technological Frontier

A second issue is addressed in Research Question 1 in order to disclose the particularities of the development of technological capabilities in the BVI. It relates to whether or not the continuous strategy of technology acquisition has helped this industry to develop local capabilities in order to narrow the gap to the technological frontier, as raised in Proposition 2.

Before advancing into the discussion proposed above, it seems useful to clarify two issues on behalf of the analysis of this proposition. The first refers to what "technological frontier" means to this research. When asked about where the frontier is in the field of vaccines, the R&D professionals interviewed during the fieldwork

[300] The Brazilian public market is being considered here as attractive, not only due to the volume of vaccines purchased by the government but also due to the new technologies/proprietary products introduced in the immunization routine.

pointed out a vast range of new concepts, products and processes. Chapter 5 (Section 5.5, in particular, on pg. 118-119) provides the same broad view when approaching the aspects of innovation on vaccines.

This seems evident for multi-disciplinary sectors such as vaccines, pharmaceuticals and others, and means that a firm/industry in those sectors can reach the technological frontier in some areas whilst not in others, as in the case of electronics in East Asia revealed by Hobday (1995). However, this is not useful for the purpose of evaluating the referred proposition. On the other hand, managers in charge of the strategies formulation of the main firms of the BVI, also interviewed during the fieldwork, stated that the firms are not seeking technological and market leadership but rather to become both innovative in order to develop the vaccines of interest to the PNI (be they existing technologies or new to the world technologies), and competitive in a niche market (see third and fourth paragraphs of pg. 194 in Sub-section 7.5.1).

Literature focusing on transition (Dutrénit, 2000, 2007; Hobday et al., 2004) refers to firms approaching the innovation frontier as those that are looking for leadership through new products developed by in-house R&D, a broader meaning. This research draws on the objectives of the main firms of the BVI and sets up that reaching technological frontier means to acquire the ability to develop new to the world vaccines, even though not aiming at challenging the leaders in the international scenario.

The second issue refers to the notion that narrowing the gap to the technological frontier is a matter of being quicker than the leaders, as if in a race, or being directly linked to R&D spending. As literature shows this may be misleading. It is true, as noted by Hobday (1995), that the technological frontier is continuously advancing and that this can lead to a continuous cycle of catching-up behind the frontier, as shown by Hobday et al. (2004:1450). It is also true, however, that successful catching-up has been mainly based on “running in a new direction”, rather than a simple matter of speed, to quote the words of Perez and Soete (1988:460), and in line with other works of Gerschenkronian inspiration cited in the previous sub-section.

In addition, although the vaccine sector is regarded as requiring high R&D investment, successful innovation is frequently a result of the content of R&D rather than of R&D

spending itself. This is demonstrated by Forbes and Wield (2002) through the examples of Honda and Toyota compared with Ford and GM in the 1970s and 1980s. Mastering the capabilities for generating innovation is, in this sense, what really matters, as stated by many authors (e.g. Dahlman et al., 1987; Bell and Pavitt, 1995; Radosevic, 1999; Tidd et al., 2001; Rush et al., 2007).

In order to analyze the proposition, therefore, this sub-section looks for new and different evidence/new directions, and once more the innovation transition approach is used to support the assessment. In this case the analysis and discussion are put forward by taking advantage of the results of the survey carried out to assess the technological capability level of the main firm of the BVI (see Section 7.6 on pg. 201-206). This survey, based on the audit tool developed by Bessant et al. (2001), showed that the firm is very close to the highest level considered in the tool, not too far to conclude the transition to the competitive/creative level. Here the specificities of some of the dimensions of technological capabilities approached in this audit tool are borrowed in an attempt to raise evidence of the contribution of the technology transfer processes to the current level of the firm.

The first dimension to be approached relates to the level of awareness. It seems undoubted that the technological transfer processes have raised this ability inside the firm. As shown throughout Chapter 7, the firm has made use of increasingly advanced technologies, even though they are acquired ones, to fulfil the demands of the PNI and to consolidate its position in the public market. Moreover, the last agreements show the acquisition of some of the most recent technologies available in the international scenario (see Table 7.1 on pg 165), making the firm able to accurately frame where the frontier is and its position in relation to this frontier. Straightforwardly, it seems reasonable to think that dealing with up-to-date technologies strengthens the ability to recognize what makes sense and what is feasible in terms of new technologies, infrastructure and market needs, which is in direct connection with other dimensions such as “search” and “assessing and selecting”.

The successful negotiation of the agreements for licensing and transferring the technologies clearly indicates other skills that have been enhanced in recent times. Two aspects evidence this assertion. One regards the complexity of the agreements, which

involves proprietary products of market leaders and the approval of the national authority on intellectual property. As revealed in informal conversations with some interviewees, the first complex agreement in 1999 was the most difficult as there was little experience in either the formal aspects of this type of agreement or the negotiations with leading international corporations' businessmen. In subsequent agreements the firm's negotiators felt themselves more confident to bargain better contractual conditions.

The second aspect is directly linked to this increasingly improved skill and is related to the attempt to capture knowledge and learn from the agreements. The most visible example is the inclusion of R&D cooperation for the development of new to the world vaccines in the most recent agreement (see first paragraph of pg. 173 in Sub-section 7.2.3 and footnote 250 in the same page). This inaugurated a new era in technology transfer agreements for this industry as it introduced a shift in the partnership between both firms and establishes a longer term and more strategic alliance between them, as in the case of the firms approaching the innovation frontier shown by Hobday (1995:204). Within the audit tool proposed to discuss the referred proposition, the above examples are very suggestive of the strengthening of some skills in the "technology acquisition" and "learning" dimensions of technological capabilities.

The "implementing and absorbing technology" dimension is the subsequent step after the acquisition of a technology in the model developed in the audit tool and, therefore, it is inherent to the discussion proposed. As is well known, technology transfer is not an automatic process. The complexity of the process of manufacturing a vaccine, as demonstrated in Section 5.4 (pg. 115-118), make it extremely hard in the field of vaccines. It involves the need for further development in several areas of the firm in order to succeed in the absorption of the technology. In this case many examples of benefits that can be used in the discussion were already referred to previously in Chapter 7. These include the improvement of the quality system, the creation of project management activities, the development of new capabilities in the engineering area, and the development of capabilities to adapt, sometimes even improve, foreign advanced technologies (see footnote 262 on pg 177). Moreover, new and different facilities and adaptations are currently in the process of being built to make feasible the implementation of the most recent technology transfer agreements, with technical

support of the technology transferor (see third paragraph of pg. 170 in Sub-section 7.2.2).

"Exploiting external linkages and incentives" is the last dimension to be approached. According to the audit tool, successful firms are well aware of a wide range of external sources of knowledge and resources and make use of them to develop (Bessant et al., 2001:28-29). In this case the contribution of the technology acquisition strategy to the strengthening of some of the skills required in this dimension is also visible in the empirical findings. The link with the international leaders itself is an example.

Notwithstanding, the technology transfer processes of advanced technologies have frequently required new links with international suppliers of materials and capital goods, some of them the same suppliers of the technology transferor, in order to meet with the quality levels of these technology transferors. In one specific case the technology transferor provided equipment specifications through the agreement, and the Brazilian firm established links with the local capital goods industry to have this equipment developed and produced (see footnote 245 on pg. 170). The interactions mentioned above are certainly a valuable source of knowledge for the recipients of the technologies and corroborate the idea developed here.

To conclude, using the way proposed above to interpret the contribution of the technology acquisition strategy, it seems evident that, overall, these processes of foreign technology acquisition have helped the main firms of the BVI to strengthen their technological capabilities and absorptive capacity. Consequently, they increasingly mastered a variety of new capabilities required to make them able to narrow the gap to the technological frontier. Moreover, a shift in the type of capabilities that have been enhanced can be noticed as the later agreements have resulted in a more systematic strengthening of the managerial ones.

These findings do not contradict the idea that the acquisition of foreign technology is a necessary but not sufficient condition for development, as put forward by Radosevic (1999:4) and others. Similarly, it does not intend to deny that narrowing the gap to the technological frontier depends much more on a combined set of factors, internal and external to the firms, than on technology acquisition in isolation, as shown by Hobday

(1995). Rather, they emphasize the fact that the contribution of the acquisition of foreign technologies during the latecomer industries transition may be higher than revealed so far and not only important during their initial phase of development.

