



State and Innovative Enterprises: The Case of the Cuban Biopharmaceutical Industry

Andrés Cárdenas O' Farrill

Innovative business enterprises are part of complex and interrelated sets of heterogeneous elements, which are deeply rooted in historic specific contexts. This is particularly true when we analyze the peculiar case of the Cuban biopharmaceutical industry.

Even when the pervasive lack of data makes it difficult to establish an accurate picture about the innovative outcomes of Cuba's bio-pharmaceutical industry, the available evidence of its achievements seems to be unequivocal. For instance, nearly 80 percent of finished pharmaceutical products used in the country are locally made and several of the products manufactured and exported by the industry are not just generics, but include a significant number of innovative drugs and vaccines, some of them recipients of international awards.

The first question that arises from this reflection is: how did a country like Cuba managed to achieve these results? By "country like Cuba" it is meant an essentially non-market, almost absurdly state-controlled (and mostly inefficient) economy; virtually detached from the world technology networks by virtue of the US embargo. A close examination shows, however, that many of these handicaps might have become the very strength of the Cuban biopharmaceutical industry.

In this contribution we will trace a causal chain account of how various conditions and variables interacted over time to produce this historical outcome. It will be argued how the long-term government efforts to finance and integrate all these institutions around a common organizational culture have been critical to the innovative outcomes achieved by the industry. It will be also discussed that far from being an exceptional tropical rarity; this case might just be the confirmation of a -hitherto ignored- robust body of cross-country historic evidence, which shows that to assume the government away is not part of the solution, but actually part of the problem that most of the world faces today.¹

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1. Introduction

The significant role played by the state in the emergence and evolution of innovative firms and industries within a complex economy has been shown by a good deal of historical evidence (Reinert 1999, Chang 2002, Ruttan 2006, Block 2008). The evidence has also shown that the debate on state intervention focused on the notion of market failure is problematic because it still relies on the idea of an “ideal free market” as a point of departure. This line of reasoning fails to acknowledge the institutional and political nature of the market, the state being the agent that actually designs the markets and their boundaries (Chang 2002).

In this paper it will be argued that the development of the Cuban biotechnology industry must be understood in the context of a carefully conceived industrial policy, in which government-based, non-firm entities are the greatest contributor to the high levels of organizational integration within the industry. This concept stems from the theory of the innovative enterprise proposed by Lazonick (2002) and is defined as “a set of social relations that provides participants in a complex division of labor with the incentives to cooperate in contributing their skills and efforts toward the achievement of a common goal” (*Ibid* p 14). Being conceived as a social condition, this concept explores the idea of business enterprises as social structures that are in turn embedded in larger (typically national) institutional environments.²

State intervention can be either bad or wrong depending of the kind of institutional incentives activated, but it has always been there. In fact, a great deal of historical evidence on the nature of innovation is telling us that government has been behind the emergence and further evolution of the most radical and disruptive forms of innovation (Chang 2002, Mazzucato 2011). This is particularly true in the biopharmaceutical industry; where industrial policy, science, and technology policy; and health policy represent three critical dimensions which must be taken into account when designing a pharmaceutical policy at national (and even international) level.

However, innovation cannot be explained by the amounts of R&D spent on the economy alone, as the theory of endogenous growth suggests, or by assuming a linear causation between this amount and innovation/economic growth (Freeman 2008). That is, a country with less R&D can display a better innovative performance than others with higher R&D spending.³ Nor can innovation be understood as a process where optimizing firms merely adapt to market and technological conditions, which have been taken for granted.

Rather, innovation is actually a non-linear, cumulative, uncertain process, which can be better captured by thinking of it as a system or as a network of organizations and institutions in constant organizational learning. This is broadly known in the literature as innovation systems. In this literature not only traditional firms, but also a much broader ecology including non-firm organizations (NFOs) (many of them government-based) and non-market institutions are taken into consideration as key elements of the innovation and production processes. Within this perspective, more emphasis is given to the systemic

² This concept provides a basic framework, flexible enough, for analyzing institutional and organizational complementarities in a particular historical context (see Lazonick 2002).

³ Consider the case of Japan and the Soviet Union. During the 1970s the former spent 2.5 percent of its GDP on R&D, while the latter spent four percent. Yet Japan grew into a much more sophisticated and faster growing economy.

ability to make it possible that knowledge embodied in capabilities and technologies can be absorbed and disseminate through the economy. The notion of organizational integration is employed here with the aim to conceptually capture this systemic ability in the Cuban biotech, but also to capture the separate contribution that each component of this set of heterogeneous agents.

