The Cuban Biotechnology Industry: Innovation and universal health care

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Abstract

The analysis of Cuban biotechnology reveals how important it is to rely on country-specific institutional innovations in order to evolve coherently from lesser to more technology-intensive industries. In this short contribution, it is argued that the development of the Cuban biotechnology industry must be understood in the context of the Cuban socio-political context. Indeed, the Cuban biotechnology has been conceived as an element of the state-funded health system, and is part of a broad strategy designed primarily to preserve a healthy population. The government investments and strategic involvement have been essential to create a research and production infrastructure and a qualified workforce which led to the creation of the West Havana Biocluster. Another feature of this industry has been the widespread and long-term state-fuelled integration of the biotechnology in a multi-institutional system, aimed at supporting interdisciplinary collaboration and knowledge sharing. It will be argued that these characteristics are critical to the high innovation rate achieved by this industry.

Keywords: Innovation economics, development economics, Biotechnology Industry, Cuban health system, Technological change

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Introduction

Even when the pervasive lack of data makes it difficult to establish an accurate picture about the innovative outcomes of Cuba's biotechnology industry, the available evidence of its achievements in this field seems to be unequivocal. According to a World Bank report[1], "[…] at present, nearly 80 percent of finished pharmaceutical products used in Cuba are locally made". A few lines earlier, the report also states that"[…] the growth of the local pharmaceutical industry, which by the mid-1990s was bringing Cuba some 100 million dollars a year in export earnings, has not only covered domestic demand for medicines, but has also led to the development of products that compete on the international market. Cuba is the only country in the world, for example, that has come up with an effective vaccine against meningitis B". This vaccine (VAMENGOC- BC®)[2] is now exported primarily to Latin

[1] Kaplan W, Laing R (2005), Local Production of Pharmaceuticals: Industry Policy and Access to Medicines. Health, Nutrition and Population Discussion Paper, The World Bank Jan16

[2] A *halal* version of the vaccine is being currently developed. The initial markets would be Malaysia, Indonesia, Singapore and Brunei , see USM, Cuba's Finlay develop halal vaccine for meningitis, Business Times,

America, including Brazil, Argentina, Colombia, Venezuela, and Uruguay, but also to countries in Asia and Europe.

An article from the MEDICC Review[3] states that "[…] a recent Ernst & Young report puts exports of biotech products at USD$300 million in 2005". The recombinant hepatitis B vaccine (see figure 11) has received pre-qualification from the World Health Organization (WHO) in 2001 for international use and is now commercialised in more than 30 countries worldwide[4]. Cuba recently developed the world's first synthetic vaccine (Quimi-Hib) against Haemophilus influenzae type b (or Hib), a bacteria that causes nearly 50% of all infections, some of which lead to deafness and mental retardation, in under five-year-olds worldwide[5]. According to a Chemical and Engineering News report[6], this is the first commercial vaccine made from a synthetic carbohydrate, which is said to be cheaper than those based on natural carbohydrates; and to envision a new generation of carbohydrate-based vaccines. Cuba's Centre for Neurosciences electroencephalography and electromyography equipments are being exported to over 20 countries in North America, Asia, Africa, Europe and Latin America under the Neuronic trademark[7]. This Saragossa-based (Spain) Cuban company has earned the European Union's certification for sale in Europe and won in April of 2009 the National Exporter Award for the volume of goods commercialized[8].

The Centre for Genetic Engineering and Biotechnology (CIGB), located in the Western Havana Biocluster in Cuba, is one of the most important companies in Cuba and "has a long and distinguished record of producing innovative biotech products for the country's healthcare system"[9] (See Figures). Joint venture projects and licences include countries such as Canada, Great Britain, Algeria, Brazil, Canada, China, India, Malaysia, Mexico, South Africa, Tunisia, and Venezuela. Firms such as GlaxoSmithKline (England), CancerVax (US), Biotech Pharmaceutical Ltd (China), Oncoscience AG (Germany), YMBiosciences (Canada) are among the foreign collaborators. According to a study from Nature Biotechnology[10] by 2004, Cuba had registered some 100 patents and applied for another 500 patents throughout the world. The US Treasury Department has approved several clinical trials of Cuban products within US territory, despite the US trade embargo against Cuba (see below).

Biotechnology is undisputedly the most innovative Cuban industry. An understanding of the underlying causes of its evolution could help to design much more effective upgrading and development strategies. In that sense it is required a theoretical explanation of the

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2010/03/01, Online: http://www.btimes.com.my/Current_News/BTIMES/articles/vacin/Article/. See also http://wsicubaproject.org/halalvaccine_1107.cfm

[3] Evenson D (2007), Cuba's Biotechnology Revolution, *MEDICC Review*, Vol 9, No 1

[4] WHO list of vaccines for purchase by UN agencies as of March 2010, http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/

[5] http://www.globalexchange.org/countries/americas/cuba/foodAndMeds/1510.html.pf

[6] Carbohydrate Vaccines: Novel chemical and enzymatic oligosaccharide synthesis techniques could lead to a new generation of carbohydrate-based vaccine agents, August 9, 2004, Volume 82, Number 32 pp. 31-35, Online: http://pubs.acs.org/cen/coverstory/8232/8232vaccines.html

[7] Riding the Brainwaves of Cuban Science, MEDICC Review, Spring 2008, Vol. 10, No. 2

[8] Cuba's Neuronic company doing well in the World Market, http://www.cubaheadlines.com/2009/11/09/18557/cuba%E2%80%99s_neuronic_company_doing_well_world_market.html

[9] Lopez et. al. (2007), Taking stock of Cuban biotech Nature Biotechnology 25, 1215 - 1216

[10] Thorsteinsdóttir H et. al. (2004), Cuba-innovation through sysnergy, Nature Biotechnology , vol. 22, Dezember 2004

mechanisms, which are taking play here. What kinds of institutions are supporting this industry? How could a country like Cuba be able to develop an internationally competitive biotechnology industry? Are we talking about an exceptional case? What role do country-specific institutional innovations play in the process of technological change? This sort of questions motivates this analysis. This paper will mention some aspects, which could be taken into consideration when explaining the emergence, evolution and current existence of the Cuban biotechnology. This contribution is intended to discuss the subject in an abbreviated manner and give by no means definite answers as these issues are themselves part of a research in progress.

Analytical Points of Departure

The abovementioned World Bank report also states that"[…] probably because of its unique political history, Cuba is an atypical example of a small country that is a local producer of assured-quality pharmaceuticals". Indeed, the development of the Cuban biotechnology industry (especially the health biotechnology) has to be understood in the context of the Cuban socio-political project. Cuba's socialist state has devoted a great amount of resources to the development of well-functioning health, education and scientific research infrastructures, which happen to be deeply interrelated with the Cuban biotech. This long-term commitment to organisational integration in order to accomplish social objectives is the main reason behind the success of this industry in Cuba.

Several international organisations' reports place Cuba between the countries of Latin America and the Caribbean, which more spend on R&D as a percentage of the GDP (second with 0,8% behind Brazil with 0,9%)[11]. A more recent report places Cuba in third place with 0. 6 % [behind Brazil 0,9% and Chile 0.7[12] (UNESCO Institute for Statistic Fact Sheet October 2007 No.5)]. Notwithstanding the small differences, Cuba's spending of R&D /GDP is one of the biggest in the region.

However, this alone cannot explain the existence of an innovative high technology industry in a poor country like Cuba. R&D expenditure is certainly important for the development of science in a country. No country will be able to achieve and durably maintain prosperity and a high quality of life without using the results of science and ensuring a well-educated population. However, Cuba's R&D shows nothing exceptional when compared with the rest of the world. Most countries spend between 0.25% and 1% of GDP on R&D. Nevertheless, Cuba has been able to develop a high technology industry at the level of countries such as Finland (3,5%), United States and Canada (2.7% and 2% respectively) or Denmark, France, Germany (the figure ranges from 2% to 3%)[13].

The case of the Cuban health system is of special interest because of its developed-country health outcomes despite its developing-country economy. Cuba spends just 7.4% of its GDP[14]

[11] Measuring progress towards knowledge societies, A World of SCIENCE, Vol. 2, No. 1, January–March 2004 (http://www.unesco.org/science/awos/knowledge_societies.pdf)

[12] Another database places Cuba in position 45 in the World with 0,65% and Chile in the position 50 with 0,61 according data of 2003. Brazil remains the regional leader with 0,98% (http://www.nationmaster.com/red/graph/eco_res_and_dev_exp_of_gdp-economy-research-development-expenditure-gdp&b_printable=1)

[13] Ibid

[14] Richard et al.(2006) refer to 16% of GDP, which would represent $320 per capital, but this does not essentially change our argument. (Health in Cuba, International Journal of Epidemiology 2006;35:817–824)

on health care, compared with the 13.6% spent in the United States[15]. Health expenditure per person is $193 in Cuba contrasted with $4540 spent in the United States. Cuba's GDP per capita is one of the lowest in the Western hemisphere[16]. Nevertheless, Cuba, unlike most Latin American countries, has achieved health outcomes comparable with those of the United States and Europe.

The abovementioned is confirmed by a report from the US based World Security Institute[17], supported by data from the World Health Organization[18]. According to this report, "in 2002 Cuba boasted 66,567 doctors, totalling 5.91 doctors per 1000 people on the island. This exceeds the doctor per capita totals of both the United States, with 2.56 doctors per 1000 people in 2000, and the UK[19], with 2.30 in 1997. Life expectancy and infant mortality rates are comparable to those of most industrialized countries, at 75 years for Cuban males and 79 years for Cuban females, as compared to 75 years for American males and 80 years for American females. British males are expected to live 77 years, and British females 81. As of 2007, the mortality rate of infants under one year old in Cuba was 6.04 per 1,000 live births, comparable to 6.37 infant deaths per 1,000 live births in the United States, and 5.01 in the United Kingdom. Nonetheless, total per capita expenditure on healthcare in Cuba at the international dollar rate in 2004 came to $229.10, while in the United States it was $6,096.20 and in the UK it was $2,559.90. In 2004, the total health expenditure totaled 6.3 percent of the Cuban GDP, while it was 15.4 percent of U.S. GDP and 8.1 percent of UK GDP".