Therefore, linking the above findings with the current level of technological capabilities of the firms as revealed in Chapter 7, it seems not an overstatement to say that the strategy adopted has effectively helped the industry to develop new local capabilities and get closer to the technological frontier. Furthermore, it seems likely that there may be other under-investigated dimensions of technological capabilities, the development of which the acquisition of foreign technology has effectively contributed.

8.2.3 Overall Findings of Research Question 1

Research Question 1 is about unveiling the overall way technological capabilities have been evolving in the Brazilian vaccine industry. It focuses on the aspects involved in the strategy of technology acquisition adopted to address the assumption that this industry has overstressed the importance of this mechanism in its process of development. In this regard two specific propositions were posed. The first one relates to whether or not the BVI has developed through a distinct pattern of technological capability building, and to the importance of technology acquisition and other specificities of the context of this industry to this process. The second proposition goes deeper into the importance of the technology acquisition strategy to technological accumulation by considering whether or not it contributes to the development of local capabilities in order to narrowing the gap to the technology frontier.

With regard to the first proposition, the analyses were primarily made from a linear perspective of the catching-up process, represented in this research by the model in Figure 3.2 (pg. 53), that is, by assessing the trajectory of the importance of the sources of technological knowledge. Although the analysis under this perspective was not conclusive in terms of significant differences that could characterize a distinct pattern, it revealed some characteristics of the process that provided the elements for the analysis under the perspective of Gerschenkron. New directions are then clearly suggested. Three facts support this evidence. The first relates to the distinct objectives of the strategy of technology acquisition. When the focus is on the first phase of its development, it is clear that the acquisition of foreign technologies was used with the

specific objective of developing the technological capabilities of the firms. When the focus is on the transition phase, still in progress, the evidence indicates a shift in the objective of the strategy. In this period, especially in the most recent times, the strategy of foreign technology acquisition has been adopted to quickly fulfil the needs of the Brazilian public market, thus avoiding the government's requirement to import vaccines while the innovative capabilities inside the firms are not fully developed. Furthermore, this strategy has been perceived by some of the managers interviewed as of lesser importance to the development of internal innovative capabilities more recently. Indeed, the firms have increasingly relied on incremental innovation and in-house development of technologies, and their technological capabilities have reached a high level, as shown in Chapter 7.

The second fact relates to the strong influence of the government to the success of this second objective. By using its huge and attractive public market and its purchase power to protect local firms, the government managed to persuade the "Big Pharma" firms to license proprietary technologies, some of them recently developed and launched in the international market. A strong role of the government and the influence of its market are, therefore, the main drivers to this distinct pattern.

The third evidence is found in the R&D pipeline of the two main firms. In this case the development of vaccines for local/regional neglected diseases is a promising new direction for addressing particular needs of the Brazilian government, as well as for exploiting opportunities in export markets.

On the other hand, the assessment of Proposition 2 reveals a surprising outcome and strengthens the outcomes of the analysis of the previous proposition. By using some dimensions of technological capabilities, and their underlying themes borrowed from the audit tool developed by Bessant et al. (2001), it was possible to show that the technology acquisition strategy adopted by the BVI has made, more recently, an additional contribution to the development of important capabilities to the process of innovation of its main firms. This result is surprising in two senses: firstly, it discloses the real way the above mentioned strategy has contributed to the development of the capabilities of the BVI, apparently still not approached in the literature. Looking at the process in its entirety, it is evident that the technical capabilities were addressed more

intensively in the first phase, including the beginning of the transition phase. The more recent part of this transition phase, however, has been characterized by a more intensive strengthening of the kind of managerial capabilities. These capabilities are equally vital to the innovation process and the lack of them is amongst the constraints to the completion of the transition phase, as revealed in the works on innovation transition (see Table 3.3 on pg. 62-63).

The second surprising finding is related to how the importance of the foreign technology acquisition strategy (the acquisition of packaged technology, as defined in Sub-section 3.4.1 on pg. 52) has recently been perceived by the actors of the context. Despite the fact that embedding R&D collaboration, as in the last agreement signed by one of the firms, denotes a higher awareness of the importance of the strategy as a tool for its development, it seems that the most recent strengthening of some important capabilities to the process of innovation as a whole – the managerial capabilities – has not been perceived as a result of these technology acquisition processes, either by most of the managers interviewed or by the government. As a consequence, the potential for the use of this strategy may be higher than has been comprehended so far. And the awareness of that has important implications for management and policy.

Finally, and briefly, the findings of the analysis of the two propositions suggest that, more recently, the Brazilian vaccine industry has developed its technological capabilities through a distinct pattern. This pattern is in line with the argument of "new directions/paths" first stressed by Gerschenkron and further developed by some contemporaneous authors. In addition, they suggest that this particular pattern is driven by a strong role of the government and by its local public market, and shaped by distinct roles of the foreign technology acquisition strategy.

8.3 Development of Innovative Capabilities within the Transition Phase

This section focuses on the transition phase, the period when the main firms of the BVI started a more strategic approach to technology. It addresses the issues raised by Research Question 2 and its propositions. In the Sub-section 8.3.1 the current level of technological capabilities of the firms, the landmarks and drivers of this transition phase are discussed to address Proposition 3. The hindrances to the completion of the transition phase are analyzed in the subsequent sub-section (8.3.2) in order to interpret

the claim in Proposition 4. In Sub-section 8.3.3 whether the evidence gathered can support the existence of a relationship between the hindrances of the unfinished transition and the strategy of continuous foreign technology acquisition adopted by the industry is analyzed, in order to examine the claim in Proposition 5. As in the previous section, the last sub-section (8.3.4) summarizes the issues discussed in the previous sub-sections in an attempt to frame the overall answer of the research question.

8.3.1 Technological Capabilities in Transition

This Sub-section addresses Proposition 3 by approaching the specificities of the development of technological capabilities by the main firms of the BVI during the transition phase. Initially the emphasis is on the current level of innovative capabilities, but it also embeds the "how" and "why" issues about the process. The term "innovative capabilities" is being employed in this research with a broader meaning and encompasses not only the ability to produce new technological knowledge inside the innovating units of the firm, but also the ability to exploit outside sources of knowledge.[301]

The elaboration of Proposition 3 departed from the assumption that the excessive reliance on foreign technology acquisition by the main firms of the BVI could mean a lack of existence of significant innovative capabilities inside these firms. One of the works inspiring this assumption was carried out in 90 firms located in three countries of South America, and found a strong correlation between the licensing of foreign technologies and low engagement in own R&D, especially in state-owned firms (Mytelka, 1978).[302]

Notwithstanding, data gathered during the fieldwork proved this assumption is wrong in the case of the BVI. Section 7.3 on pg. 173-189 provides an incontestable picture of the development of significant innovative capabilities by the main firms of this industry, especially during the transition phase. This is illustrated by several incremental innovations, the development of some new to the firms'/country's vaccines, and the existence of other new to the firms/country and of some new to the world vaccines in the firms' R&D pipeline, some of them in a very advanced stage (see Figure 7.3 on pg.

[301] The meaning adopted is stressed in more detail in Sub-section 3.4.1 on pg. 52.
[302] The work was carried out in metalworking and chemical industries in Peru, Ecuador and Colombia.

179). The specificities and high complexity of the vaccine sector and of the process of developing vaccines, as stressed across Chapters 5 and 6, further enhance the importance of these achievements. Moreover, the development of clinical trials capabilities inside the BVI is also emphasized in Section 7.3 on pg. 182-184.

This type of capability is considered as essential but very specialized in the pharmaceutical industry being, for this reason, dominated by few firms in the world scenario (WHO, 2002b). The empirical data also show that product innovation in the BVI has been increasingly supported by links with outside sources of knowledge, be they internal or external to the firms, in the national or international contexts, which, according to some authors (Galambos and Sewell, 1995; Galambos and Sturchio, 1996; Galambos, 1999; Wilson et al., 2007), is critical to vaccine R&D. Finally, all these empirical data, clearly showing the development of the main firms of the BVI, were endorsed by the results of a survey carried out in the biggest firm. In this survey an audit tool specially developed by Bessant et al. (2001) to assess the level of technological capabilities of firms was applied, and the results revealed that the firm assessed had reached a high level of technological capabilities development within the transition phase (Section 7.6 on pg. 201-206).