Like the rest of the Cuban sectors, the Cuban biotechnology industry results from an overwhelming constellation of government-based, non-firm organizations. However this industry, it is argued, has managed to show more superior outcomes than the rest of the Cuban industries essentially because a better innovation-based coordination system has been set up. This paper will present the case of the Cuban biopharmaceutical industry and analyze the causal chain of events that led to the creation of its most important components. We intend to make the case that the Cuban biotechnology industry is a networked structure that fits very well with the literature of innovation systems, especially within the notions of both national and sectorial systems of innovations. Particularly, it is intended to explore the crucial role played by government-based, non-firm organizations in the learning process – i.e. mobilizing resources and allowing knowledge and innovation to disseminate across the sector – within the Cuban biotech.

The analysis will proceed as follow: section 2 will briefly discuss both the implication and necessity of assuming historic specificity as a property of complex economic systems. It will be argued that including the historical element in the economic analysis is crucial if we are to be able to make sound explanations and reasonable policy recommendations. Section 3 will present some evidence on the outcomes of the industry. It will be argued that even if scattered and unsystematic, the available evidence of the Cuban biotechnology achievements seems to be unequivocal. In section 4 we will sketch very succinctly the situation of the industry worldwide. It will be argued that there exists a huge need for organizational integration in the industry. Section 5 (the longest) will be devoted to the organizational analysis of the Cuban biotech sector. It will be shown how the integration of pharmaceutical, public health, and industrial development policies has led to innovation and better health standards. By promoting and funding research and development over the whole spectrum of activities, government-based NFOs (or simply NFOs) have provided incentives to knowledge sharing and openness, which have contributed to economies of scale and scope within the system. Section 6 outlines some conclusions of the paper.

2. The Historical Dimension of Economic Evolution

A very important property of complex economic systems has to do with the need to place them in an explicit historical time dimension (Foster 2005). Theoretical questions concerning the emergence of institutions, innovation diffusion, selection, and system maintenance do not happen in ahistorical contexts. In this section we will briefly outline the implications of assuming historic specificity as a property of complex economic systems.

Several authors have argued against the ahistorical nature of modern, mainstream economic theories. For instance, Hodgson (2001) illustrates in a magisterial fashion how the problem of “historical specificity” was ignored by the mainstream economics that emerged after the WWII. He argues that “all socio-economic systems are necessarily combinations of dissimilar elements. These combinations will, in turn, depend on historical and local circumstances” (*Ibid* p 44). Acknowledging the importance of

historically specific phenomena leads to a need for creating theoretical **devices** that match the given context.

Earlier contributions dealing with this problem date from the fifteenth century with the works of, for example, Antonio Serra and Giovanni Botero. Another significant contribution to the theoretical exploration of the historical specificity came in the nineteenth century from Marx on the one side; and from the German historical school (List, Sombart, Weber) on the other. According to Hodgson (2001), Marx and the German historical schools emphasized that the premises of the study of economic systems “must be based on a real object, rather than being arbitrary assumptions” (*Ibid* p 60). These explorations exerted a big influence in the further development of the American institutional school (Veblen, Commons, Ayers).

The conventional economics have focused fundamentally on a methodology based on the neoclassical constrained optimization (Lazonick 2002/Foster 2005) models to understand the behavior of the firm. These models examine how business enterprises as individual economic agents make resource allocation decisions at a particular point of time under extremely tight and unrealistic market conditions. By focusing on constrained optimization, conventional economists exclude historical and institutional evolution of the economic analysis and this invalidates the economic development as a primary object of intellectual endeavor.

The advent of today's traditional, constrained optimization methodology contributed to the separation between what was called political economy after Stanley Jevon's *The Theory of Political Economy* (1871) and Marshall's *Principle of Economics* (1890); and the political economy as practiced by the Classical School. Even when the fundamentals of the marginal revolution are to be found in the Classical School, it can be said that there was no insurmountable tension between (wrongly called) normative and positive issues because it was (somewhat tacitly assumed) that both belong to the realm of science. Adam Smith himself, as a moral philosopher, made a number of normative statements in his works.

However, the law of diminishing returns as elaborated by eighteenth-century French economist Jacques Turgot,⁴ and by nineteenth-century British economists David Ricardo and Thomas Malthus on the one side; and the law of diminishing marginal utility as defined by nineteenth-century German economist Hermann Heinrich Gossen⁵ relying on Bentham's Utilitarianism, paved the way for the marginal revolution (led by Stanley

⁴ See *Reflections on the Formation and Distribution of Wealth* (English version) written in 1786 and published in 1769-1776.