International agencies such as the World Bank have suggested that per capita income in Cuba is under $1000 per year; Cuban estimates, which take account of subsidies, are higher, in the range of $2–5000 per year.[20] Using either measure, however, when health outcomes are correlated with GNP, Cuba is clustered with North America on the former scale and with countries like Bolivia on the latter, as the figure suggests (see figure 1)

Beyond quantitative indicators

The use of comparative data indicators could be confusing in the Cuban case. Though useful for descriptive purposes, correlations of social indicators among countries require strong assumptions about the accuracy and comparability of the measures. One of the cited reports acknowledges, that "regional ratios are, of course, directly biased by the weight of the major countries (Brazil, South Africa, China, Japan, etc.), which can cloak the reality of other countries in the same region"[21]. Specifically in the biotechnology industry, national producers rely often on different methodologies. A recent OECD` s comparability report suggest to be cautious by

[15] According to the US Department of Health & Human Services this number was 16,2 in 2008, up from 15.9 percent in 2007

[16]The World Factbook: Cuba, Central Intelligence Agency https://www.cia.gov/library/publications/the-world-factbook/geos/cu.html

[17] The Cuban Health System, US-Cuba Cooperative Security Project, World Security institute, December 2007 , http://www.wsicubaproject.org/cubahealthsystemfactsheet.cfm

[18] WHO Statistical Information System (WHOSIS), http://www.who.int/whosis/en/index.html

[19] According to the Nation Master this figure was 2.2 for UK in 2002 and 2.3 for the US in the same year, http://www.nationmaster.com/graph/hea_phy_per_1000_peo-physicians-per-1-000-people

[20] Dresang et. al (2005), Family Medicine in Cuba: Community-Oriented Primary Care and Complementary and Alternative Medicine, JABFP July–August , Vol. 18 No. 4

[21] Measuring progress towards knowledge societies, A World of SCIENCE, Vol. 2, No. 1, January–March 2004 (http://www.unesco.org/science/awos/knowledge_societies.pdf)

"comparing biotechnology activities among countries when the data are obtained from studies with very different methodologies" [22]. Factors, such as differences in the definition of biotechnology, whether or not all firms innovate, specific national innovation systems, accounting methods or data availability will tend to reduce comparability. Additionally, drug discovery and manufacturing practices contain a strongly tacit dimension. Data interpretation remains dependent on training idiosyncrasies, non-codified routines and other elements. Even if causality is properly established, the results do not tell us what specific rules, legislation, or institutional design are actually responsible for the outcome being measured.

Furthermore, most of comparative studies and measurement attempts are frequently based on uncritical assumptions about the superiority of certain institutions (private property rights, shareholder oriented corporate governance system, individualised material incentives, and so on), without considering that, historically, pro-developmental institutions have been mostly context-specific (Chang 2007 p 17-31, Rodrik 2004). In this sense, even recognising the need for such studies, the Cuban (as other) experience shows that, in order to explain the innovative behaviour of firms and industries, it is essential to go beyond quantitative elements. The majority of the relevant elements of Cuban biotechnology have to be explained in terms of a broad-oriented and strategic development policy supported by a well conceived institutional setup. At the same time, and in order to avoid cultural or geographic determinism, we need a theoretical framework that allows extracting characteristic patterns from the study of particular business or national industries cases, while openly acknowledging their specificities.

It will be argued that the institutional setup designed by the state, together with the existence of certain social conditions surrounding the Cuban (or any) society, shape the way in which competencies are acquired and unstructured problems are solved (Lazonick 2006, Freeman 2008, Chang 2002). This supports the view that confronting and changing technological and market conditions, rather than assuming them as a constraint for its activities, is the main force behind the innovative business enterprises, which are in turn the major determinant of economic development. Similar arguments are defended in many (and sometimes conflicting ways) by several scholars in the field of development economics such as Chang (2008/2002) Hirschman (1958), Freeman (1995/2008), Stiglitz (2002/2007), Abramovitz (1986/1994) and innovations economics[(Dosi 1988/2007), Cimoli/Dosi/Stiglitz (eds. 2009 forth), Cimoli et al.(2006), Elsner (2006), Lundvall (2002), Lazonick (2002/2006), Nelson (2006)]. In this paper it will be attempted to explain the unexpected innovative activity of the Cuban health biotechnology by shedding some light on these elements.

The central argument here is that the existence of Cuban biotechnology has been made possible due to the state's long-term commitment to promoting the sector, despite difficult economic times. The success of this industry must be analysed as part of a comprehensive development strategy intended to maintain a healthy population and diversify exports through the creation of new patterns of knowledge accumulation by catching up with more advanced nations. Secondly, it is argued that, in contrast with the development of the industry at a global level (especially in developing countries also involved in biotechnology, including, but not limited to India, Brazil, South Africa), Cuban biotechnology is profoundly integrated with the state-funded health system[23], which allows a smooth process of knowledge-sharing and incremental innovation. Thirdly, it is argued that the ability to set up a coherent and long-term

[22] OECD Biotechnology Statistics 2009

[23] Halla Thorsteinsdóttir, Role of the Health System in Health Biotechnology Innovation in Developing Countries, University of Toronto/ Canadian Program on Genomics and Global Health, *IKD Research Workshop*: Bridging the gulf between policies for innovation, productivity & industrial growth & policies to reduce poverty , London 18-20 November 2005

collaboration between biotech and state representatives allows the allocation of resources to innovative and well conceived strategies.

Based on Lazonick (2006), three social conditions are identified that yield innovation and economic development: the *long-term financial commitment* (in this case the state as investor) in the development of a high tech industry, the *organisational integration* of the industry and the *strategic control* over the allocation of resources. These conditions are contextualised in the background of the Cuban biotechnology; and are found to distinguish it from the majority of the industry worldwide.

This analysis reveals how important it is to rely on country-specific institutional innovations in order to evolve coherently from lesser to more technology-intensive industries. If innovation is to be linked with economic development, we have to take institutional and technological change as conscious and highly idiosyncratic policy-based processes; uniquely influenced by political and cultural factors (Lazonick 2006, Chang 2002, Cimoli et al. 2009). Again, this is not to say that characteristic historical patterns cannot be identified. For example, a growing research agenda based on the comparative-historical analyses of national determinants of innovations and industrial leadership asserts that elements such as long-term governmental commitment and organisational integration have been more the rule rather than the exception in the history of technological upgrading and economic development (Chang 2003/2008, Lazonick 2006, Freeman 1995/2008, Evans et al. 1985/1999).

Strategic control

A first important feature of the Cuban biotechnology is the strategic controlling over the allocation of resources. *Strategic control* is meant to transform strategy into innovation and is defined as a "set of relations that gives decision-makers the power to allocate the firm's resources to confront the technological, market, and competitive uncertainties that are inherent in the innovation process" (Lazonick 2006). Abilities and incentives must be set in motion, in order to orientate the investment towards innovative strategies.

The strategic network of the West Havana Biocluster is formed by a small group of in-house integrated firms (see figure 2), which are under the control of the Council of State[24]. In order to set up the framework of the industry, a monthly (sometimes weekly) meeting is held by the representatives of the companies, the government and governmental regulatory agencies. This body can be defined as the *Strategic Decision Body* of the Cuban biotechnology Industry; whose existence enables clear definition of the general objectives (e.g. group diseases to be combated in the country, risky social groups, contracts with international organisations, etc) and orientation of investments around the population's current needs and/or export niches.

The Cuban biotechnology is a huge cross-sectoral institutional structure, whose affiliates are part of different ministries. As already mentioned, these institutions work under high grades of integration; both at company and industry level. Each centre of the strategic network management council has the task of designing and implementing its R&D projects. However, given its priority Status, these institutions are actually subordinated to the Council of State. They were shifted[25] from the ministries to the Council in 1990 in order to protect them from

[24] A specific office within the Council of State is responsible for the matters related to the biotechnology industry.

[25] In March 2009 the responsibility for the Cuban biotechnology was transferred from the Council of State to the Ministry of Science, Technology, and Environmental Issues (CITMA). This change responded to a government

the severe economic measures imposed on all other sectors after the dissolution of the East European communist's collaboration system. Since then, the Strategic Decision Body is in charge of the core allocation decisions within the in-house integrated companies (i.e. strategic network) of the industry.

Each sales or joint venture contract will be approved by the Strategic Decision Body on a case by case basis (Lopez et. al 2006). This body is also regularly informed about specific research proposals and projects progress. Again, it does not mean that companies lack decision-making power; actually they have a high degree of autonomy. In order to function properly as knowledge producer, the biotechnology industry requires large extents of horizontal communication and operational freedom. In fact, most of the ideas for innovative strategies discussed on these meetings are brought by the representatives of the firms.

However, innovative products demand organisational integration (see below); which in turn requires strategic control (Lazonick 2008). That is, the close contact between companies´ and State of Council representatives is crucial for the making of adequate strategic and tactical choices within the industry. Strategic network managers can be defined as administrators, facilitators, and generators of knowledge and data to be used as input for the decisions made by the Strategic Decision Body. This enables coherent confrontation of the inherent technological, market, and competitive uncertainties of the innovation process.

As can be inferred from the abovementioned, the Strategic Decision Body has the major say in the funding decision of the industry. It should be recalled that, similarly to venture capitalists, the Cuban biotechnology is the result of risky investments of the Cuban government. In fact, the Cuba's state investment has been called the "Cuba's Billion-Dollar Biotech Gamble"[26]. The difference is that the State is focused not only on fast returns, but also on long term socioeconomic targets. Consequently; and as a main provider of financial resources, it must (just as venture capitalists do) be as directly involved in the business as possible in order to increase the likelihood of success. The survival of the whole nation's health system depends on the good performance of the biotechnology sector.

In this sense, export revenues created by the commercialising branches are subject to control of the Council of State i.e. the Strategic Decision Body. Managers have the task of generating financial returns, but they do not control alone the generated cash flow. Instead, the export revenues go to a Council of State's account; and then, after deliberation of the Strategic Decision Body, are redistributed to the centres to cover operational costs[27] and investments. The new business and production targets are carefully expressed in a comprehensive budget, which is also regularly controlled or corrected according to the information brought by the managers. Whenever specific expertise is needed, temporal allocation of human resources can also be carried out from a centre to another, which in turn increases the perception of common interest, collaboration and consensual culture among the employees. In the same way, managers can be hired or fired, whenever the case.

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reorganisation process initiated in 2009. However, the new minister appointed in office (José Miyar Barrueco), is the one who has been directing the Strategic decision Body in the Council of State. This could be interpreted as a signal of the industry maturity and should by no means as a decline of strategic control.

[26] See Science and Business: Cuba's Billion-Dollar Biotech Gamble**,** Science, Vol. 282. no. 5394, pp. 1626 – 1628, 27 November 1998, http://www.sciencemag.org/cgi/content/summary/282/5394/1626

[27] However, the way in which these resources are used (e.g. salary incentives) are decided within the centres.

The case of the state participating in the strategic allocation of resources can be extended to other countries. Lenovo and the chemical producer China National BlueStar, a subsidiary of China National Chemical (ChemChina), both have significant state-based monitoring and control structures but are nonetheless valuable partners for suppliers and customers, as well as astute managers[28]. High degrees of governmental strategic control are also one of the reasons behind the economic successes of countries such as Japan, Taiwan and South Korea, but also France, Austria and Finland, to cite a few examples (Chang 2008/2009, Evans et. al. 1999, Cimoli et al. 2009, Lakhwinder, 2006). The Strategic Decision Body of the Cuban biotechnology does not represent some totalitarian aberration, but just another case for the confirmation of a historical pattern, which have been somewhat forgotten by orthodox economists.