Achieving a high level of technological capabilities as above discussed, was neither easy nor quick. Analyzing the process of technological accumulation in the BVI with the use of the innovation transition approach, represented here mainly by the works of Dutrénit (2000, 2007) and Hobday et al. (2004), has helped to understand the details of how it has unfolded. Some landmarks and main drivers of this process that emerged from the empirical data may be instructive for the learning process of other firms and are then discussed here.

One benefit of the use of the approach was the clear identification of how and when the transition phase started. In a broad sense it started in the BVI in the same way as in the firms analyzed in the works above mentioned, that is, from a more strategic approach to technology. In a more specific view this happened, in the case of the BVI, by the time the firms decided to build dedicated facilities and establish organizational structures to their R&D activities from the mid-1980s. The firms explored two slightly different routes in the first phase of the learning process (the pre-transition phase, as it was

named in this research) to pave the road that allowed this more strategic approach to technology. One more intensively based on the acquisition of foreign mature technologies, its absorption and adaptation, and the other on imitation of old technologies.

A second point, that naturally follows the first, relates to the time this transition has lasted. So far around 25 years have passed but the transition has not been completed and it is not possible to predict accurately when it will. Although empirical data show that the main firms are not too far from achieving the end of the technological transition, the process seems to be lengthy especially due to the specificities and complexity of the field of vaccine, but other reasons are also contributing to delay the process, as is shown in the next sub-section.

Other landmarks of this more strategic approach to technology which characterizes the transition phase, are the sharp growth of personnel allocated to R&D activities, especially highly skilled people, growing investment in R&D and training, and the development of some specialized capabilities closer to the knowledge frontier (e.g. in genetic engineering). Table 7.5 on pg 200 presents a broader range of the characteristics of this phase.

Another relevant aspect that arises from the transition analysis concerns the role of government and institutions in promoting the development of the BVI. Government investments and the huge and protected public market created by the PNI, have reduced the risks and uncertainties for the manufacturers, provided a good manufacturing infrastructure, influenced the "Big Pharma" firms to transfer proprietary technologies to them and, as a consequence, resulted in the sharp growth, the development of world class operating capabilities and new directions in the path of development. On the other hand, little attention was paid to the development of innovative capabilities itself. Only more recently have the firms started benefiting from new national policies directed at fostering innovation, and from more substantial resources of government financing agencies to fund R&D. The results, however, are still to come.[303]

[303] This issue is approached in the next sub-section.

8.3.2 The Hindrances of the Unfinished Transition

This sub-section analyzes and discusses the claim that the speed of change in the scientific/technological frontier is possibly the main hindrance to the completion of the transition phase, as posed in Proposition 4. Two main issues in the vaccine context inspired the above proposition: the first relates to the extent of the technological breakthroughs in the knowledge frontier, and the high complexity of the vaccine innovation process, as stressed throughout Chapter 5. The second relates to the dynamics and economics of the vaccine business and, more specifically, the power of the "Big Pharma" firms, which constitute the oligopolistic core of this industry, as detailed throughout Chapter 6 (see Sub-section 6.2.1 on pg. 121-125, and Section 6.3 on pg. 144-145).

In an article about the Brazilian and Indian vaccine industries, Milstien et al. (2007) assessed the impacts of the TRIPS agreement on technology access in both countries.[304] Although emphasizing that it is too soon for a definitive conclusion since there are some problems in the implementation of the agreement in these countries, the authors expect that intellectual property rights will force emerging manufacturers to resort increasingly to technology transfers and licensing agreements rather than to develop new vaccines. In other words, this paper means that the extent of new scientific and technological knowledge protected by patents, especially within the "Big Pharma" firms' domains, is an important constraint to emerging manufacturers in reaching the technological frontier. This is a matter of concern for other experts in the vaccine field, as stated in other literature (e.g. Plotkin, 2005c).

One certainly cannot deny or underestimate the achievements of the "Big Pharma" firms in the last 50 years as well as the impact of patents to knowledge creation, but there are some aspects to be considered here that are of interest to the specific discussion about transition. Firstly, even though molecular biology and genetic engineering has been considered by several vaccine experts as one of the main revolutions in vaccine development in the knowledge frontier in this period, few "genetic vaccines" were actually introduced to the market so far (see Item G of Sub-section 5.3.1 on pg. 105 and Table 5.4 on pg. 104). Although promising results have been announced for the near

[304] The Brazilian firms approached in this paper are the same two approached in the present research.

future, this model of development seems to follow the same "well-established, historical pattern of slow and incremental technology diffusion" found by Nightingale and Martin (2004:564) in the drug business of the pharmaceutical industry.

Secondly, as shown by Wilson et al. (2007), for most of the vaccines developed and launched by the "Big Pharma" firms in the same period the basic research was mainly carried out by universities and public or non-profit research institutions, often financed by public funds (see Sub-section 5.3.2 on pg. 107 and Table 5.5 on pg. 108). This confirms both the findings of Galambos and Sewell (1995), that the ability of building networks is critical to vaccine innovation, and the importance of what Nightingale and Martin (2004:564) call a "translation of science into technology" as another strong capability of these firms. Therefore, drawing on these two previous points, and on the concept that managing the innovation process is imperative to the success of firms, as pointed out by Tidd et al. (2001), it seems plausible to conclude that, although issues of a scientific and technological nature are certainly important hindrances to the firms of the BVI, no less important are the problems of a managerial nature they currently face in accomplishing the innovation transition.

This is in line with the findings of the works on innovation transition in Mexico and Korea, as summarized in the section "constraints to complete transition" in Table 3.3 on pg. 63. This statement is also supported by the empirical findings of this research. As shown in Table 7.5 on pg. 200 most of the reasons for the slowing of the rate of technological capabilities development in the BVI refer to managerial issues (e.g. low investments in R&D and in training, inadequacy of facilities, unavailability of technological platforms).[305] Other issues of same nature are also presented in that table. These include the lack of administrative flexibility (which is a characteristic of the public sector in Brazil) and of a strategic mindset by the main actors; it also includes the need for exploiting strategic partnerships more efficiently. In addition, the results of the survey indicate other weaknesses linked to the managerial process such as the organization of technology activities, the learning process, and the ability in building core competencies (see Section 7.6 on pg. 201-206).

[305] Low investments are considered when compared to those of the "Big Pharma", in the case of R&D, and to international standards, in the case of training (see Section 7.3 in Chapter 7 on pg. 182 and 188, respectively).

One further issue revealed during the analysis and discussion of Proposition 2 (Sub-sections 8.2.2 and 8.2.3 above) seems symptomatic of the importance of the managerial dimension to the completion of the transition phase. It regards the shift in the role of the technology acquisition strategy as a source of knowledge during the transition phase. As firms have approached the innovation frontier the strengthening of managerial capabilities have been much more intense than technical capabilities, even though the firms do not seem completely aware of that.

Notwithstanding, the evidence raised has shown that the hindrances to the development of the BVI are not limited to scientific/technological and managerial issues. The last component of this triad is of a broader nature and concerns the national system and the role of government and institutions. Although the country has well recognized strong science capabilities, the absence of articulation amongst ST&I policies has been pointed out by some authors (Gadelha and Azevedo, 2003; Gadelha, 2005; Temporão and Gadelha, 2007) as one of the factors setting back the development of the BVI (see Sub-section 6.4.2 on pg. 156-157). Dutrénit (2007:143) points out that countries like Mexico and Brazil (and other transition economies) present an imbalance between science and innovation capabilities, with the former being more developed than the latter. This poses a challenge to the catching-up process and to "the development of a more problem-oriented science". This is a problem also raised by one of the interviewees (interview 5 – see last paragraph of Sub-section 6.4.2 on pg. 161). Several authors have stressed the importance of the policy environment to the effective development of industries (e.g. Lall, 1992; Bell and Pavitt, 1995; Kim, 1997; Ernst et al., 1998a; Forbes and Wield, 2002, among others). More recent initiatives of the Brazilian government in terms of policies and programmes in an attempt to overcome the above fragilities were identified in some paragraphs of Sub-section 6.4.2 (pg. 156, 160 and 161), but it seems too soon for concrete results in a long-term innovation process as is the case of vaccines.