⁵ His most important book was *Die Entwicklung der Gesetze des menschlichen Verkehrs, und der daraus fließenden Regeln für menschliches Handeln* (The Development of the Laws of Human Intercourse and the Consequent Rules of Human Action) published in 1854.

Jevons⁶ in England, Carl Menger⁷ in Austria, Leon Walras⁸ in France and Vilfredo Pareto⁹ in Italy) of the late nineteenth century. The combination of these two elements gave sense to the idea of a natural balancing mechanism of supply and demand, namely the market price (as previously suggested by Adam Smith).

This notion of equilibrium builds the core of the methodology of orthodox economics, which was given further theoretical and mathematical rigor by the models of Hicks,¹⁰ Samuelson,¹¹ and Arrow/Debre¹² (neoclassical synthesis¹³). As already noted, *economics* (in contraposition to political economy) ended up being a science of automatic, market-based, regulated exchange between atomistic and identical agents, which left out the important, inherent tendency toward disequilibrium existent in the economic systems. In this context, historic specific elements such as technology, government policies, political culture, etc. became part of the things politicians and other “non-economic” actors were supposed to deal with.

However, life has shown that such a vision is unable to explain even the most ubiquitous economic questions. The division between economics and political economy

⁶ In his *General Mathematical Theory of Political Economy* (published in 1862) he outlined the marginal utility theory.

⁷ He was the founder of the Austrian School and a formidable opponent of the German Historical School. His methodological debate with Gustav Schmoller was the most important element of the so-called Methodenstreit (see *Die Irrtümer des Historicismus in der Deutschen Nationalökonomie* (The flaws of the historicism) published in 1884).

⁸ His masterwork was *Elements of a pure Economics*, written in 1872. Walras derived his notions of static equilibrium from the *Elements of Statics*, published in 1803 by the French mathematician Louis Poincaré.

⁹ In his work *Manual of Political Economy* (1906) he introduced the notion of Pareto-optimality, which is the condition under which markets reach equilibrium so that no further trades can be made without making someone worse off. The Pareto optimal is not necessarily the point at which value is maximized for the entire group, as there might be some trades that would harm some people for the benefit of others, but would nonetheless raise the sum total utility of the group (see Beinhocker 2006 p 36). Together with Walras, Pareto belonged to the Lausanne School of economics, sometimes referred to as the Mathematical School, and both represent the second generation of the Neoclassic Revolution.

¹⁰ His main work is *Value and Capital*, which was essentially a synthesis of the works of Walras, Marshall, and Pareto into a coherent theory.

¹¹ In his *Foundations of Economic* he took Hicks's theory, added his insights on revealed preferences; and turned it into a dazzling mathematical theory that became the standard model for the workings of markets.

¹² Arrow and Debreu connected Walras's notion of a general equilibrium with Pareto's concept of optimality in a very general way, thus creating the Neoclassical theory of general equilibrium. According to Beinhocker (2006) “[a]t the height of the Cold War, it was eventually interpreted in the political realm (albeit incorrectly) as final mathematical proof of the superiority of market capitalism over socialism” (p 38).

¹³ This synthesis was essentially microeconomic at the beginning, but during the 1960s and 1970s, economists such as Milton Friedman and Robert Lucas (Chicago School) began to apply the techniques of neoclassical microeconomics to macroeconomics, and concepts such as rational utility-maximizing consumers and optimal equilibriums became a core part of orthodox macroeconomic theory as well.

has proved to be spurious and prejudicial, in terms of both theory and policy. In fact, economic systems are part of complex and interrelated sets of heterogeneous societal elements, which remains in constant disequilibrium. This feature has been gradually reflected by a broad spectrum of insights provided by Veblenian, Schumpeterian and neo-Schumpeterian economists, business historians, evolutionary-based institutionalists, innovation economists, development economists, and complexity economists. In many of these insights (if not with the same intensity) the argument in favor of including the historical element in the economic analysis has been clearly advanced, in order to better deal with the complex nature of economic systems.