To strategically control the resources have historically been related to organisational learning. This is one of the processes, which have allowed innovative products and industries to emerge. According to Lazonick (2008), the separation of these processes thorough the segmenting of the top executives interests during 1960s made US corporations less innovative. This phenomenon started during the 1950s; which is the time when stock market began to perform a compensation function for top executives, which created an "opportunistic separation of the reward of the executives from the pay structures of the organisation over which they exercised strategic control" (Lazonick 2008 p 254).

In respect of the biotechnology industry, most of the small biotech companies worldwide lack the downstream capabilities to design any commercial scheme, necessary to strategically control their R&D assets. They must instead (as will be mentioned later) rely on R&D contracts with established corporate companies in the pharmaceutical industry, which are fundamentally focused on responding to the short-term demands of the capital market. It seems to be that only vertically integrated firms of the first generation of biotechnological firms (almost exclusively Amgen, Genentech) have been able to design long-term plans and achieve strategic control over their resources; thus showing the best historical results in the industry.

Financial commitment

Indeed, the development of the Cuban biotechnology industry is the result of very particular circumstances. In order to attenuate the hardships imposed by the US embargo[29] on Cuba over the last five decades, the Cuban government, based on its previous health and education achievements, committed, from the beginning of the 80s, to create an industry which could produce the greatest possible number of biomedical applications at a domestic level. This became even more relevant after the collapse of the Soviet Union and the *real existing* socialist world in the 90s. In fact, as stated by a 2004 study in Nature Biotechnology, "the economic conditions called for more exploitation of domestic capabilities, because the country simply lacked the resources to import solutions". As the country had already developed some capability in the health biotechnology (see below *Cuban biotechnology: A*

[28] Woetzel J, Reassessing China's State-Owned Enterprises, McKinsey Quarterly, Forbes, JULY 2008 http://www.forbes.com/2008/07/08/china-enterprises-state-lead-cx_jrw_0708mckinsey.html

[29] This poses a major challenge to the introduction of the Cuban industry in the major industrialised market. Based on the number of biotechnology companies, both public and private, USA topped the list with a little less than 1500 companies, followed by Canada (470) and Germany (340) during 2003. The USA formed the largest chunk of revenues with USD 35.9 billion, which constituted 77% of the global biotechnology revenues, followed by Europe (USD 7.5 billion), Canada (USD 1.7 billion) and Asia-Pacific (USD 1.5 billion) (Exim Bank: Research Brief No. 12 February 2005)

short story), the field was viewed as a chance the country could use to maintain a healthy population and diversify exports.

However, innovative investments, especially in biotechnology, are very uncertain and require long-term commitment from financial institutions. This allows the capabilities resulting from collective learning to develop over time, despite the intrinsic uncertainty which the innovation process entails (Lazonick 2006). Moreover, it guarantees the allocation of funds to sustain the cumulative innovation process until it generates financial returns. Between 1990 and 1996, a critical period of biotech development, the government invested around US$1 billion to give rise to what is currently known as the Western Havana Biocluster, which comprises around 52 institutions[30]. The whole complex includes hospitals, R&D institutions, manufacturing plants, universities, regulatory agencies and other specialised facilities (labs that house more than 10 000 of workers, of which more than 3 000 are scientists and engineers[31] . The strategic core of the industry is formed by a small group of institutions, which have been designed to cover the entire value chain of a product (see below *Closed Cycle).*

The Cuban state has spent about 1.2% of its GDP[32] on biotechnology development. This is more than the money spent in R&D in the whole country, but still nothing compared to the high figures at a global level (Pisano 2006, Ernst &Young report 2008/2009, Lazonick/ Tulum 2009, OECD 2009). Much more important is the fact that, even with no real prospects of success in the short term, the state was ready to invest in the long-term, no matter how risky (and biotech innovations always are) the project[33]. In contrast, the funding patterns in the global industry are characterised by strong short-term biases.

The classification of the funding patterns of an industry in terms of the long-run/short-run distinction varies according the kind of activity of the industry. It is not the same to devise a strategy for the development of products within the car industry; as to do it for the computer industry or for the biotechnology industry[34]. In each case, the design, engineering or marketing expertises needed; and the way they are combined, varies. The time required to develop and sell a product will depend on these and many other factors. Specifically referred to the biotechnology industry, its funding strategy has been negatively affected by the incidence of stock market oriented investments, whose nature might not be assuring the necessary financial commitment required for the development of innovative products (Lazonick / Tulum 2009).

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[30] Currently, there are biotechnology institutions all over the country. However the most significant clusters of institutions is found in West Havana. The rest, albeit no less important, are extensions from this one.

[31] Castro's son explains the foundation of Cuba's biotech success, Engineering News, 11 April 2008, http://www.engineeringnews.co.za/article/castro039s-son-explains-the-foundation-of-cuba039s-biotech-success-2008-04-11

[32] Campillo et al. (2005), La Biotecnología en Cuba, Informe elaborado por Trikarty e Hiperion Biotech para Genoma España, Genoma España , GEN-ES06005

[33]Certainly the Cuban example is not the only example of government support. Lazonick /Tulum (2009) demonstrated in a detailed study that the US government has been a very significant source of financial resources for the biopharmaceutical industry in the US. However (as we will argue later), elements such as strategic control and organisational integration must play a complementary role. For example, long-term financial support could be totally misused by a short-term oriented strategic control.

[34] Unlike a software company, a biotech start-up's capital needs have always been enormous and probably always will be—at least until a new model is refined that reduces capital requirements, Broderson H(2005), Virtual reality: the promise and pitfalls of going virtual, Bioentrepeneur, September, http://www.nature.com/bioent/building/managing/092005/pf/bioent881_pf.html

Commenting on the effects of the most recent financial crash on European firms; and making explicit references to the just abovementioned subject, an article of Business Today[35] cites Professor Mazzucato from the Open University; who asserts that "There is in fact ample evidence that the stock market often punishes firms for investing in expensive long term innovative projects, and that financial institutions do not always reward the most innovative, and productive firms. Understanding why this is, and how this differs between different countries, industries and different phases of the industries' life-cycles is key for designing EC financial and innovation policies which will better prepare European companies for the next crisis".

Funding patterns of the industry worldwide

During this first 30 years of existence, the funding pattern in the large biotechnology trading block comprising USA, Canada and the EU has been determined by the combination of sources such as capital ventures (Owen-Smith/Powell in Braunerhjelm/Feldman 2006 p 61-83, Senker in McKelvey et. al. 2004 p 113-114, Pisano 2006 p 136-142, Ernst & Young 2008) [36], R&D contracts with major pharmaceutical firms[37] (Willians 1998, Danzon et al 2005) and government agencies funding (Lazonick / Tulum 2009, Ernst & Young 2008 p 15, Senker in McKelvey et. al. 2004 p 112-113).

Venture capitalists exercise a degree of strategic control, and often play the dominant role in a project. They are directly involved in the business in order to increase the likelihood of success; and influence and monitor the process. This funding model has been the fuelling force behind Silicon Valley. However, even when a liquid stock market is essential for VCs, its innovative potential here was the result of a co-evolution with the industry, i.e. institutions and technology shaped each other over the years; creating self-reinforcing networks routines (Kenney and Patton in Braunerhjelm/Feldman 2006 p 38-60). Investors were willing to make some type of investment in a business with no expectation of turning a quick profit. They waited until an innovative product was there before doing an IPO (initial public offering).

Conversely, during the 1990s VC performance began to be related to stock market-centric economies. The high-technology bubble, which took place during these years, led to the creation of volatile high technology stock markets outside the US[38]. Stock option-based forms of compensation became a major feature of the new economy. Lazonick (2008) shows how the emergence of NASDAQ during the 1970s enhanced the prospect of an early and successful IPO boosted the New Economy explosion in the US, leading to a highly speculative, more insecure and probably unsustainable development model.

[35] Winning advantage through innovation, Business Today Issue 4, 2009 (p 24-25), http://www.ukbusiness-today.co.uk

[36] In Canada, the average venture capital investment in life sciences is 173.5% of the average for all types of venture capital investments or 73.5% larger than the average for Canada. In Germany is 42.1% greater than the German average for all venture capital investments and in the United States is 26.4% greater than the American average (OECD Biotechnology Statistics – 2009)

[37] http://leda.law.harvard.edu/leda/data/625/Cha_redacted.html

[38] By 2003 a number of these such as the German Neuer Markt and Japan's JASDAQ had collapsed in scandal, while others were virtually moribund, e.g., France's Nouveau Marche, Italy's Nouvo Mercato, Hong Kong's GEM, and Malaysia's MESDAQ. In 2001 EuroNM Belgium had been closed and in 20o4 NASDAQ Europe. Many of the new stock markets did not survive the avalanche of exits by bad firms. See Giudici G, Roosenboom P eds. (2004), The rise and fall of Europe's new stock market, Advances in financial economics, Elsevier, Vol. 10

The ability to do an IPO, even without a product, is also the major inducement for venture capital to fund the biotech industry, since it does not have to wait until revenues are generated from a product to get returns on its investments. Venture capitalists have a time frame of about 3 years (Pisano 2006 p 139, p 155), while the product development time in the biotechnology industry is much longer. The reason for this time-frame is that closed-end funds are raised from institutional investors for a ten-year period[39], and the VCs are then under pressure to have the fund invested and returns to the institutional investors within this time-frame. For example, during the period 1991-2004, 88 percent of biotechnology companies were making IPOs, but only 20 percent had any product on the market[40]. The vast majority were still in pre-clinical and discovery phases (ibid).

In the microelectronics industry, for which the Silicon Valley VC industry was developed, 3-5 years was adequate. Nevertheless the development of the VC industry and related institutions such as NASDAQ made it possible to make use of VC for biotech, as long as the stock market remained sufficiently speculative (Lazonick / Tulum 2009).

Similar to venture capital, the ability to do an IPO, even without a product is also an inducement for big pharmaceutical companies to do R&D contracts with biotech start-ups since when the start-up does an IPO the big pharmaceutical partner can get a return to its R&D investment by cashing in the equity stake it has as part of the R&D contract (ibid). Within this context, the average R&D alliance lasts less than four years (about one- third of the expected product development cycle) (Pisano 2006 p 155, p 179). Alliance partners are fundamentally focused on the firm achieving the next milestone. If the biotech firm fails, the relationship may be terminated. This means that the tacit technical and organisational knowledge and routines required by R&D has not been accumulated by the industry.

According to the OECD Biotechnology Statistics (2009), this form of agreement reached its peaks in the late 1990s in the US, but it has shown some increases in other regions. For example, the 20 largest pharmaceutical firms signed an average of 1.4 alliances per year with a biotech company during 1988-1990, but 5.7 such alliances per year in 1997-1998 (Danzon et al 2005). The United States accounted for 86.1% of the 519 biotechnology alliances between 1997 and 1999, compared to 71.3% of the 1 396 biotechnology alliances between 2004 and 2006[41]. Between 1997 to 1999 and 2004 to 2006, the share of alliances involving European firms increased from 46.2% to 49.7% and the share of alliances involving Japanese firms increased from 8.1% to 10.0%[42].