One further issue that arises from the specific context where the BVI is inserted refers to markets and the complex relationship between the BVI firms and the government. What the evidence shows is that government has apparently seen the firms as exclusively dedicated to fulfil the Brazilian public needs. This is due to the strategic nature of the vaccine sector set up by the government in the past, the huge investments it has made in the infrastructure of the firms, the big and stable protected market it has provided, and

the public (and non-profit) nature of these firms (see Section 7.4 on pg. 189-192). What the empirical evidence does not show is whether this big and highly protected market, along with the high dependence of the firms within it, has so far hampered the innovation transition of the firms. Notwithstanding, markets are commonly regarded in the literature as one of the most important sources of knowledge and a necessary condition to stimulate investments in innovation. The transition issues of the firms of the BVI cannot be disconnected to them. As shown by Forbes and Wield (2002:50) imbalanced infant-industries policies led, in many cases in industrializing countries such as India, Brazil, Mexico and others, to the fostering of permanent infants.

8.3.3 Unfinished Transition and Foreign Technology Acquisition Strategy

This sub-section analyzes and discusses the possible existence of a causal relationship between the persistent strategy of foreign technology acquisition adopted by the BVI, and the constraints of its unfinished technological transition in order to address Proposition 5. As in Propositions 2 and 3, this proposition assumes, once more, the possible existence of negative effects of that strategy on the development of the industry, reflecting concerns of some actors of the context of the BVI. This has obvious implications for policy and management. In those cases (Propositions 2 and 3), however, this assumption was demystified.

As noted by Hobday (1995:202) in the case of East Asian countries the then current weaknesses (as well as advantages and opportunities) of latecomer firms were directly linked to their origins, paths and strategies. Kim (1997:225) analyzed the technological learning in Korean firms and found that the acquisition of foreign packaged technologies through licensing from single sources (as in the case of the main firms of the BVI) leads to a "passive attitude toward the learning process". The findings of Mytelka (1978) in several firms of some South American countries are not dissimilar, as already emphasized in Sub-section 8.3.1 above. The findings of the above literature are suggestive of what the proposition implies.

In general, the evidence of the BVI case points to the opposite way. In some ways the analysis and discussion in the previous sub-sections have already addressed this issue. It would certainly be a mistake to deny the influence of origins, culture and path amongst the drivers of the current weaknesses of the firms of the BVI and, by extension, of the

constraints to finish their technological transition, but the technology acquisition strategy itself is certainly not amongst them.

As shown before, this strategy was and still is important to the development of the BVI. Besides being an important source of knowledge to strengthen technical capabilities in the past, it is currently contributing to increase the size of the firms, to fulfil the short-term demands of the public market, to a more strategic alliance with the technology transferors, and to strengthen some managerial capabilities. Moreover, it has not hindered the development of innovative capabilities, as empirical data and the analysis in the previous sub-sections have proved. On the contrary, the high awareness of the importance of technology led to the deployment of several initiatives toward the learning process and the development of R&D and of other innovative capabilities and, as a consequence, to the development of some new products. Additionally, several important hindrances to the unfinished transition concern local, national and legal issues, as emphasized in Sub-section 8.3.2 above, and the technology acquisition processes will not fill this gap.

Therefore, the constraints to the completion of the technological transition in this industry seem not a matter of what has been done, as the case of the strategy of continuous foreign technology acquisition adopted so far, but rather of what has not been done, which stands for not addressing adequately the main hindrances of the process. The attempt to link the strategy of technology acquisition with the unfinished transition helps neither the understanding of the real problem nor the design of strategies and policies to overcome the existing constraints.

8.3.4 Overall Findings of Research Question 2

Research Question 2 was formulated to address the assumption that, although the BVI might have already achieved the technological transition stage, it might not have yet caught-up and reached the technological frontier. This was due to an excessive reliance on foreign technology acquisition processes, and to the dynamics in the knowledge frontier dominated by a few oligopolistic firms – the “Big Pharma”. The use of the innovation transition approach made the gathering of very rich empirical data possible. This in turn provided a clear and detailed view of the characteristics of the process of developing more advanced technological capabilities by the main firms of the industry

in comparison to the context of firms in other developing countries. Moreover, a survey based on an audit tool developed to assess the technological capabilities of firms was carried out in the biggest firm, thus enhancing the main empirical data gathered and the results of the analysis, as well as working as a triangulation of the data.

Overall the results of the analysis and discussion of Propositions 3 to 5 were revealing and fairly surprising. They were revealing because several aspects of the micro dynamics of the transition phase of the industry were disclosed. Amongst them were the facts that characterized the start-up of the transition phase. The events that later unfolded, such as special capabilities developed, R&D investments, initiatives in training, strengthening of external links and the consequent achievements in terms of incremental and product innovation, are other important aspects unveiled. Also, the main hindrances to the completion of the transition phase were stated amongst the results of this research question. One further and important aspect revealed relates to the role of the foreign technology acquisition to the development of the firms during the transition phase.

On the other hand some of the results were, to a certain extent, surprising. First is the current high level of technological capabilities achieved by the BVI firms as revealed by empirical data and confirmed by the survey. According to these findings, although it is not possible to predict a time in the future, the firms are very close to complete the transition phase. It is worth remembering that the firms of the BVI are not seeking to leader but to acquire the ability for technical change and to be competitive in a niche market.

A second interesting point relates to the just above-mentioned role of foreign technology acquisition, especially during the most recent part of the transition phase. Although it has been adopted with the main objective of quickly fulfilling the short-term demands of the public market whilst more advanced technological capabilities are being developed inside the firms, the analysis points out a more important role not perceived by most of the actors of the industry. In this regard the analysis revealed that several managerial capabilities and skills have been strengthened lately through technology transfer agreements, and that this is an issue that should be further exploited by the firms.

The last surprising fact revealed is linked to this latter one. Innovative capabilities should be further developed within the transition phase, but managerial issues and some factors in the national context arise as other important hindrances to be overcome by the firms. This seems to be the big challenge for them and an interesting aspect of the transition phase of latecomer firms.

To sum up, Research Question 2 has helped to understand how far the BVI has come within the technological transition phase and how the process has unfolded. The context of development, the achievements and hindrances to the completion of this phase indicate the conclusions and some implications for the future of this industry. These are issues to be approached in the final chapter.

Chapter 9 – Conclusions and Implications

9.1 Introduction

This research has investigated the development of the Brazilian vaccine industry (BVI). It was motivated by preliminary data suggesting that its sharp growth in the last decades could be related to scientific, technological, political, social, organizational and economic specificities of its context, a persistent strategy of foreign technology acquisition, and an unclear level of innovative capabilities developed by public firms dealing with advanced technologies and seeking to reach the technological frontier. The main argument of this thesis was built drawing on studies on the dynamics of technological capability building in catching-up firms/industries of latecomer contexts, especially during the transition period when they are approaching the innovation frontier. It also draws on those studies focusing on new directions/paths as an alternative strategy that some catching-up firms/industries adopt to overcome barriers and disadvantages to development. It is argued that the specificities of the Brazilian context and of the vaccine sector might be determining a particular pattern of technological accumulation within the BVI, and that interpreting its pattern of development may be useful to understand how and if this industry has overcome its disadvantages to develop.

The simple conceptual framework, as developed and stressed in Chapter 3 (Figure 3.2 on pg. 53), integrates the linear catching-up and the innovation transition approaches and claims that the development of technological capabilities in catching-up firms/industries of latecomer countries performs a common/linear pattern during the period; this may be represented by the level of importance of two complementary sets of sources of knowledge – foreign technology acquisition and local innovative capabilities – and by the influence of other internal and external elements present in their contexts. In addition, it is claimed that, during the transition phase, firms develop the kind of more advanced capabilities needed to approach the innovation frontier. This research uses this simple framework as a benchmark tool to look for similarities and differences in the pattern of development of the BVI and to unveil its main characteristics.

By interpreting the empirical evidence gathered in the light of the linear catching-up approach, this study has provided a broad picture of the development of technological capabilities within this industry. It did not reveal differences in the trajectory of the two sources of technological knowledge investigated in terms of their level of importance, but it provided the elements for the analysis in the light of the Gerschenkronian perspective. Under this latter perspective new directions in the path of development of the BVI were clearly shown, suggesting that the development of this industry may be performing in a distinct pattern. On the other hand, the integration of the innovation transition approach in the conceptual and analytical frameworks made it possible to unveil the special characteristics of the most recent period of development of this industry. This indicates a very high level of technological capabilities development within the transition phase, and suggests possible alternative explanations for the constraints in completing the transition.