The abovementioned elements have had a strong impact in defining the methodological foundations of the work of some important contemporary scholars (although still a minority). For example, the institutional methodology proposed by Wilber/Harrison (1978) advocates for holistic explanations that take into account the complexity of economic reality; and recognize the need to contextualize economics models building by acknowledging the social and historical specificity of particular situations. In recent times, the utilization of case studies and qualitative historical-comparatives studies in the fields of economics has experienced an authentic renaissance, mostly as a reaction to the ahistorical methodology employed by the neoclassical economics in the last three decades. Particularly during the last decade or so, many scholars have confirmed, beyond any doubt, the validity and usefulness of the historical scrutiny of the economic performance.

To avoid any misunderstanding, it should be observed that to call attention to historical specificity does not mean to reject the importance of general statements when studying the functioning of economic systems. The present study is not advocating any post-modernistic¹⁴ or extreme relativistic view on the social sciences at all. On the contrary, *our point of departure is that explanatory unifications and general frameworks that explain real causal mechanisms are unavoidably central purposes of science*. As Hodgson (2001) also points out, “science cannot proceed without some general or universal statements and principles” (p 54). He also makes clear that to be able to deal “with complex (socio-economic) systems, we require a combination of general concepts, statements and theories, with particular concepts, statements and theories, relating to particular types of system or subsystem” (p 55).

In fact, the paramount objective of the present study is to suggest that *the mechanisms behind the functioning of a specific institutional framework (Cuban biotechnology industry), may fit very well the set of mechanisms described by more general (and historically informed) theoretical frameworks (e.g. national and sectorial system of innovation perspectives, theory of the innovative firm)*. Even if specific institutions differ from the ones employed by other countries, a much closer evaluation might be telling us that what actually matters in the understanding of economic systems is the developmental function played by the institution and not only the historic specific form of that developmental institution.

For example, a general framework could be that there exists strong historical evidence about the systematic use of industrial policies to advance economic development, but to understand the development of a given economic system, we cannot merely make that

¹⁴ A further discussion on the damage caused by this perspective in the social science, in particular in the heterodox economics and in sociology see Hodgson (2001).

statement. Actually we would need to know the specific historical institutions and type of organizations that shape that system, if we are to be able to make sound explanations and reasonable policy recommendations. A transnational historical perspective may be employed to look for more encompassing general mechanisms, which might be expressed in very different and specific institutional frameworks. In this sense Chang (2003) talks about “persistent historical patterns” (p 6) and Reinert (in Cimoli et al. 2009) refers to “mandatory passage point[s] in human history” (p 100).

This issue is covered in the present study by relying in such qualitative tools as process-tracing and cross-level reasoning. These tools will be used to evaluate causality within the case and to build (or invoke) a theory-based explanation by re-contextualizing the contextual evidence (abductive logic).

3. The Cuban Biotech Industry

The pervasive lack of data makes it difficult to establish an accurate picture about the outcomes of Cuba's biotechnology industry. Official statistics do not provide, for example, disaggregated figures of patent registration, R&D expenditures, or turnover of dedicated biotechnology companies. However, even if scattered and unsystematic, the available evidence of the Cuban biotechnology achievements seems to be unequivocal. As Pfeffer (in Burns ed. 2005 p 111) affirms, in clear recognition of the inherent difficulties of relying on financial measures to assess the achievements of the biotechnology, its impact in the healthcare system is perhaps the most obvious way to measure its success.

This is especially true if the biopharmaceutical industry is conceived as part of a highly interrelated and complex biomedical research ecosystem, which is composed of a broad variety of organizations, government being a crucial player, aimed at “harness innovation in health technology in an efficient and effective manner.”¹⁵ This has finally begun to be recognized by the movers and shakers of the pharmaceutical industry worldwide, which has experienced a set of gradual transformations in its business model.

Most pharmaceutical companies have been moving away from their monolithic blockbuster business model, dubbed “Pharma 1.0,” to a more collaborative, global and value-driven model called “Pharma 2.0”. However, new and sweeping trends have emerged that are shifting the industry towards Pharma 3.0 business model focused on health outcomes. While Pharma 1.0 and Pharma 2.0 paid more attention to developing and marketing drugs, Pharma 3.0 is a reconfiguration of the model with a focus on health outcomes where the traditional product – a drug – is only one part of pharma's value proposition.¹⁶ Seen from this perspective it cannot be overemphasized that the Cuban biopharmaceutical business model has actually been a (neglected) forerunner of Pharma 3.0.

¹⁵ “Biomedicine and health innovation: Synthesis report,” *OECD Innovation Strategy*, November 2010.

¹⁶ See Flochel P/ Kumli F (2011), “Pharma 3.0: delivering on health outcomes,” *Journal of Business Chemistry*, available at <http://www.businesschemistry.org/article/?article=125>, see also Ernst &Young (2011), *Progressions: building Pharma 3.0*.