Government subsidies are also an important source of funding of the industry. State-based agencies such as the National Institute for Health in the US[43] have played an important role in

[39] Venture Impact: The Economic Importance of Venture Backed Companies to the U.S. Economy, http://www.nvca.org/index.php?option=com_content&view=article&id=255&Itemid=103

[40] Capital raised declined sharply in 2008. Companies in the Americas and Europe raised US$16 billion in 2008, a 46% decline from 2007. IPO funding fell 95% to US$116 million. Publicly traded biotechs have always achieved net losses globally. The global industry's net loss improved 53%, from US$3 billion in 2007 to US$1.4 billion in 2008 (Ernst &Young Report 2009)

[41] In contrast to the decline of alliances in the U.S, venture capitals investments have dramatically increased. In 2007 the biotechnology industry raised for first time in history more than 5 $ billions in venture capital (5,5$b), Ernst & Young (2008)

[42] OECD Biotechnology Statistics – 2009

[43] The NIH have funded $555 billion (in 2008 dollars) since 1976; the year Genentech was founded as the first biotech company, in life sciences. Through the NIH, the US government, and by extension the US taxpayer, has long been the nation's (and the world's) most important investor in knowledge creation in the medical fields(see Lazonick / Tulum 2009)

the promotion of life science research. Countries such as Germany, France and the UK[44] are also known for their government-funded research sectors (Senker in McKelvey et. al. 2004 p 112-113). In the US, the Orphan Drug Act along with the NIH-funded knowledge has also been an incentive for venture capitalist and established pharmaceutical companies to continue to invest in the biotechnology.

However, expecting that a speculative stock market[45] will enable them to secure returns investments long before the actual products in which they have invested generate substantial sales may serve to undermine the extent of the investments that companies make in generate innovative products (Lazonick / Tulum 2009). There has been therefore little incentive within the industry to promote organisational learning and build long-term capabilities. It is no surprise that net profits have remained negative for the global biotechnology industry over the 30 years of its existence.

To maximise shareholder value may not be compatible with innovation. From an agency theory perspective, the performance problem of the industry has been mostly treated as one of information asymmetries. Better monitoring and covenants, more banking regulation and transparent accounting methods or better disclosure can reduce opportunism and overoptimistic valuations. A more efficient stock market would create better exit mechanisms to venture capitalists and better prospects for shareholders. However, shareholders as principals monitor managers as agents to ensure that they act in shareholders interests, not how managers engage in innovative strategies. Nor is the ability of a new venture to do an IPO a sign that the innovative strategy has been a success (Lazonick / O'Sullivan 2004). The rational-individualistic foundation of this perspective, while useful for other analyses, limits its ability to understand the uncertain and collective nature of the technological learning process, which is essential for innovation, growth and economic development.

In contrast to agency theory, a theory of innovative business enterprise proposed by Lazonick (2002) suggests to analyse the social conditions-strategic, financial and organisational- related to the institutions under which innovative outcomes occur. This perspective pursues to understand how societies can create a corporate governance system that ensures strategic decision makers to have the abilities and incentives to make investments in innovative strategies (Lazonick / O'Sullivan 2004 p 5). Given that in the innovation practice, relevant information is not hidden or asymmetric but unknown to the participants in the process, it would not always be possible for a country to follow "market" signals closely in order to enter or remain in an industry. In actual fact, firms with uncertain prospects will need to be created, subsidised, and nurtured, possibly for decades, if industrial upgrading and innovation are to be achieved. For instance, the Cuban state decided that it needed to invest in an innovative strategy to develop the biopharmaceutical industry; and then it mobilised the financial resources to do it, even without expectation of turning a quick profit. Historically, many other cases are to be found in this direction[46].

[44] The UK venture capital market does not serve the smaller firms well. As a response to this, government money has been concentrated on seed and early stage funding, see: UK Biotechnology Industry, House of Commons Trade and Industry Committee, Twelfth Report of Session 2002–03, London, Published on 3 September 2003

[45] Over the past two decades, but especially in the 2000s, the executives of US business corporations, encouraged by Wall Street, have become committed to the practice of allocation substantial corporate resources to buy back their own corporate stock (Lazonick/Tulum 2009 p 21)

[46] Paradigmatic examples of long-term commitment are the cases of Toyota and Nokia; the Korean car industry and the microelectronic and the first generation of the semiconductor industry in the United States (Lin J/ Chang H 2009) Lazonick 2006/2008).

Moreover, agents` interaction and integration within that process will be also required for organisational learning be able to take place. In the next section, it will be analysed in more detail the institutional form taken by organisational integration, as social condition, within the Cuban biotechnology industry.

Organisational integration

Another relevant feature of Cuban biotechnology is the high degree of integration between research institution, universities, the health system and the governmental regulatory authorities. Organisational integration is defined as the set of social relations that create incentives for people to engage in cooperation and joint organisational learning (Lazonick 2008). In the case of the Cuban biotechnology, downstream complementary capabilities such as clinical trial expertise and regulatory knowledge are also part of the health system, and are completely integrated into the functioning of the industry.

1989 saw the creation of the CECMED, Cuba's medication regulatory agency. It guarantees protection of the public health through a sanitary control and regulatory system, ensuring that drugs and diagnostics, imported or locally manufactured, are safe, effective and of accepted quality[47]. This institution is also responsible for approving the Clinical Trials and authorising marketing, post-marketing and licensing activities. The good functioning of these factors allowed the pre-qualification of the Hepatitis b vaccine by the World Health Organisation (WHO)[48].

The National Coordinating Center of Clinical Trials (CENCEC**)** was similarly created in 1991, and is the first Clinical Research Organisation (CRO) created in Latin America. Its main objective is to guarantee clinical evaluation for sanitary registration and marketing of pharmaceutical and biological products, as well as medical devices in the industry in Cuba and other interested countries [49]. It possesses a wide coordination network of clinical trials at national level, supported by a specialised staff in each of the provinces of the country for the conduction of these studies.

Research collaboration between the universities and the other research institutions has been encouraged, and some universities have made impressive contributions to health biotechnology. Network collaboration among institutions is so close that it is often difficult to define the formal line between them. Medicine professors are simultaneously medical institutes' doctors and direct researchers in biotech facilities. Additionally, the family doctor network, a primary care system based in neighbourhood *consultorios* (clinics), provides the

[47] Equivalent of the American FDA

[48] Jacobo Casanueva O (2007), Role of the National Regulatory Authority in Prequalification of Vaccines. Experience of CECMED, Developing Countries Vaccine Manufactures Network (DCVMN) mimeo, http://www.fiocruz.br/bio/media/DCVMN%202007/apresentacoes%20dia%2012/Table%201/Olga%20Jacobo%20Casanueva%20CUBA/2_olga.pdf, see also http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/

[49] CENCEC also conducts evaluations of therapies to solve the population's health problems. It possesses a wide co-ordination network of clinical trials at a national level; there are specialised staffs in each of the provinces of the country to conduct these studies. This network comprises 10 Coordination Groups and 4 Sub-centres for Clinical Trials, which govern the activities of the region in which they are located, under the supervision of our centre. Advice can be provided in all phases of clinical development of pharmaceutical, biotechnical products and medical devices.

general public with information on new products, and explains their use and the effectiveness of biotechnology products. They thereby encourage the acceptance of local health biotechnology by participating in clinical trials (see figure 10).

Within a firm, this practice produces general skills and category-specific skills in designing and managing trials. At the same time, network relationships with the clinicians who conduct the trials and with regulators who evaluate them, allow them to run trials more efficiently and avoid errors. All this process enables important feedback to be obtained from clinical trials (and money to be saved)[50] and a rich flow of information and knowledge sharing to be promoted, which in turn builds a good foundation for innovative thinking by helping to constantly improve the products and processes.

An example of the just mentioned process is the existence of an institution like the tropical medicine institute 'Pedro Kourí' (IPK). This centre belongs to the national health system and focuses on the study of communicable diseases, medical microbiology and Social Research. It is involved in several important joint-investigations and has developed national and international undergraduate and postgraduate activities. At the same time, IPK includes a hospital to offer medical care to patients suffering from any infectious pathology, which are also employed in running early clinical trials of novel medicaments. This activity allows crucial data about the product impact to be channelled to the rest of the industry, which is relevant for research and marketing purposes. The hospital represents the nucleus of the epidemiological control system in Cuba; and offers advice to all the medical units across the country.

Cooperating and qualified workforce

The Cuban biotechnology has also become an important pool of high qualified workforce. Different forms of incentives are employed to attract young graduates and to make them engaging in organisational learning. Additional wage remuneration is only one part of the story. This form of motivation is (without discussion) important and very much appreciated by workers within the industry. Its application depends on certain standards of work discipline and practical/ scientific contributions. However, even when salary rewards are acceptable by Cuban standards, they are far from American or European standards. Although there has been some *brain drain,* which in the case of Cuba has always extra political implications[51], there is so far no indication that the loss of researchers and other experts is any larger in Cuba than in any other developing countries[52]. According to a report of the World Health Organisation, in 2004, the Neonatal mortality rate of Cuba was of 4 per 1000 live births, placing the country at the level of countries like Denmark, Canada and Austria (3 each country). Additionally, in 2007 the sector was the second biggest exporter (350 $Million) of the Cuban economy[53].

[50] Clinical trials are the basis for deciding how good and safe new drugs are. However, from the 1980s to the 1990s, the clinical trial costs of drug development increased 5 times faster than pre-clinical costs in the global industry, increasing the development costs of the product, and in many cases hampering the development of new medicines. In 2003, some health economists in the United States estimated the average cost of launching a drug on the market at US$802 million. Estimates of typical research and development costs today (2009) are in the US$1.3 billion-to-US$1.7 billion range [Collier R (2009), Rapidly rising clinical trial costs worry researchers, Canadian Medical Association or its licensors, 180(3), February 3]

[51]Wine into vinegar: the fall of Cuba's biotechnology Nature Biotechnology 19, 905–907 (1 October 2001). This article is a critic view of the Cuban biotechnology; and was written by José de la Fuente, a Cuban exile and former director of the Centre for Genetic Engineering and Biotechnology (CIBG) in Havana.

[52] Thorsteinsdóttir, et. al. (2004)

[53] http://www.tmcnet.com/usubmit/2008/07/20/3556464.htm

To explain the motivation of the workforce in the Cuban industry it is required to consider elements other than salary compensation. The programme of the institutional political economy proposed by Chang (2002) maintain that institutions do not only shape individuals motivations by punishing or rewarding particular types of behaviour, but also are able to change the motivation itself. Institutions embody certain values, social norms and moral codes, which individuals operating under these institutions ultimately internalise; having themselves changed during the process (Chang 2002). To devise a system of incentives, which boost the teamwork-employment security, career opportunities, and collective purpose (Lazonick 2002) - is a critical developmental source of competitive advantage for any innovative industry and also for the Cuban biotechnology industry. If only material incentives would count, then 1) it would be impossible to differentiate management quality levels and 2) it would be impossible to explain the existence of the Cuban biotechnology.