This chapter summarizes the main findings of the research (Section 9.2) and, in addition to indicate some implications for policy, management and for the future of this industry (Section 9.3), it points out contributions and limitations of the work (Section 9.4). It also suggests issues and questions for further research (Section 9.5) and briefly presents some final remarks (Section 9.6).

9.2 Main Findings

The research questions and their propositions were approached in the previous chapter. They were posed with the objective of addressing the research problem, and the analysis carried out to answer them provided both a broad view of the development of the Brazilian vaccine industry in the last four decades, and a detailed view of its most recent period of development and of its determinants. The findings were meaningful and revealing. The main findings of this research are summarized in the following three sub-sections.

9.2.1 Technological Accumulation in the BVI – Similarities, Differences, New Directions and Specificities of the Context

The assumption of the existence of a particular pattern of technological accumulation in the development of the BVI was investigated in the light of a benchmark model that was built based on linear approaches of the catching-up process of firms/industries in

latecomer contexts (Figure 3.2 on pg. 53). The analysis under the linear perspective of catching-up did not reveal significant differences; on the contrary it evidenced similarities with the pattern represented in the model. In this regard it was shown, for example, that the importance of foreign technology acquisition as a source of technological knowledge has decreased, despite the increasing intensity of adoption of this strategy, while the importance of local innovative capabilities has significantly increased.

Revealing this distinction between importance and intensity of the acquisition of foreign technologies, however, made it possible to identify new directions in the path of technological accumulation of this industry. In fact, the strategy of foreign technology acquisition was adopted with distinct objectives. In the first phase, it was clearly used to help the development of strong technical/operating capabilities; that was achieved by the early 2000s.[306] In the second phase, while firms were developing the innovative capabilities needed to reach the technological frontier, the strategy was clearly adopted to avoid the re-emergence of vaccine imports and the weakening of the incentives and protection assured by the Brazilian government to these firms. This more recent objective of the strategy was an articulation of the firms with the government (Ministry of Health), who used its purchase power related to its huge and attractive public market in order to persuade the "Big Pharma" firms to license and transfer recently developed proprietary products to the firms of the BVI. This strengthens the notion of new directions/distinguishing paths in the BVI, and evidences the strong role of the government and of its public market as some of its main drivers.

Other evidence also suggests the existence of new directions in the path of development of the BVI. By looking at the R&D pipeline of the two main firms (Figure 7.3 on pg. 179) we can find several projects addressing local/regional diseases that are important to the Brazilian and other developing/poorer countries needs, but that are not of interest of the "Big Pharma" firms for economic reasons. Although it is not possible to predict if and when these projects will be concluded, developing these vaccines not only constitutes competitive advantage to fulfil special needs of the local market, but also opens up opportunities to exploit export markets in more advantageous conditions.

[306] This is approached in more detail in the next sub-section.

Table 9.1: Context of Development of the BVI: Dimensions, Determinants and Specificities

Dimension	Determinants	Characteristics/Specificities
Scientific/ Technological dimension	. *Technological specificities and complexities of manufacturing and developing vaccines;*	. tacit knowledge and prior experience as key to the learning process; . requires multidisciplinary knowledge; . requires a good national basic science infrastructure; . long period of development – over 10 years typically; . high investment in adequate manufacturing facilities and in R&D needed; . tight governmental regulation; . capabilities to overcome the gap between basic/applied research and technological development required;
Policy-making dimension	. *Strong support and protection of the Brazilian government to the BVI with sole aim on import substitution to fulfil the local public market;*	. set up vaccine industry as an strategic sector; . creation of an outstanding and huge public market via PNI, which has grown fast and required quick responses of the BVI; . little concern about the international public market and the private market – local and export; . lack of applied research induction; . short term approach of the innovation policies until recently; . recently a more strategic approach of the innovation policies still not mature;
Organizational and Market dimensions	. *The ability of developing new to the world vaccines in few hands – the oligopolistic "Big Pharma" firms;*	. existence of very good organizational capabilities; . able to afford high R&D investments; . high capability for exploiting external sources of knowledge – networking; . heavy and dynamic business game – mergers, acquisitions, alliances;
	. *Organizational rigidities within the BVI due to the public nature of the firms;* . *Marketing rigidities;*	. lack of managerial flexibility in several areas; . high dependence on government protection and investments; . need of WHO pre-qualifications to supply UN agencies; . focus on the Brazilian public market almost exclusively;
Social dimension	. *Government and Institutions;*	. High engagement of governments, UN agencies; public and private institutions in fostering vaccine production and development, especially to supply low-income countries;
Economic dimension	. *PNI feasibility;* . *Firm's size;*	. vaccine shortages in the international market; . high price of imported vaccines; . need of the firms to grow to afford the high R&D investments required;

Source: Own elaboration based on the empirical data gathered.

The specificities of the context of the BVI are summarized in Table 9.1 above. They are presented to qualify the quite distinct context in which the development of technological capabilities of the BVI has happened. This quite distinct context has, in many respects, no parallel in the literature approaching technological capabilities, although some of its characteristics may be found in the context of other industries in developing countries. They constitute, therefore, the specific elements of the sectoral, national and international system of innovation of this industry and represent many of the barriers and opportunities faced by the BVI.

To sum up, the evidence above suggests that the pattern of technological capability building of the BVI is marked by distinct phases. The first presents similarities with the common/linear approach of catching-up. The second reveals new directions in an attempt to overcome some barriers and explore some opportunities present in its quite specific context. A third phase, not mentioned above, is still in its infancy, but strengthens further the notion of a distinct pattern. It is approached in the next sub-section, which summarizes the importance of the process of foreign technology acquisition to the development of this industry. However, the evidence indicates that, although important technological capabilities have been developed within this industry, the new directions revealed above have not allowed the firms to overcome all the barriers within the transition phase to date. This is an issue approached in Sub-section 9.2.3.

9.2.2 The Roles of Foreign Technology Acquisition

Using the integration of the innovation transition approach to interpret the technological capabilities development of the BVI helped to understand the details of the most recent period of its development. It also showed that the role of the process of foreign technology acquisition to the development of the BVI should not be underestimated. On the contrary, the use of this channel as a source of knowledge has provided clear and planned results as well as unexpected and less perceived ones. In addition the most recent evidence shows a potential new role for this strategy as a new direction of the main firms to catch-up and reach the technological frontier.

Consequently, the concerns of some actors about the context of the BVI with regard to possible hazards to the development of this industry due to the extent of the use of this

strategy seem unjustified.[307] In addition, the findings of this research found no resemblance to the empirical findings of two works that approached the relationships between foreign technology acquisition and development of innovative capabilities in latecomer contexts. In one case Mytelka (1978) discovered a strong correlation between the licensing of foreign technologies (the same channel used by the BVI firms during the last decade) and low engagement in own R&D, especially in state-owned firms. Yet Kim (1997) found that licensing from a single source (as has also been the case with each of the main firms of the BVI during the last decade) leads to a "passive attitude toward the learning process" (p.225).

The findings of the current research about the development of the BVI were exactly the opposite of the findings of both these works. In the specific case raised by Kim, the more intensive relationship with a single source of technology developed by the firms of the BVI seems to have increased the confidence of the transferor in the capabilities of the transferee, thus helping the negotiation of the subsequent agreements. Moreover, the two smaller firms of the BVI, not approached in depth in this research for methodological reasons, were exposed to the same context of the larger ones, but have not made use of foreign technology acquisition. Coincidently or not they have lagged far behind the two main firms.

One important aspect of the process of foreign technology acquisition by the main firms of the BVI concerns the distinct roles of this source of knowledge along the process of developing technological capabilities. During the first phase of the development of this industry the main role of this strategy was linked to the technical aspects of manufacturing vaccines and, by extension, to the innovation process of vaccines. Among the main capabilities acquired and developed during this first phase, are those to design adequate facilities, to oversee the building of these facilities, to deal with new production processes and techniques, and with more advanced technologies during the manufacturing process, and to produce vaccines fully complying with international quality requirements. In addition, the firms' efforts to adapt the acquired technologies and improve old ones were reported as having partially benefited from the same

[307] From the literature review chapter (Chapter 2) one can infer that opposition to the use of foreign technology acquisition is not uncommon in Brazil, as shown by the work of Dahlman and Fonseca (1987) about the development of a Brazilian steel company (see pg. 27, quotation).

processes of technology acquisition. A secondary, but also important, role during this phase was the increasing fulfilment of the needs of the National Immunization Programme (PNI) with consequent contributions to the import substitution policy of the government. Furthermore the main firms of the BVI had clearly built world class manufacturing capabilities at the end of this phase.