3.1. From a Health Economics Perspective

To begin with, the costs of the Cuban health system remain low compared to its health standards, even if health services have become recently more expensive in Cuba¹⁷ (measured in terms of total expenditure as percent of GDP). To show this, we rely on the definitions given by both the System of Health Account (SHA) of the OECD¹⁸ and the National Health Accounts (NHA) of the WHO,¹⁹ which term current health expenditure as “the sum of health care goods and services for final consumption of resident units” (SHA 2011). The most important here is that this definition includes the cost of the goods and services produced by a country and therefore gives a good idea of how expensive is its health system.

By taking a look to the per capita total expenditure on health of Cuba, it will be found that even while Cuba spends more than the average of upper middle income countries,²⁰ it spends substantially less than high income countries (in current US\$).²¹ However, the country has managed to achieve health outcomes far superior to those of its income group; and more importantly, comparable with those of the high income countries (Table 1). This could be interpreted as a comparative advantage in term of cost of the medical services and goods produced in Cuba.

¹⁷ This has become apparent since the 2006 and can be at least partially explained by the increasing number of medical professionals on temporary foreign contracts. Although this practice has been a cornerstone of Cuban foreign policy since 1959, from the nineties on, however, and due to preferential commercial agreements with Venezuela and other countries, the number of doctors abroad has sharply increased. This has originated tensions in the preventive concept of the Cuban health system and has contributed to increase the role of curative medicine (which is more expensive), expressed in the increase in the use of first line emergency services. Another element is the demographic ageing process, which demands more day care homes for the aged and the technical upgrade of diagnostic and treatment capacities. For further details, see Vos et al. (2008) “Commentary: Cuba’s health system: challenges ahead, Health Policy and Planning,” (Published by Oxford University Press in association with The London School of Hygiene and Tropical Medicine); See also De Vos et al. (2008), Uses of the first line emergency services in Cuba, Health Policy, Jan; 85(1): 94-104.

¹⁸ See OECD, Eurostat, WHO (2011), “A System of Health Accounts,” *OECD Publishing*.

¹⁹ The definition given by the *Indicator* code book of the WHO identifies total expenditure on health (THE) as the sum of all outlays for health maintenance, restoration or enhancement paid for in cash or supplied in kind.. It is the sum of General Government Expenditure on Health and Private Expenditure on Health (p 187-190).

²⁰ According to the World Bank income group definition.

²¹ When we consider the PPP int. \$, we have that in term of its living standards Cuba spends even less than the upper middle income group in average. According to the WHO (2011) Cuba’s per capita health expenditure in 2008 was of \$495 in comparison with \$830 spent in average by its income group and \$4246 spent by upper income countries (representing countries such as the US an extreme in this list with \$7164). We employ, however, the current figures given the tradable nature of the products and services considered.

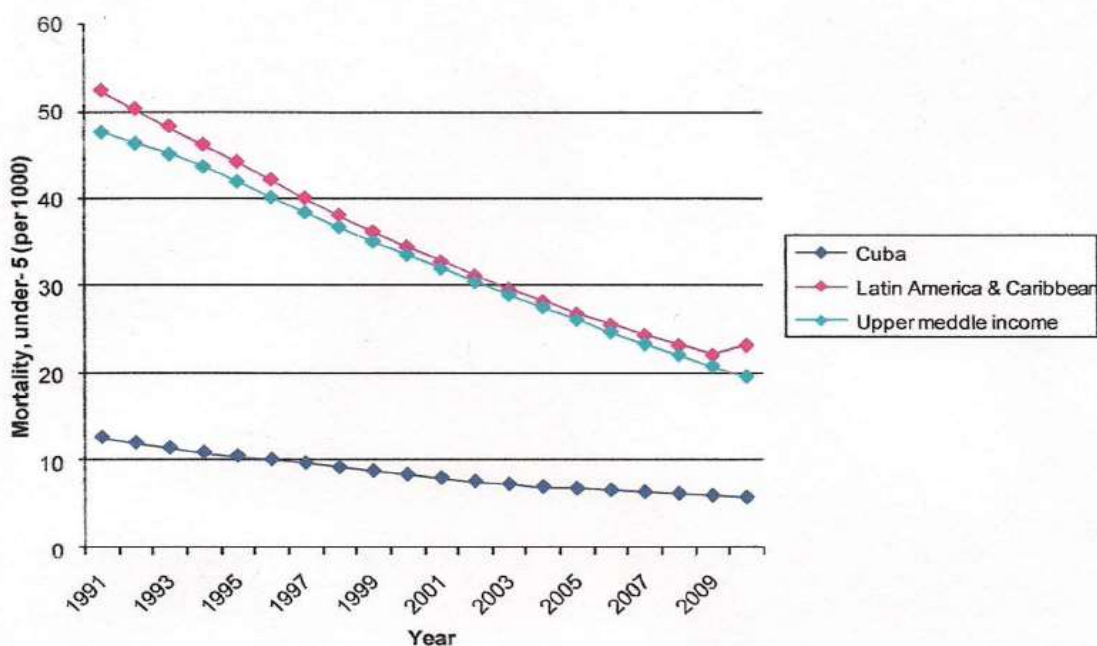
Table 1: Health Indicators and Health Expenditures (2009)
All figures are US\$