A mixture of broad social commitment and personal self-realisation could be appropriated to explain the motivational mechanisms of the workforce in the Cuban biotechnology industry. In first place, the fact of having a stable and relatively well paid job; with security for the employees' families[54] gives good prospect about the kind of dedication that is expected from them. On the other side and perhaps a major determinant for the dedication of the workers is the fact that, young scientists (the majority of the workers of the centres) have strong incentives to develop their capabilities. The idea of being an employee of a world-class Cuban industry brings a sense of social prestige and acknowledgement. Moreover, to have access to the most recent information and state of art technologies in their fields, and having the chance; but also the obligation and the institutional support to do cutting edge research; and to publish it in the most recognised journals worldwide can probably be the best incentives for a young scientist in any field. Additionally, the success of the industry makes them trust in and embrace the collaboration culture in which the innovative outcomes of the Cuban biotechnology are based.

As abovementioned, innovation needs organisational learning, which depends on the actors' integration within an industry. This integration will be achieved by necessarily overcoming behavioural opportunism and engaging in cooperation (Lazonick 2002). "Organisational integration can transform ´individual rationality` into ´collective rationality`" (ibid p 15) and thus unbound the cognitive abilities available to the industry. Innovation is a collective and cumulative process, which allows upgrading technologies and to produce better quality products by integrating otherwise isolated agent-specific productive capabilities.

Closed Cycle

The geographical aspect (regional proximity) has played an important role in Cuban biotechnology, but is far from being the fundamental aspect behind innovation. Spatial clustering is important because it can create channels for transmitting tacit knowledge and creating beneficial interdependencies for all individual firms. However, this does not mean automatic adaptation capacity. Internal co-ordination capabilities actually depend much more on the organisational structure of the agglomerated industrial system (Bianchi/Lavory 2004, Rosenberg 1997, Saxenian 1994).

[54] Kindergartens with special schedules and apartment buildings have been built near of some of the centres in order to support the families and the well-being of the employees. Examples are the scientific communities of Flores and Santiago de las Vegas, located at the west and south side of Havana respectively.

The most distinguishing feature of Cuban biotechnology is the full integration of all the phases of the development process. This is called a *closed cycle* and consists of an operability form resembling a vertical integration structure, but at the same time excluding hierarchical forms of interaction. It comprises in-house *research-production-commercialisation* facilities (in-house integration), which constantly interact with each other to create essential collective intangible assets and long-term learning relationships within and among the firms. This interaction excludes competition between individual firms (contrary to Silicon Valley) and focuses on collaboration.

The *closed cycle* means that the centre is in charge of the whole value chain from research and development through manufacturing, marketing and sales. The fact that the whole process functions under the same roof creates a special sense of commonality and shared responsibility within each centre. That is, within an in-house integrated institution, researchers are encouraged to learn about business and marketing experts and engineers to do it about biomedical science. Each research project follows high science standards, but bearing in mind from the very beginning the patent possibilities. The philosophy here is to investigate not only what you want to investigate, but also what it is necessary to investigate.

Closed should not be taken literally; in the sense of total disconnection from external communication, but as a way of describing integration. In actual fact, each in-house integrated facility has a commercial arm, which is usually involved in international collaboration with private sector firms around the world. Additionally, academic collaboration networks have been one of the most employed forms of knowledge exchange from the very beginning of the Cuban biotechnology. Closed cycle means *vertical* integrated firms working under a *horizontal* regime (not to confuse with horizontal integration), a combination, which is defined here as in-house integration. A small group of the 52 institutions of the industry work under this model, and build the strategic network of the Biocluster (see Figure 2). The strategic network institutions are directly under the control of the Council of State, which allows close ties with the country's central decision-making powers.

Even when each in-house integrated centre is equipped to cover the complete product development process, collaborative research projects among them (and with other non-strategic facilities) are also frequent. Informal knowledge sharing between individual researchers and the usual lending and borrowing of technical equipment in joint R&D projects, and in integrated manufacturing lines are characteristic features of the Cuban industry. Again, cooperation rather than competition is the motto of the Cuban biotechnology.

A recent example of the abovementioned is the world's first synthetic vaccine; designed and obtained as a joint project. To produce this vaccine "involved over 300 investigators and technicians and several different Cuban biotech institutions. The Synthetic Antigens Lab worked on making the synthetic antigen, the Finlay Institute worked on the protein carrier, the Centre for Genetic Engineering and Biotechnology (CIGB) joined the two compounds and the National Centre for Bioproducts bottles the vaccine in dosage-size flasks which will be commercialized under the registered name of Quimi-Hib"[55] by Heber Biotec (the commercial arm of CIGB, see next section). This kind of cross-cooperation allows using the specific competences created by the *vertical-like* in-house integration in other projects and avoids costly duplication in research and development.

[55] See article "The World's First Synthetic Vaccine for Children: The Cuban Face of Biotechnology, Global exchange, November 28, 2003, http://www.globalexchange.org/countries/americas/cuba/foodAndMeds/1510.html.pf and Chemical &Engeneering news online: http://pubs.acs.org/cen/coverstory/8232/8232vaccines.html

The example of the chaebol semiconductor maker in South Korea builds also a case of cross-cooperation among vertical integrated companies and organisational integration. Also to avoid cost duplication, the Korean government decided during the 1980s to design a national project of R&D on the 4M DRAM. A government research institute served as coordinator in a consortium formed by Samsung, LG, Hyundai and six universities (Kim 1997). The case of institutions such as lifetime employment and cross-shareholding, allowed better utilisation of technology by creating more integrated forms of production in Japan; which led in the end to outcompete its U.S counterparts (Chang 2008, Lazonick 2008, Scher 2001).

Only the first generation of biotech firms at a global level integrated their process vertically. Vertically-integrated firms such as Amgen und Genentech[56] are two of the small number of cases who registered profits in the industry (Pisano 2006 p 126, 185, Ernst & Young 2008). Second and third generations have been characterised by small and specialised firms, which lack the additional capabilities and the financial resources to enter the industry on their own. One way of overcoming this is through an R&D alliance with established pharmaceutical firms; creating a market for know-how. In other words, some forward integration will be needed to generate the large amounts of data required for formal regulatory submission. Given the cost implications of integration, more commitment to product and capabilities development (i.e. organisational learning) should be expected from pharmaceutical companies.

Cuban biotechnology: A short story

Integration has been fostered since the very beginning of the industry. Most of the Cuban biotechnology research centres have emerged from already existing centres, as the Cuban state had been investing in scientific research from the 1960s. The main organisation created then was the National Centre for Scientific Research (CNIC) in 1965. Similar to other countries experiences, this multi-disciplinary institution is considered to be the *incubator*[57] of the rest of Cuban scientific institutions today; and was established to promote the development of research and training activities in fields such as bio-chemistry, computer sciences and microbiology. Strong investments in medicines school and in a comprehensive health system were made around the same period. By the end of the 1970s Cuba had developed a well integrated structure comprising higher education, biomedical science and the public health system. The created pool of trained specialists became the very base of the 1981´s Biological Front (Thorsteinsdóttir, et. al. 2004, Lopez et. al 2007)

The Biological Front was an interdisciplinary scientific consultative body created to coordinate the interests of the different ministries and institutions, which were related to the development of the biology and the biotechnology. The first obtained product was the *Interferon* in 1981. A few Cuban scientists were sent to Helsinki, in order to be trained on the production of the Interferon developed by the Finnish Serum Institute[58]. By the end of 1981

[56] During the period 1975-2004 these two firms generated more than 53% of the positive cashflow of the Industry (Pisano 2006 p 115)

[57] Finland, for instance, is typical of countries that locate incubators to nurture startup firms near universities that host biotechnology centres of excellence, See: Senker et. al. (2000), European exploitation of biotechnology—do government policies help?, Nature Biotechnology, Vol. 18, June

[58] International linkages played a central role in building expertise in the Cuban biotechnology. Cuban specialists were sent abroad to obtain PhDs in pioneering life science institutions in Western Europe and the United States, including the Curie Institute (Paris), the Pasteur Institute (Paris), Heidelberg University (Heidelberg, Germany) and Harvard University (Cambridge, MA, USA)(Thorsteinsdóttir, et. al. 2004). However substantial learn

the first interferon had been obtained in Cuba. This accomplishment was only possible given the capabilities cumulated during early periods. Cuba had become capable to emulate high developed skills and know how in the field of biotechnologies and expressing them in targeted product developing projects. Similar to other development experiences, catch-up process, especially in its early phase, involves a lot of imitation, reverse engineering, marginal modifications of products and processes, and straightforward copying (Cimoli et. al. eds. 2009, Chang 2008)

After few successful pilot projects, in 1986 was opened the Centre for Genetic Engineering and Biotechnology (CIGB)[59], which is the most important of the strategic centres of the industry (see figures 2,3,4 5,6). Subsequently, were created the in 1987 the Centre for Immunoassay (CIE), the National Centre for Bioproduction (BioCEN) and the National Centre for Production of Laboratory Animals (CENPALAB). However, the most important institutions together with the CIGB are the Centre for Molecular Immunology (CIM)(see figures 8,9,10) and the Finlay institute, created in 1994 and 1991 respectively. The former focuses on therapeutic cancer vaccines and monoclonal antibodies; while the later in more classic vaccines.

At the beginning, these Centres were conceived as *research-production* facilities, but the need to acquire marketing and sales capabilities led to the creation of a commercial arm; completing the *closed cycle*. That's the case, for example, of Heber Biotec; the commercial arm of CIGB (see Figure 2). This 1991´s company is a spin-off from a laboratory of the centre, which have become an independent legal instance. It has the marketing rights of all novel products manufactured by CIGB[60]. With the association between CIGB and Heber Biotec a complete cycle of research, development, production and commercialization was accomplished. CIGB-Heber guaranties the purpose of having all way from the idea to the market.

From the very beginning, Heber Biotec started to create a solid worldwide network of partners and distributors that constitute one of its larger strengths; and one of the cornerstones of the industry's business strategy. To mention a few examples, in 2000 the Indian company Panacea Biotec entered in a joint venture with Heber Biotec in order to manufacture Hepatitis-B in bulk form. A new company - Pan Heber Biotec Ltd - was formed for the purpose in which the two partners hold equal stake[61]. More recently, the leading Brazilian pharmaceutical company EMS has signed an agreement with Heber Biotec for a joint drug development venture[62]. Under the terms of the agreement, Heber Biotech will provide technology transfer and marketing rights for products developed by the Centre for Genetic Engineering and Biotechnology of Cuba. EMS will provide infrastructure and logistic support for the global distribution of Heber's products. EMS is present not only in Brazil, but in more than 15 other foreign markets, including European destinations[63].

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capabilities and in-house research effort was required to absorb and translate the acquired knowledge into innovative world-.class products.