As the main firms developed more advanced innovative capabilities, and became able to fulfil some of the needs of the PNI for more advanced technologies by their own technological efforts, the benefits from foreign technology acquisition to the development of technical capabilities became limited. The second phase of development identified by this research, still in process today, showed a shift and a dual role of the strategy. Intentionally, the strategy has been mainly used with market motivations, that is, to quickly fulfil those new demands of the PNI for proprietary products and to increase the size of the firms.[308] In addition, as emphasized in the previous sub-section, by quickly fulfilling the new needs of the PNI, the firms clearly tried to avoid the weakening of the protection policy granted by the government. The second role of this source of knowledge during this phase appears to be a "by-product" of the more recent decision of keeping (or even increasing) the intensity of adopting the strategy of foreign technology acquisition (especially by the biggest firm of the BVI).

In this case some managerial capabilities that are important to the process of managing innovation have been developed instead. To cite only a few:

- The capability to better assess the technological frontier and the position of the firm in relation to it in terms of available resources and needs;
- The ability to negotiate increasingly better technological conditions in complex contracts;
- The opportunity to establish linkages with the own suppliers of materials and capital goods of the "Big Pharma" firms.

A curious finding of this research was that this new role is not clearly perceived by most of the actors of the context of this industry and, therefore, possibly not fully exploited

[308] As tacit knowledge is key in the learning process of the vaccine industry, technical capabilities will always be important during the processes of foreign technological acquisition. However, they tend to be related more to the secrecies of the process of manufacturing the specific technology being transferred than to the acquisition of new technological techniques/platforms.

by the firms. Since it appears to be unintentional it was not approached before, but it seems to constitute an important new direction to be exploited by the firms.

The third role of the foreign technology acquisition is very recent and overlaps with the second: it was established in the last technology transfer agreement but is still to be implemented. It is being considered here as a distinct role because it makes the bridge to a new and very important kind of relationship between the Brazilian firm and the "Big Pharma" firm who is transferring the technology. In this case the agreement goes beyond the simple technology transfer process to form a long-term strategic R&D alliance to develop new vaccines.[309] Although it is too soon to assess the impact of this initiative to the Brazilian firms and to the BVI, it clearly indicates a decisive step in the way to approach the technological frontier, in the same sense identified by Hobday (1995:204) about the most progressive firms of East Asia. This finding also shows that the role of foreign technology acquisition may be much more important than has been rationalized so far, and that the building of new paths is actively in progress.

9.2.3 The Unfinished Technological Transition – Key Issues

The aspects of the transition phase during the development of the BVI were raised and interpreted drawing mainly on the pioneering works of Dutrénit (2000, 2007) and Hobday et al. (2004). An audit tool developed by Bessant et al. (2001) to assess the level of technological capabilities of firms, as well as determining weaknesses and strengths in their process of technological accumulation, was also applied. The findings proved that the main firms have currently reached a high level of technological capability, and that the threshold to catch-up and reach the technological frontier is not too far. They also provided a very rich picture of the characteristics of development of these firms during this transition phase. Finally these findings shed light on the crucial part of the development of this industry, that is, on the aspects of the unfinished transition. The two key issues of the transition phase during the development of the BVI to be highlighted, therefore, concern how it started and why it has not yet finished.

[309] Although the expression "simple technology transfer" is being used, it actually encompasses the transfer of the most recent proprietary technology developed by the "Big Pharma" firms, recently licensed in the international market and one of the most important in the international market today.

On the first matter there is clear-cut evidence of the time when the transition phase started for the two main firms of the BVI and of the conditions that make the shift possible. The pre-transition phase was characterized by the development of what Dutrénit (2007:132) has termed as "minimal essential knowledge". In the case of the BVI this type of knowledge was built through the acquisition of mature foreign technologies and imitation of very old technologies. However, until the mid-1980s, innovative capabilities were rather informal. From this time, the empirical evidence clearly shows that these main firms contemporarily presented a more strategic approach to technology, considered by Hobday et al. (2004:1438) as a typical sense developed by firms in transition. The organization of R&D activities, the building of dedicated R&D facilities, and the allocation of more skilled people to these activities, are representative of this strategic approach to technology by the two main firms of the BVI.

Notwithstanding, as well as the importance of identifying the starting time of the transition phase or how the firms developed the preceding capabilities, it is also important to approach the context where this phenomenon happened. In this sense three factors found in the context of the BVI seem to exemplify some distinguishing characteristics of its transition phase. The first is that this transition phase started at a time of the Latin-American context regarded by several authors as not stimulative to innovative behaviour, this due to several decades of economic protection and marked by macro-economic instability, as pointed out by Dutrénit (2007:140). The second regards the market more specifically. The beginning of the transition phase and the successful development of the main firms of this industry so far have been sustained by a huge and protected local public market that has increasingly demanded new technologies. According to Radosevic (1999) this is not usually available in latecomer contexts that suggests export as an essential element for growth. The third factor relates to the internal decision of the firms that originated the beginning of the transition phase. Although it coincides with the launch of an important governmental programme to stimulate national self-sufficiency in immunobiologicals production – Programme of National Self-sufficiency on Immunobiologicals (PASNI) – and one of the main firms of the BVI has benefited from resources of this programme to build a biotechnology centre, the PASNI indeed paid little attention to the development of innovative capabilities. Therefore, the "strategic approach to technology" presented by the firms was probably linked to the historical culture of the firms and the high awareness of the

importance of technology inside the firms, rather than to direct governmental stimulus. [310]

On the matter of why the transition phase has not finished so far the findings were enlightening. The assumptions that major breakthroughs in the knowledge frontier and the speed of innovations determined by the few oligopolistic "Big Pharma" firms could be the main factors hindering the completion of the transition phase were knocked down by the evidence gathered. Although technical and scientific issues have been crucial for the development of the vaccine sector and constituted important barriers to the BVI, the evidence pointed to managerial issues as the most significant elements of the unfinished transition of the BVI. In this regard, organizational structures and capabilities gain an increasing dimension to the understanding of the determinants that influence the transition process. Furthermore, the findings of the research indicate a fair awareness of the managers of the firms of the managerial problems but a low awareness of what to do to overcome these problems.

The works of Dutrénit (2000, 2007) and Hobday et al. (2004) also identified the managerial dimension as being amongst the constraints faced by firms approaching the innovation frontier in latecomer contexts. The findings about the BVI led to two conclusions: firstly, drawing on the conclusions of the works cited above, it indicates that the BVI has reached a high stage in the development of technological capabilities; secondly, the managerial issues seem to be the last stage of the transition process of latecomer firms/industries, as it starts overlapping with issues found in the organizational context of large firms of developed countries. As argued by Pavitt (1998):

> … in the late twentieth century, lack of technological knowledge is rarely the cause of innovation failure in large firms based in OECD countries. The main problems arise in organization and, more specifically, in coordination and control (p. 434-435).

Moreover, the evidence also indicates one or two policy issues that have also influenced and delayed the transition of the firms. More recently, the government has tackled the lack of articulation among ST&I policies of the 1990s, but it could not produce concrete results to date due to the long-term nature of the vaccine innovation process. A second

[310] See details about the PASNI in sub-section 6.4.2 of Chapter 6 on pg. 159-160.

issue relates to the policy model adopted by the vaccine sector in Brazil. An import-substitution/infant industry model has been used by this sector since the 1980s and across discontinuous policy regimes in the country in the 1980s, 1990s and 2000s. This model has helped the firms to develop important technological capabilities and implement new directions in their path of development, but has not stimulated them to compete both in the national (public) and international contexts.

Finally, Figure 9.1 attempts to illustrate the main characteristics of the development of the Brazilian vaccine industry summarized in the three sub-sections above, mirroring the benchmark model developed in Chapter 3 (Figure 3.2 on pg. 53).