	Infant mortality rate (per 1000 live births)	Life expectancy at birth	Under five mortality rate per 1000 live births	Per capita expenditure on health (current US\$)	Total expenditure as % of GDP(2000)	Total expenditure as % of GDP(2008)
Cuba	5	78	6	672	6,7	12,1
High income average	6	80	7	4590	10	11,1
Upper middle income average	19	71	22	570	5,9	6,3
Global average	42	68	60	854	8,7	8,7

Source: Based on WHO 2011

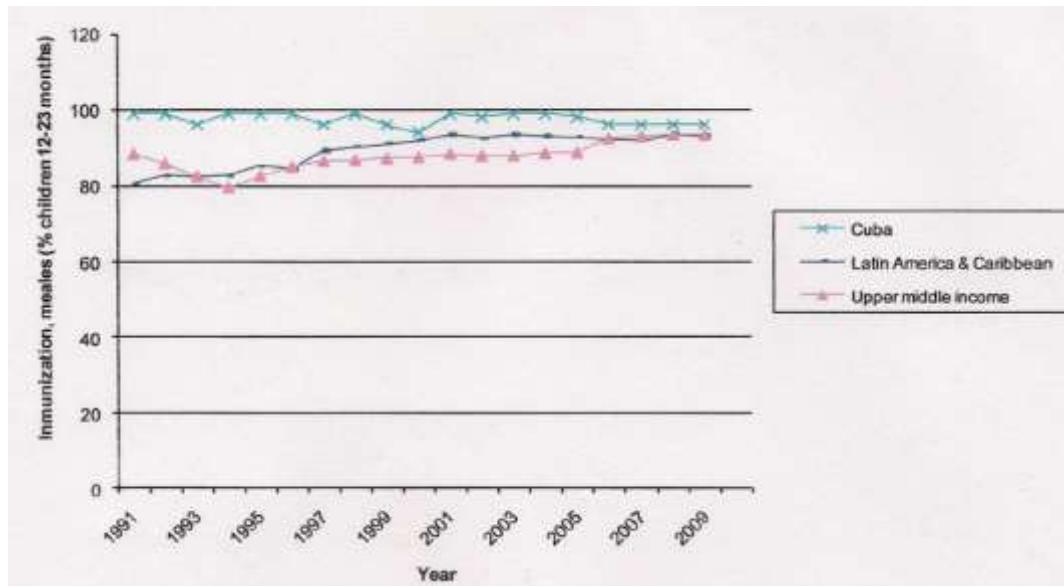
The results are also significant at the regional level. For instance, according to the World Bank statistics, GDP per capita in 2008 in Latin America was \$7844.5 US\$ (in current US\$) compared to \$5565.3 US\$ in Cuba (World Bank). Nevertheless, the country excelled in several indicators of mortality and disease prevention (Figure 1 and Figure 2).

Figure 1: Mortality, Under-5 (per 1000) 1991-2009



Source: Based on World Bank Data

Figure 2: Immunization, Measles 1991-2009



Data Source: Own estimates based on World Bank Data

Considering the whole region of the Americas in 2008 (Canada and U.S. included) we have, according to the WHO, that the per capita expenditure on health was of \$2902 US\$ compared to the \$672 US\$ in Cuba. However infant mortality in the region was of 15 per 1000 live births, compared to 5 per 1000 in Cuba. Using whatever measure, when health outcomes are correlated with GDP per capita, Cuba is clustered with high income countries such as Canada and the U.K. on the former scale and with upper middle income countries on the latter (Figure 3).