[59] This centre specialises in recombinant technologies based on single cell organisms. Its products are mostly vaccines and therapeutic, but also have made important contribution in the industrial and agricultural biotechnology (Lopez et. al 2007)

[60] As already suggested, in practice and given the intense integration of all institutions within the industry, products manufactured by centres other than CIGB are frequently commercialised by Heber Biotec.

[61] http://www.moneycontrol.com/company-facts/panaceabiotec/history/PB02

[62] Bussines monitor international, EMS signs JV with Cuba's Herber Biotec, jan 7 2010, http://store.businessmonitor.com/article/318588/

[63] ibid

Other examples of the same kind are the 1999´s joint venture agreement of Finlay Vacunas (commercial arm of Finlay Institute, see figure 2) with SmithKline Beecham (now part of GlaxoSmithKline, Brentford, UK) to produce and distribute the meningitis vaccine in Europe and North America[64]. In 2004, an agreement between CIMAB (the commercial arm of the Center for Molecular Immunology) and CancerVax, of Carlsbad, California was signed, to undertake joint development and licensing of Cuban cancer vaccines. The deal was approved by the US Treasury Department, despite the US trade embargo against Cuba[65]. CIMAB has also established a joint venture, called CIMYM (a joint venture between CIM (20%) and the Canadian firm YMBiosciences (80%), to develop and market monoclonal antibodies-based cancer therapeutics[66]. To accomplish this purpose, YMBiosciences usually finances the R&D costs, the clinical trials in Cuba and abroad and the patent protection fees. It also shares development costs according to a structure of up-front fees, R&D funding and milestone payments previously discussed. CIM retains manufacturing rights and obtain royalties from the sales of the products. In 2009, Cancer product Nimotuzumab was approved to be used in clinical trials in the US under application from YMBiosciences, which would hope for another exemption to the American embargo[67].

Through these agreements, the Cuban biotechnology has gained additional market exposure in foreign markets, access to capital and commercialization expertise. But another important aspect of this business model is the non-exclusivity of the patent licences. For example, in the case of Nimotuzumab, the firm YMBiosciences would hold the marketing rights for Europe Japan, South Korea and the United States; reaping 80% of the returns from the sales in these markets. However, CIMAB have the option to establish partnerships with other companies; and to negotiate different terms with them. In this option the licensees for Nimotuzumab include Biocon BioPharmaceuticals Ltd. (BBPL) in India, Biotech Pharmceutical Co. Ltd. in China, Delta Laboratories in Colombia, Eske Group in Peru , Eurofarma Laboratorios Ltda in Brazil, Ferozsons Labs in Pakistan , Innogene Kalbiotech in Indonesia, Laboratorio Elea S.A.C.I.F.yA in Argentina and Laboratorios PiSA in Mexico[68] . This product has already been approved for sale in 22 countries and is being studied in clinical trials in 10 countries.

Intellectual Property

Another important factor affecting integration and knowledge-sharing in this industry is the form in which intellectual property is negotiated. There is an increasing body of literature addressing the inconvenience of individual patenting in complex product industries in general;

[64] The deal was later ended as the United States had allowed the company to sell the drug on the US market, so long as it passes clinical trials (Thorsteinsdóttir, et. al. 2004). However, this unusual step from the U.S government shows the real possibilities of innovative products.

[65] Buckley et. al. (2006), Off the beaten path, Nature Biotechnology 24, 309 – 315, http://www.nature.com/nbt/journal/v24/n3/full/nbt0306-309.html, see also: TECHNOLOGY; U.S. Permits 3 Cancer Drugs From Cuba, New York Times, Jul 2004, http://www.nytimes.com/2004/07/15/business/technology-us-permits-3-cancer-drugs-from-cuba.html

[66] Thorsteinsdóttir, et. al. (2004)

[67] Bussines monitor international, EMS signs JV with Cuba's Herber Biotec, jan 7 2010, http://store.businessmonitor.com/article/318588/, see also: Clinical Trial.gov, http://clinicaltrials.gov/ct2/show/NCT00600054, and the article: Cuban cancer drug undergoes rare U.S. trial, Miami Herald, August 2009, http://www.miamiherald.com/living/health/story/1207536.html

[68] YM Biosciences, Inc, http://www.ymbiosciences.com/products/nimotuzumab/licensee_links.php. Ferozsons Labs in Pakistan could not be confirmed among the information given by YM Biosciences, Inc. They are only mentioned without any reference in: http://en.wikipedia.org/wiki/Nimotuzumab

and in the biotech industry specifically (Bessen and Masking 1999/2006, Boldrin and Levine 2008, Clark et. al. 2001, Shapiro 2004, Dosi et al. 2009, Chang 2008, Cohen et al. 2000). The main argument is that too many isolated patents in complementary assets in a common technology system inhibit innovation by increasing licensing and transaction costs[69]; thus slowing or stopping the knowledge-sharing and the development of new products.

The process of ownership fragmentation of complementary assets and high transaction costs has increased the innovation costs and uncertainty in a field like biotechnology, whose very innovative force resides precisely in the ability to build long-term knowledge-sharing of tacit information. This mutual blocking of property rights has been described by Michael Heller as the *Tragedy of the Anticommons* (Heller 1998). This phenomenon is a pervasive element of most alliances and licensing agreements in the biotechnology industry (Pisano 2006, Heller 1998, Shapiro 2004). Consequently, a big lag between R&D spending and R&D output has emerged. While R&D spending has increased over the last 15 years[70], the rate of introduction of new applications has fallen (Pisano 2006 p 118). To stimulate innovative products, many pharmaceutical companies focus more on redundant products, whose expensive patent protection incurs added costs for the consumer for no good reason[71].

Historic evidence suggests that learning activities by catching up countries and the development of innovative industries have taken place in environments with lax conditions regarding patent enforcement. Boldrin and Levine (2008 p 214-225) show the case of the pharmaceutical industry in Europe; being Italy, Switzerland, France and Germany well known. It is also suggested that, even after the Bay-Dole Act of 1980[72], no "major scientific discoveries have been pouring out of American universities´ laboratories at an unprecedented rate (ibid p 228). On the contrary, this institution, together with others, is said to have helped to increase litigation costs and the possibility to use intellectual property to as an instrument to pressure competitors. The 1995´s World Trade Organisation's (Geneva) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), pose even more entry barriers for the biopharmaceutical industry, especially for developing countries. Cuba, as a signatory of this agreement, had to find some IP strategy to overcome this disadvantage.

The solution was found in the state ownership. The patents of the Cuban industry are owned by the government agency, which avoids the problem of mutual blocking. This agency functions as a kind of patent pool, where every firm has the possibility of using complementary knowledge to advance new products. In practice, companies co-operate with each other informally, without needing to return to the agency. This resembles more an *internal* open source of innovation, which is no surprise at all, as the notion of 'cooperation instead of competition' is one of the most promoted values in the industry at a national level. This process in the Cuban biotech is also coherent with a growing body of literature, which

[69] Commenting on the high litigation cost in Europe, a very well documented study on the European patent system (the most expensive in the world according this report) states that, only putting in place a "single patent court in Europe would produce savings of €148 to €289 million for business". See: Pottelsberghe B (2009), Lost property: the European patent system and why it doesn't work, Bruegel Blueprint Series, Brussels (p 14)

[70] It is also stated that thirty top pharmaceutical firms concentrate on producing low-risk mee-too drugs, which cost at twice as much in promotion and advertising they do in R&D. In actual fact, it is said that 50 % of the R&D costs are spent on advertising drugs, which does not result from innovation (Boldrin and Levine 2008). Clinical trials are also a major driver of R&D costs in pharmaceutical (see note 50)

[71] Between 1989 and 2000, 54% of FDA-approved drug applications contained ingredients already on the market. From a medical point of view, about 77% of what FDA approves is redundant. Between 1995 and 2000 R&D employees at firms making patented drugs declined slightly, while the number of employees in marketing rose by 59% (Boldring and Levine 2008 p 231)

[72] Authorised the results of federal funded research to be patented

calls for patents pools in the biotechnology industry as a way overcoming the low innovation rates in the global industry (Clark et. al. 2001, Newberg 2001, Shapiro 2004, Gilbert 2004, Lerner et. al. 2005).

Concluding remarks

According to reports from international institutions[73], Cuba is, at regional level, one of the countries with highest R&D expenditures as a percentage of the GDP(0,6-0,8 %). However, Cuba's R&D shows nothing exceptional when compared with the rest of the world. Most countries spend between 0.25% and 1% of GDP on R&D. Nevertheless, Cuba has been able to develop a high technology industry at the level of countries such as Finland (3.5%), United States and Canada (2.7% and 2% respectively) or Denmark, France, Germany (the figure ranges from 2% to 3%).

In this paper, it is argued that the development of the Cuban biotechnology industry must be understood in the context of the Cuban socio-political context, and not as direct function of the amount invested in its development. Indeed, the government investments have been essential to create a research and production infrastructure and a qualified workforce which led to the creation of the West Havana Biocluster. However, the main feature of this industry has been the widespread and long-term state-fuelled integration of biotechnology in a multi-institutional system, aimed at optimising the interdisciplinary collaboration and knowledge sharing. I will argue that this characteristic is critical to the high innovation rate achieved by this industry.

Based on Lazonick (2006), three conditions are identified, which distinguish the Cuban biotech from the majority of the industry worldwide. First is the *strategic control* of the resources. Every month, biotech (only the core in-house integrated companies and state representatives) meets to discuss, monitor and evaluate the strategy of the industry. Challenges and uncertainties are faced coherently. By contrast, the lack of real integration in the global industry impedes collaborations from exercising the same strategic function. As the majority of biotech constitutes start-ups R&D entities with no downstream capabilities, they are obliged to rely on alliances with big pharmaceutical companies. However, these alliances are dominated by the stock-prices-oriented speculative behaviour of the strategic decision makers; and based on meeting certain milestones, not for the long term. Vertically integrated firms such as Amgen and Genentech[74] are up-to-date the best examples of strategic control. However, most of the companies of the second and third generations have not succeeded. It is no surprise that the global biotech industry (in contrast to the Cuban industry[75]) has shown negative net profits in the 30 years of its existence.

A second feature of Cuban biotechnology is the *long-term financial commitment* of financial institutions (in this case the state as investor) in the development of a high tech industry. This (which is not only a feature of the biotech industry) allows the capabilities which result from collective learning to develop over time, despite the intrinsic uncertainty which the innovation process entails. Moreover, it guarantees the allocation of funds to sustain the cumulative innovation process until it generates financial returns.

[73] Measuring progress towards knowledge societies, A World of SCIENCE, Vol. 2, No. 1, January–March 2004 and UNESCO Institute for Statistic Fact Sheet October 2007 No.5

[74] Both helped by venture capitals

[75] This is still a small amount ($40 Million net profits yearly) but 1) It finance the 80% of the products required by the health system 2)It is positive

In contrast, the funding pattern in the major biotechnology trading block comprising USA, Canada and EU has been based on institutional structures that disincentive the allocation of resources in innovative business strategies. These mechanisms clash with the learning necessities of the industry. Long term capabilities cannot be formed, and innovative products cannot be developed.