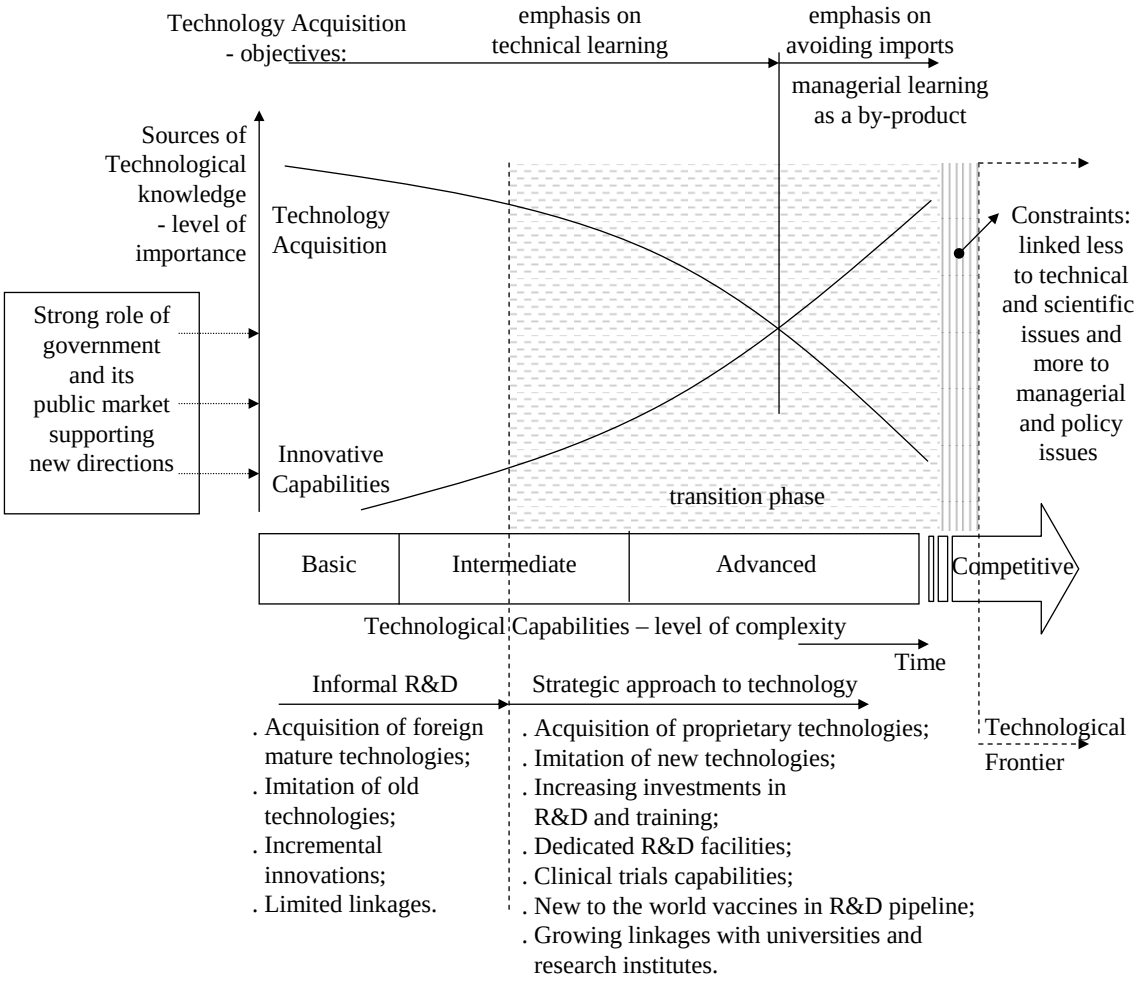


Figure 9.1: Characteristics of Technological Accumulation in the BVI

9.3 Implications

The findings of this research indicate some implications for policy and management. Although the literature has many examples showing that the specific context of each

industry, such as its own history and culture as well as the local and national advantages in terms of science and technology infrastructure, macroeconomic stability, level of education of the people, etc., poses important challenges to those industries that seek to learn from the experience of successful firms/industries (e.g. Hobday, 1995; Kim, 1997), the case of the Brazilian vaccine industry may be of interest in some specific contexts.

Firstly, for the government of most Latin American countries where the local vaccine industry was wiped out or became inexpressive in the past decade, making them completely dependent on imported vaccines, even the basic ones. Secondly, for the smaller firms of the BVI, who operate in a similar context to the larger ones and benefit from the same local public market advantages and policies, but have lagged far behind in terms of technology, production capacity and development of technological capabilities.

However, there may be lessons for the two main firms of this industry, and for the Brazilian government too. Despite the success they have achieved so far, the model of excessive dependence of the local public market and of the government protection that has been one of the drivers of their development may be reaching its limit. Although there are no elements in this research to suggest a twist in the role of the government in the near future, or to predict whether the public market will keep on growing at a similar rate and whether its growth will be able to sustain the development of the firms, relying solely on the stability of this model sounds risky. Hobday et al. (2004:1452) show that the changing circumstances of the macroeconomic environment, government policies and competitor strategies, are also critical to the successful transition of firms.

Kim (1997:239) calls attention to the new order of international trade and the pressures of the World Trade Organization (WTO) against protected markets. Forbes and Wield (2002:56) revealed that the success of East Asian Industrialization was a result of a potent combination of infant-industry protection with export-orientation, which is a missing issue in the policies for the vaccine sector in Brazil. These authors also point out that protectionism has, in many cases, “led to the fostering of permanent infants” (*ibid.* p.50). The firms of the BVI must be prepared for changes in their environment, to compete in the local market, and to explore international markets efficiently. A different context will certainly require these firms to develop a different kind of managerial skill,

a more flexible and dynamic management process, and the capability to explore and compete in new markets. This seems to be the new agenda to complement the "new directions/path" strategy of the development of this industry. It also seems to be a new agenda for driving the government policies for this sector.

9.4 Contributions and Limitations

This research was originally designed and has succeeded in contributing to literature in two areas: a) to provide a broad understanding of the development of technological capabilities in an industry context full of specific and uncommon characteristics and not approached before; and, b) to provide a deeper understanding of the micro dynamics of the innovation transition process in a latecomer context. Within these contributions this study brings to light three new themes that have been apparently neglected so far. The first shows some firms of the vaccine industry in a latecomer context looking for new directions to overcome the barriers to their development. The second concerns the role and importance of government and institutions in providing a local niche market (public) and policies able to sustain a good portion of the cycle of development of local firms of an industry. In the case of the BVI this cycle has not yet finished, and the evidence shows that there are missing issues in the policy agenda of the government to this sector. However the evidence raised also suggests that the main firms of this industry are not too far from catching-up and reaching the technological frontier. The third concerns the distinct roles of the foreign technology acquisition strategy to the development of technological capabilities of firms. In this case the findings suggest that each distinct role is linked to the stage of development of technological capabilities of the firms and that there are potential new roles/new directions to be exploited.

On the other hand this research presents some limitations due to the choices made during the research design and methodology processes. By choosing to focus on the industry context, the research paid little attention to the differences amongst the firms and therefore to the possible influence of these differences to the development of their technological capabilities. By choosing to focus on the micro dynamics of the innovation transition process this research paid limited attention to the macro determinants of the context of the industry, and to the impact of the national system of innovation to the development of innovative capabilities within the firms.

9.5 Further Research

The conclusions of the case of the Brazilian vaccine industry has revealed key issues about technological capabilities development, especially during the transition phase of its main firms, but was unable to go further in some of these issues, indicating that more research is needed. First, it was shown that managerial issues are currently one of the main constraints to the completion of the transition process in this industry, and that this seems to be the last stage in its transition process. In this specific context, further research could approach the managerial and organizational capabilities required to finish transition in more depth, as well as the determinants and constraints to develop them. In a broader perspective, new research could compare the aspects of technological accumulation and innovation transition between the context of this public industry in Brazil, and private firms of the same industry in other latecomer countries. India could be an interesting site as there are some private and public firms emerging in the international vaccine scenario. China is an alternative, although they face problems relating to regulation issues.