We could also look at the Cuba's performance rates in reduction of infectious diseases or the proportion of the immunization programs;²² or its contribution to fighting neglected diseases²³. In the same line, we could also consider the diagnosis and treatment of chronic conditions,²⁴ particularly taking into account that, according a report of the

²² See, for example Rodriguez et al. (1999), "Impact of Antimeningococcal B Vaccination, Mem Inst Oswaldo Cruz, Rio de Janeiro," Vol 44, see also Delgado et al. (2003), "Vaccination Strategies Against Hepatitis B and Their Results: Cuba and the United States," *MEDICC Review*; or Abreu et al. (2011), "Cuba's Strategy for Childhood Tuberculosis Control," 1995–2005, *MEDICC Review*.

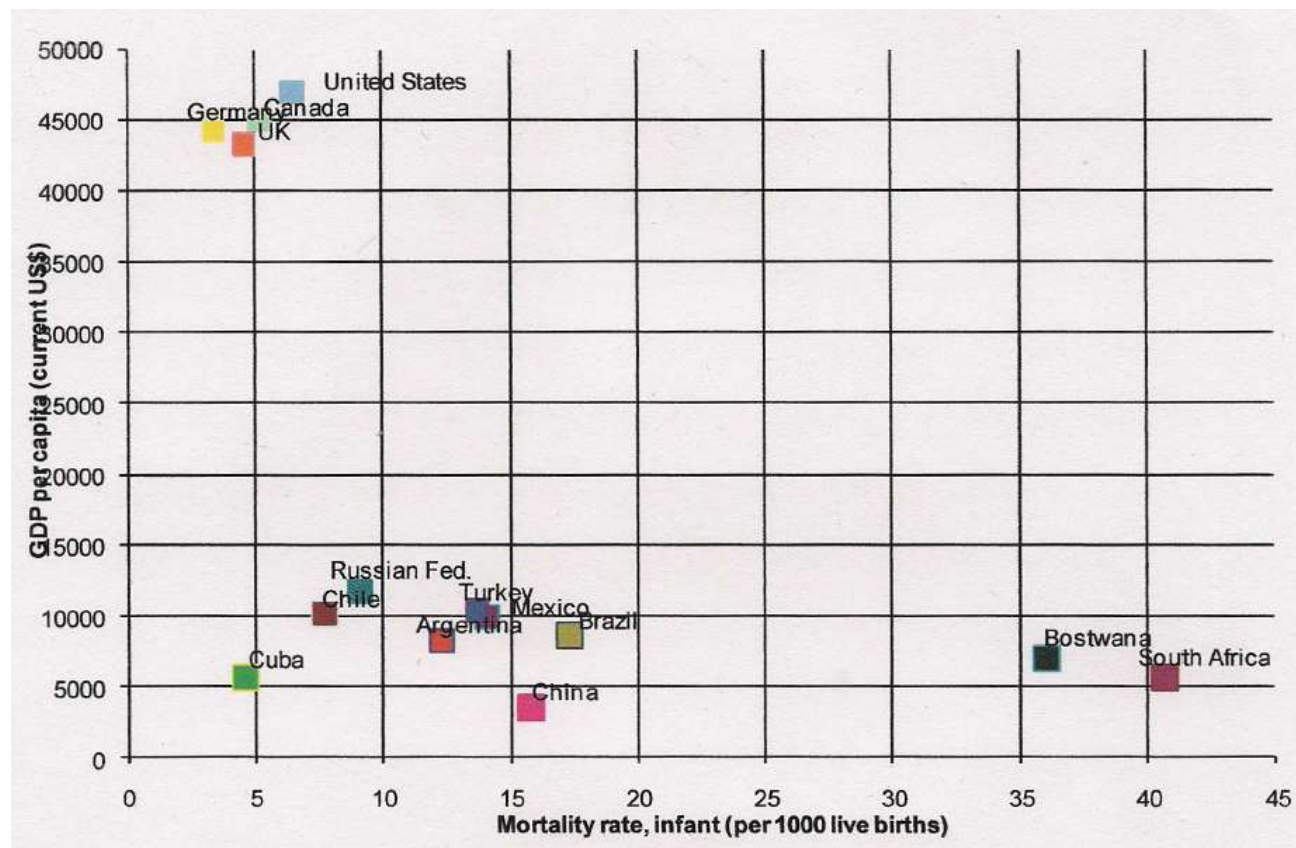
²³ See Morel et al. (2005) "Health innovation networks to help developing countries address neglected diseases," *Science*, Vol 39, July, p 401-403.