A third factor influencing the performance of the Cuban biotech is the *organisational integration* of the industry. As stated above, biotechnology is part of a network of organisations, which co-operate with each other to develop products and processes. In contrast with developing and industrialised nations, Cuban biotechnology has been conceived as an element of the state-funded health system, and is part of a broad strategy designed primarily to 1) ensure health levels in the population (as a politic objective) and 2) diversify exports[76].

Research facilities, regulatory authorities, the health system and biotech institution form synergic and innovative networks. All this increases the productivity of clinical trials by allowing faster and more accurate feedback, thus building a good foundation for incremental innovations. From the 1980s to the 1990s, the clinical trial costs of drug development in the overall industry (emphatically fuelled by the US) increased 5 times faster than preclinical costs, increasing the development cost of the product, and in many cases hampering the development of new medicines[77].

However, the critical element for achieving integration in the Cuban case is the in-house integration of the industry's core companies. The West Havana Biocluster is composed of 52 institution concentrated in this region. Even though the *clustering* effects play an important role as an integrative element, the central element is the so-called *closed cycle* observed in the core 11 strategic firms of the network. This consists of the in-house integration of research-production-commercialisation facilities, which resemble the vertical integration model characteristic of the firms of the first generation of the industry at a global level (incidentally, the only one to have survived and succeeded). The closed cycle contributes to the creation of essential collective intangible assets and long term learning relationships, crucial in a complex product industry. Since the mid 80s, many start-ups have moved from the vertical model to the product and platform-based model. However, the strategies of specialised firms to out-license their R&D results so far have not worked

A final key element in the integration process is the way in which intellectual property is managed. Cuban patents are owned by the state, and their uses are not mediated by any *mutual blocking* among complementary assets. It works like a combination of a patent pool and open source innovation. This reduces transaction costs to nearly zero, and promotes much faster research and product development. By contrast, this is one of the more pervasive problems affecting product development in the biotech industry worldwide. This situation, however, contradicts a large amount of historic evidence regarding the development of high technology-based industries[78].

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[76] Halla Thorsteinsdóttir, Role of the Health System in Health Biotechnology Innovation in Developing Countries, University of Toronto/ Canadian Program on Genomics and Global Health, *IKD Research Workshop*: Bridging the gulf between policies for innovation, productivity & industrial growth & policies to reduce poverty , London 18-20 November 2005

[77] [Collier R (2009), Rapidly rising clinical trial costs worry researchers, Canadian Medical Association or its licensors, 180(3), February 3]

[78] See the examples of the chemical, pharmaceutical, aircraft, semiconductor, electronic, automobile or software industry.

As a consequence, many potential life-saving innovations are been lost in interlocking patents, short-term monetary incentives and more expensive me-too drugs. Perhaps a closer look at the functioning of the Cuban biotech will help to demonstrate the possibility of an alternative model that channels all of the effort and funds in the industry into generating innovative products rather than the highly American-based financialized model that prevails in the worldwide biotechnology industry today.

The main challenge to the Cuban biotech is posed by the US embargo, which impedes access to international credit and scientific interchange. US firms dominate the global health biotechnology sector (2003 77% of the global biotechnology revenues). This may also limit the options for Cuba in developing joint ventures, strategic alliances and licensing of its technologies.

This last point also requires the Cuban representatives to find innovative ways to harmonise their socialist objectives with the needs of corporate capital. Cuba also encourages licensing and alliances with international firms, but under strict conditions of no negotiability of tangible assets and non-exclusivity of certain patents (Lopez et. al 2002). These aspects, which undoubtedly benefit the Cuban industry, might conflict with the short-term mentality of the industry worldwide. However, the recent trends toward patent pooling in the biotech industry (Clark et. al. 2000, Newberg 2001, Shapiro 2004, Gilbert 2004, Lerner et. al. 2005) could smoothen the way in which these negotiations take place and are understood in the future.

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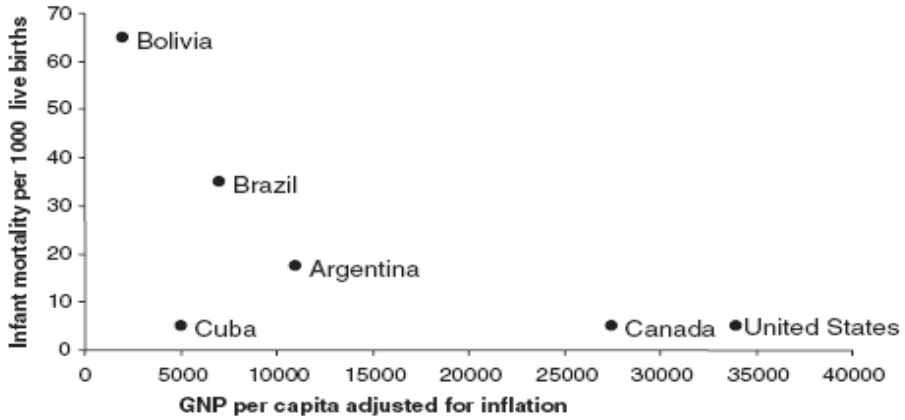
Figures

Figure 1. Infant mortality and gross national product (GNP) in selected Latin American countries and the United States, 2003



Source: Cooper et al. (2006)

Figure 2 Strategic core of the biotechnology industry

Company	Creation date	Number of workers	Extention (m^2)	Commercial branch
CIGB	1986	1245	10000	Heber Biotec
CIM	1994	400	15000	CIMAB
Finlay Inst.	1991	920	23000	Vacunas Finlay
CENSA	1980	406	8000	
CNIC	1965	1193	35000	DALMER
CIREN	1989	309		-
CIE	1987	244	9000	Tecnosuma
CENPALAB	1982	414	74000	
BIOCEN	1992	800	166000	
CNC*	1990		-	Neuronic

Complete name of the Centres

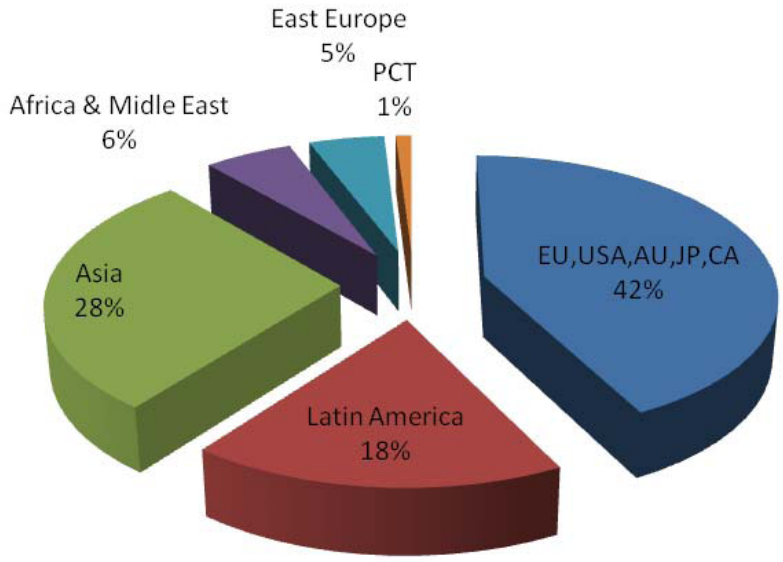
CIGB: Centre for Genetic Engineering and Biotechnology
CIM: Centre for Molecular Immunology
Finlay Inst: Finlay institute
CENSA: National Centre for Animal and Plant Health
CNIC: National Centre for Scientific Research
CIREN: International Centre of Neurological Restoration
CIE: Centre for Immunoassays
CENPALAB: National Centre for Production of Laboratory Animals
BIOCEN: National Centre for Bioproduction
CNC: Centre for Neurosciences

Notes

* The facilities of Neurosciences are still part of the CNIC. For this reason it has been difficult to localise the number of workers. New and independent facilities were under construction at the time this research was taking place.

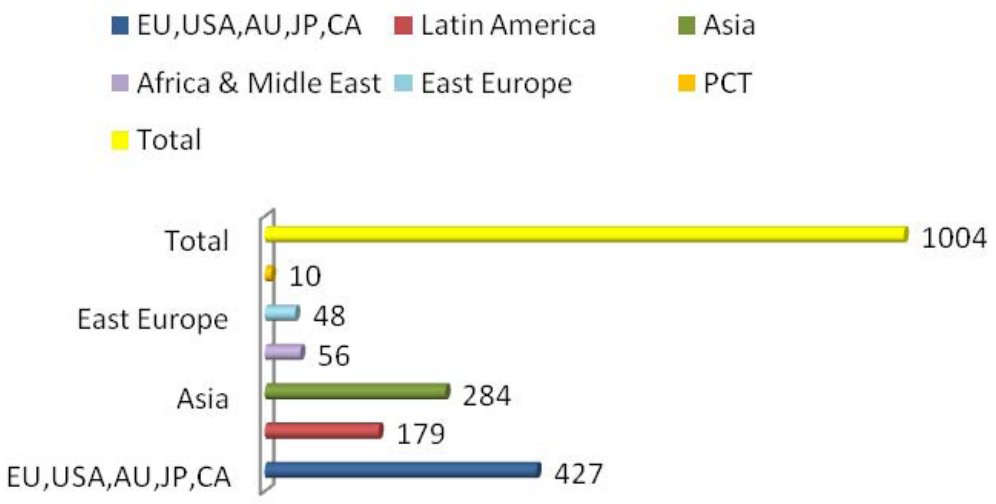
Although the also do research and innovation, CENSA, BIOCEN and CENPALAB facilities are more specialised in product manufacturing. They constantly collaborate with other institution in this endeavour. At the same time, their products are usually commercialised by Heber Biotec or any other commercial branch of the industry.