Second, the research revealed a huge public market and government policies sustaining the transition process/new directions of the firms of the BVI to date. The extent to which this model will guarantee the completion of the process or can be emulated in the context of other industries, as well as the imbalances of the infant-industry policy for this sector, are also issues to be approached by further research.

9.6 Final Remarks

The integration of the catching-up and innovation transition approaches as a benchmark model has shown to be useful in interpreting the characteristics of the development of the Brazilian vaccine industry and in revealing some similarities and differences of its more recent distinguishing path.

Although with a distinct purpose, Freeman (1988) stated that:

> A satisfactory theory should certainly be one which conforms more closely to the available empirical evidences … (p. 4).

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ANNEX A

List of interviewees, background and subjects approached

Interview – Interviewee – Position[1]	Date of the Interview	Subjects of the Interview
Interview 1 – Dr. Ricardo Galler – Director of Technological Development of Bio-Manguinhos/Fiocruz.	14 August 2008	Innovative Capabilities
Interview 2 – Dr. Antonio Risolia de Padua Barbosa – Director of Production of Bio-Manguinhos/Fiocruz.	19 August 2008	Operating Capabilities
Interview 3 – Otavio Augusto Mercadante – General Director of Instituto Butantan and former Head of Cabinet of the Ministry of Health.	21 August 2008	Corporate Strategies
Interview 4 – Dr. Ivo Lebrun – Scientific Director of Instituto Butantan.	21 August 2008	Innovative Capabilities
Interview 5 – Dr. Paulo Lee Ho – Director of the Biotechnology Centre of Instituto Butantan.	21 August 2008	Innovative Capabilities
Interview 6 – Dr. Hisako Gondo Higashi – Director of Production and Technological Development of Instituto Butantan and former General Director of the same Institute.	22 August 2008	Corporate Strategies, Operating Capabilities Innovative Capabilities
Interview 7 – Mario dos Santos Moreira – Director of Management of the IBMP and former Director of Management of Bio-Manguinhos/Fiocruz.	26 August 2008	Policies, Markets
Interview 8 – Renato Rau – Director of Production of the Instituto de Tecnologia do Paraná (Tecpar).	26 August 2008	Operating Capabilities, Innovative Capabilities
Interview 9 – Dr. Mariano de Matos Macedo – President of the Instituto de Tecnologia do Paraná (Tecpar).	26 August 2008	Corporate Strategies
Interview 10 – Artur Roberto Couto – Director of Management (1st interview) and General Director of Bio-Manguinhos/Fiocruz (currently and during the 2nd interview by September 2009).	28 August 2008 1 September 2009	Corporate Strategies, Markets
Interview 11 – Maria da Luz Fernandes Leal – Director of Quality of Bio-Manguinhos/Fiocruz, former Director of Production and General Director of the same Institute.	1 September 2008	Operating Capabilities, Corporate Strategies Innovative Capabilities
Interview 12 – Dr. Ellen Jessouroum – Manager of the Programme of Development of Bacterial Vaccines of Bio-Manguinhos/Fiocruz.	2 September 2008	Innovative Capabilities
Interview 13 – Dr. José da Rocha Carvalheiro – Vice President of Research and Technological Development of Fiocruz and former Manager of the INOVACINA Project.	2 September 2008	Policies
Interview 14 – Dr. Geraldo Armoa – Senior Researcher of the Instituto Oswaldo Cruz/Fiocruz and former Manager of the Laboratory of Recombinant Technology of Bio-Manguinhos/Fiocruz.	2 September 2008	Innovative Capabilities

Interview 15 – Marcos Henrique de Castro Oliveira – Vice President of Abifina and former General Director of Bio-Manguinhos/Fiocruz.	4 September 2008	Policies, Corporate Strategies
Interview 16 – Maria de Lourdes de Souza Maia – Senior Advisor of the Clinical Trials Advisory and former General Manager of the National Immunization Programme (PNI).	4 September 2008	Policies, Clinical Trials
Interview 17 – Dr. Cristiane Quental – Coordinator of the Master Degree on Innovation in Health of the Sergio Arouca National School of Public Health/Fiocruz and Fiocruz Representative of the Brazilian Clinical Trials Network.	4 September 2008	Clinical Trials
Interview 18 – Dr. Marcos da Silva Freire – Manager of the Program of Development of Viral Vaccines of Bio-Manguinhos/Fiocruz.	5 September 2008	Innovative Capabilities
Interview 19 – Dr. Akira Homma – General Director of Bio-Manguinhos/Fiocruz, founder of the Institute, former President of Fiocruz, former advisor of the PAHO and current President of DCVMN.	8 September 2008	Corporate Strategies, Policies
Interview 20 – Dr. Carlos Augusto Grabois Gadelha – Vice-President of Production and Innovation in Health of Fiocruz.	9 September 2008	Policies
Interview 21 – Josmar Almeida Soares da Silva – Head of the Department of Engineering of Bio-Manguinhos/Fiocruz.	26 August 2009	Engineering
Interview 22 – Reinaldo Menezes Martins – Senior Advisor and former Head of the Clinical Trials Advisory of Bio-Manguinhos/Fiocruz, Coordinator of the clinical trials of the Hepatitis B vaccine for the PNI and former President of the Brazilian Pediatrics Society.	1 September 2009	Clinical Trials

[1] Position at the time of the interview. Interviews sorted by the date of the interview.

ANNEX B

1) Survey for the Assessment of Technological Capabilities – the Questionnaire[1]

Firm: Date:

1) Select the options below that best fit your professional profile:

a. Activity area: R&D / Production / Engineering / Quality / Management

b. Post: Manager / Non Manager c. Years in the firm: less than 10 / 10-20 / over 20

d. Highest qualification: Graduation / Specialization / Masters Degree / PhD

2) Dimensions of Technological Capabilities[2] and Key Questions	**Assessment (scores)**				
	Strongly Disagree (1)	Disagree Somewhat (2)	Agree Somewhat (3)	Strongly Agree (4)	Don't Know
Awareness: 1 – Technology plays an important part in my company's business strategy; 2 – My company is well aware of the technologies most important to its business;					
Search: 3 – My firm is well equipped to assess technological opportunities; 4 – My company can assess technology threats without difficulty;					
Building Core Competence: 5 – My company has special technological strengths which it is able to exploit; 6 – My company knows which technology to outsource and which to develop internally;					
Technology Strategy: 7 – Our management is skilled at formulating a technology strategy to meet business goals; 8 – Our firm knows its main technology priority; 9 – Our firm has a well developed technology vision;					
Assessing and Selecting Technology: 10 – Our firm knows how to select the technology needed for its business; 11 – Our company knows which are the best sources of technology;					
Technology Acquisition: 12 – Our company is effective at acquiring technology from external sources; 13 – Our company has good links with important external suppliers of technology;					
Implementing and Absorbing Technology: 14 – Our technology activities (e.g. engineering and R&D) are organised effectively within our company; 15 – We have clear processes for carrying out technology projects;					
Learning: 16 – Our company has a good system for assessing technology projects; 17 – Our firm carries out post-project reviews; 18 – We are able to learn from one technology project to another;					

Exploiting External Linkages and Incentives: 19 – Government policies encourage us to invest in technology; 20 – We use external organisations (e.g. consultancy firms) to assist us with technology assessment; 21 – We use outside bodies to help us develop technology; 22 – External organisations help us assess our technology performance; 23 – We work with universities in key technology projects; 24 – We work with government research institutes in important technology projects;					

[1] The questionnaire was translated into Portuguese by the author of this research;
[2] The dimensions of technological capabilities were included here just to show which ones are related to each group of questions and they were not included in the questionnaire used in the survey.
Source: Bessant et al. (2001).

2) Operationalizing the Results

The overall audit result of the survey (see Table 7.6 in Chapter 7 – pg. 203) was calculated in the light of the levels and scores defined by Bessant et al. (2001). Table B.1 shows these figures. The final result of each dimension was determined by calculating the average of the scores of all questions related to that dimension. For example, the dimension "Awareness" got a score of 3.7, which is the average of the scores of question 1 (3.9) and question 2 (3.5). The total score refers to the sum of the scores of all 24 questions.

Table B.1: Levels of Technological capabilities and Scores Range

Capability Level		Score Range
1	Unaware/Passive	24
2	Reactive	25 – 48
3	Strategic	49 – 72
4	Creative	73 – 96

Source: Bessant et al. (2001).