Figure 3: CIGB Patents 2009



Source: Bussines Portfolio CIGB-Heber, 2010

Figure 4: Number of patents CIGB 2009



Source: Bussines Portfolio CIGB-Heber, 2010

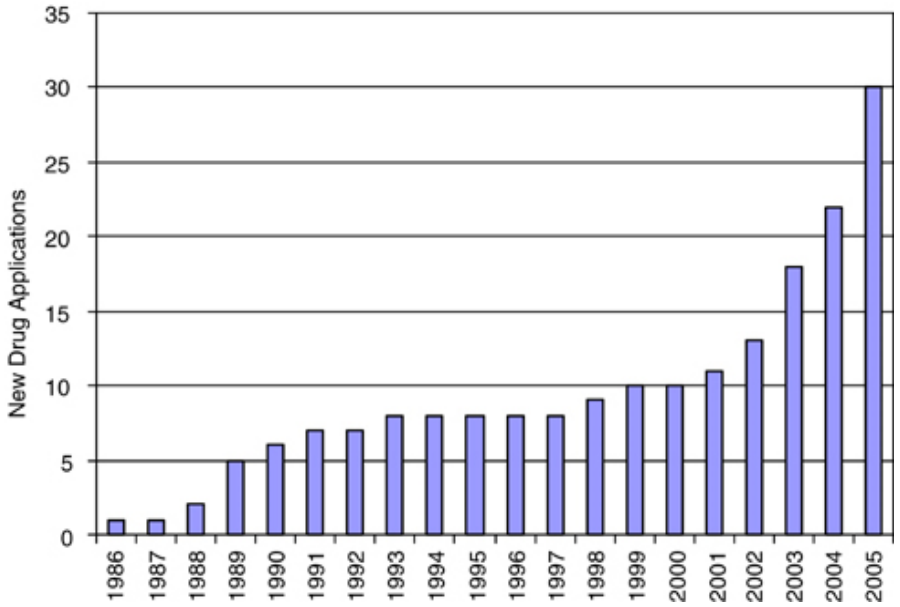
Figure 5: Historical development of CIGB products approved for commercialization

Year	Biotech product (generic name)	Indication(s)
1981–1990	Leuferon (human IFN)	Viral infections and cancer
	Hebertrans (leukocyte extract termed transfer factor)	Immune deficiencies, herpes and ataxia telangiectasia
	Heberon alfa R (recombinant IFN-α2b)	Hepatitis C and cancer
	Hebermin (recombinant EGF) produced in *Escherichia coli*)	Burns and ulcers
	Heberbiovac HB (recombinant HbsAg)	Hepatitis B
1991–2000	Heberkinasa (recombinant streptokinase)	Cardiovascular disease
	GAVAC (recombinant Bm86 protein vaccine)	Cattle tick (*Boophilus microplus*)
	Heberon Gamma R (recombinant IFN-γ)	Juvenile rheumatoid arthritis
2001–2007	Quimi-Hib (Hib vaccine)	Pneumonia and meningitis
	Bivalent 'HB-Hib' recombinant vaccine comprising HBsAg and Hib)	Hepatitis B, pneumonia and meningitis
	Trivac HB (tetravalent (DPT-HB) vaccine)	Diphtheria, tetanus, whooping cough and hepatitis B
	Heberpenta (pentavalent (DPT-HB+Hib) vaccine)	As above plus *Haemophilus influenzae* meningitis
	Heberviron (recombinant IFN-α2b and ribavirine)	Hepatitis C
	Hebervital (recombinant granulocyte colony stimulating factor)	Leukopenia, neutropenia
	Heberitro (recombinant erythropoietin-α)	Anemia
	HeberNem (*Corynebacterium paurometabolum* C924 strain)	Biological control of plant nematode infestation
	Acuabio I (invertebrate and fish nutritional supplement containing a defined combination of amino acids)	Prevention of white spot disease

[a]Table does not list new formulations of existing products, such as Heberbiovac HB, Heberon alfa R liquid without albumin, Heberon alfa R lyophilized without albumin, and Heberkinasa without albumin, Hebervis and Citoprot-P.

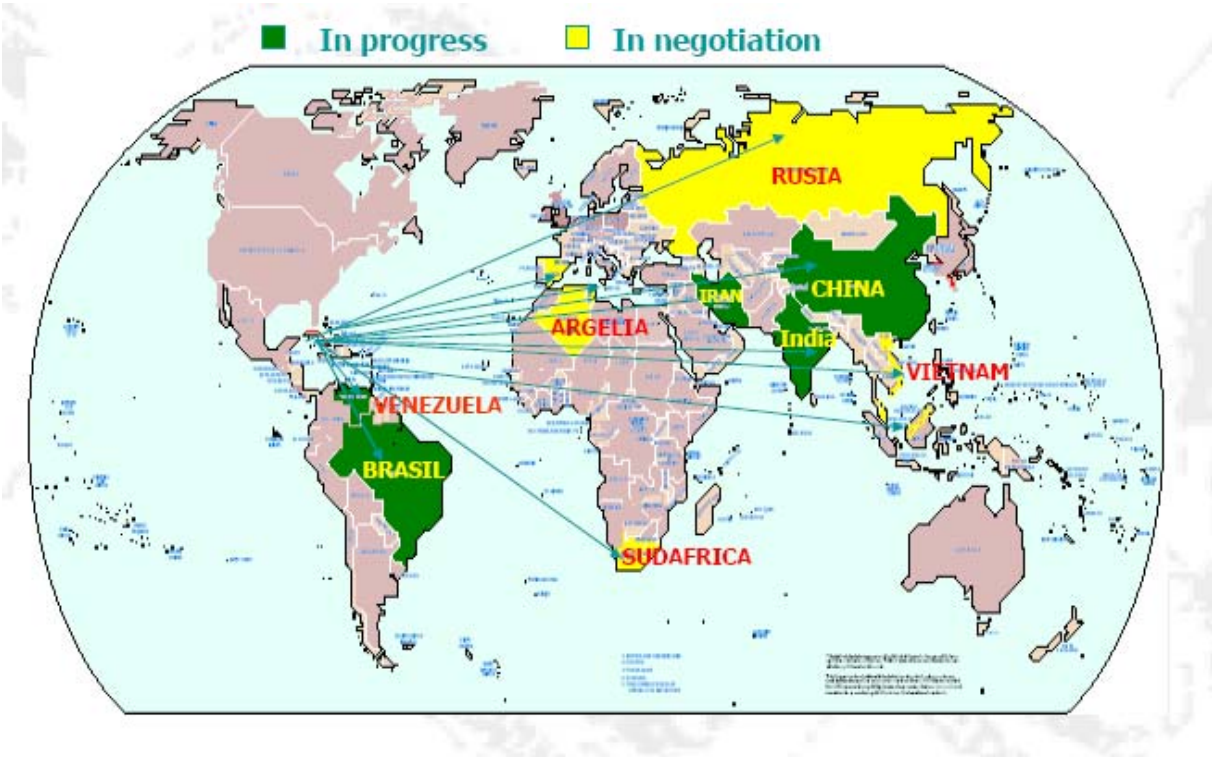
Source: Lopez et al (2007), NATURE BIOTECHNOLOGY VOLUME 25 NUMBER 11 NOVEMBER

Figure 6: CIGB Drug Applications



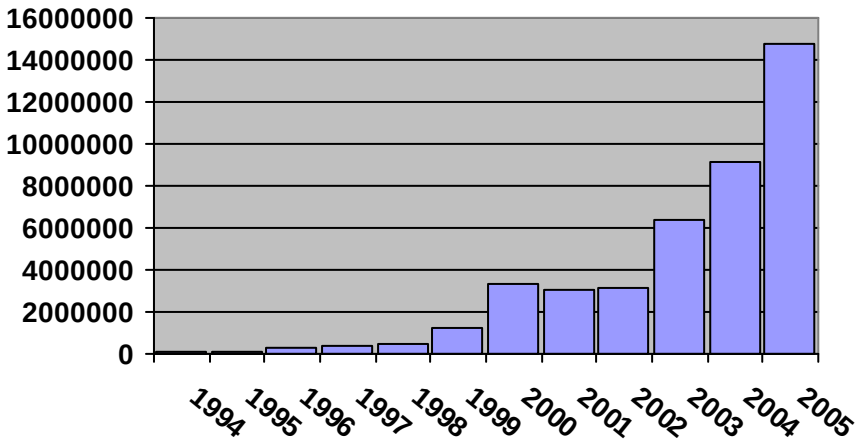
Source: Lopez et al (2006)

Figure 7: Technology Transfer Projects of the Cuban Biotechnology Industry



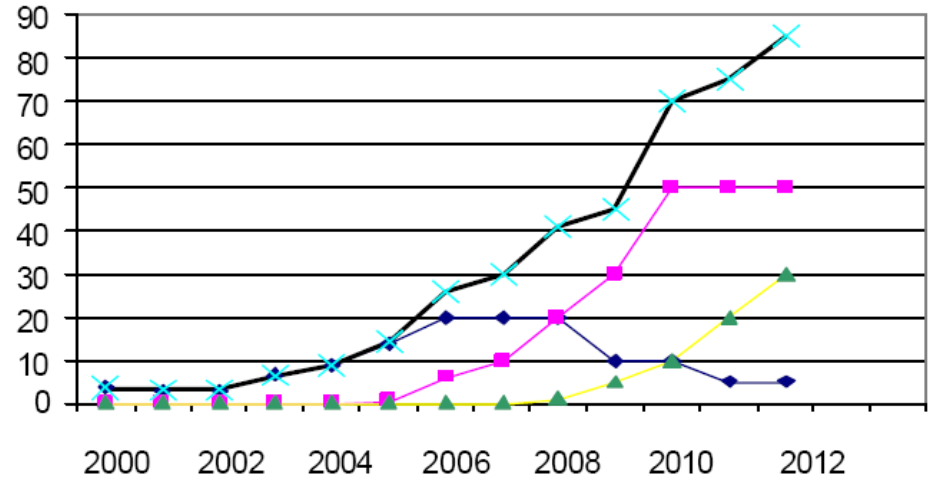
Source: Ubieta R (2008)

Figure 8: Exports CIM 1994-2005 (US$)



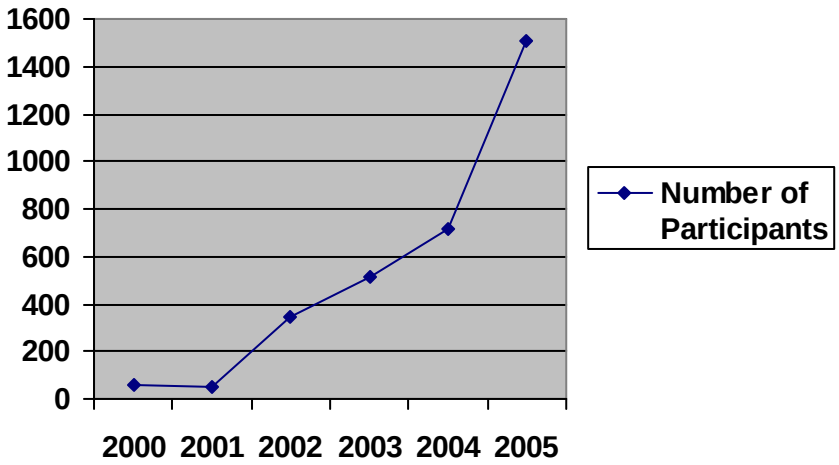
Source: Centre for the Study of the Cuban Economy (CEEC) 2008

Figure 9: Exports Forecast CIM (million US$)



Source: Centre for the Study of the Cuban Economy (CEEC) 2008

Figure 10: Clinical Trial participants CIM



Source: Centre for the Study of the Cuban Economy (CEEC) 2008

Figure 11 European Patent Hepatitis B Vaccine

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 480 525 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent: 07.01.1999 Bulletin 1999/01

(51) Int Cl.⁶: C12P 21/02, C12N 5/12, C12P 21/08, A61K 39/29 // C12N15/31

(21) Application number: 91202615.0

(22) Date of filing: 07.10.1991

(54) Method for obtaining recombinant surface antigen of hepatitis B virus (HEP B)

Source: Ubieta R (2008)