²⁴ See for example, Valdes (2005), "Cuba's National Program for Chronic Kidney Disease, Dialysis and Renal Transplantation," *MEDICC Review*, see also Reed (2008), "Chronic Vascular Diseases in Cuba: Strategies for 2015," *MEDICC Review*, Spring, Vol 10, No 25, see also "The success story of HIV and AIDS control in Cuba," In: <http://prairiefirenewspaper.com/2009/02/success-story-of-hiv-and-aids-control-in-cuba>, see also Pérez et al. (2000), "Epidemiology of hypertension in Cuba," *MEDICC Review*, see also Treatment to cure Psoriasis in Cuba, <http://ntsa.wordpress.com/tratamientos-alternativos/treatment-to-cure-psoriasis-in-cuba/>, see

WHO.²⁵ 80 percent of chronic disease deaths occur in low- and middle-income countries like Cuba.

Whatever the selected indicator, the point is that the Cuban health system has managed to achieve health outcomes at the level of high income countries while usually spending less. If the country had to acquire most of its needed medical products from foreign providers and at international prices, it would not have been able to achieve these standards at the same cost. Presumably, it would not have been able to afford the products

Figure 3: GDP/Infant Mortality 2010



Data Source: Own estimates based on World Bank Data
 GDP figures correspond to 2008
 Infant mortality figures correspond to 2010

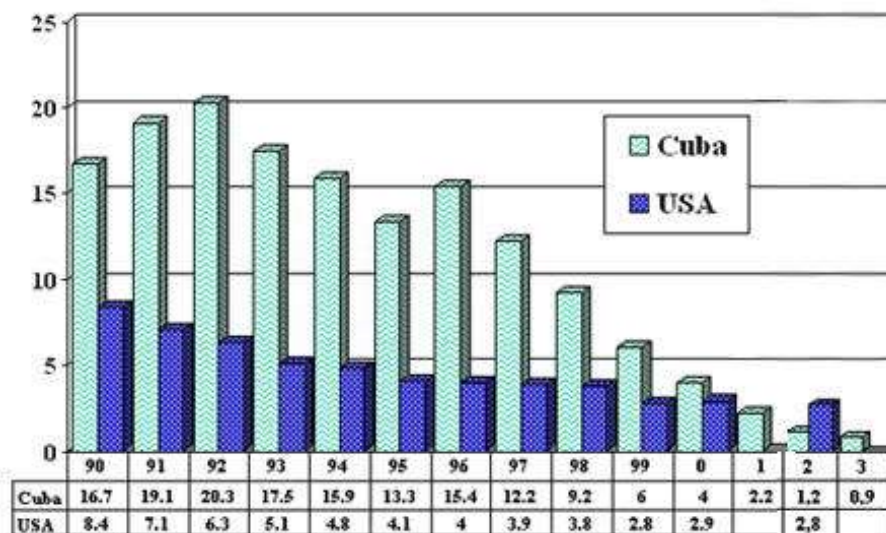
also Interview with Pedro Ordunez, Available in: http://www.londonmet.ac.uk/library/v85751_3.pdf.

²⁵ “Preventing chronic diseases: A vital investment,” *WHO global report*, available in: http://www.who.int/chp/chronic_disease_report/part1/en/index.html, see also Dy et al. (2009), “A Comparative Analysis on the Healthcare Systems of China and Cuba: Treatment of Cancer Patients,” De La Salle-College of Saint Benilde, Manila, Philippines, available in: <http://www.scribd.com/doc/55417998/Comparative-Analysis-on-Healthcare-Systems-Between-China-and-Cuba>.

at all, as is the case in most of the developing world. The use of vaccine against Hepatitis B in Cuba is a good example. Before 1990, the vaccine had not been used systematically in the country because of its high cost. It had only been imported and used on high risk groups. When the country was able to manufacture its own vaccine, it started in 1992 a universal vaccination of newborn children, coincidentally the same year the United States started its campaign.

A study covering the results of both campaigns for the period 1995-2003²⁶ shows the huge progress made by Cuba in fighting the disease (see Figure 4). The reduction of incidence of this acute disease for all ages reached 95.6 percent in Cuba and 67 percent in the United States (years 2003 and 2002, respectively). In fact, in 2001, Cuba reached the goals the United States has set for 2010. In 2010, the country has managed to eradicate the conditions in all the kids under 15. In the adult population there were also huge improvements. If in 1992 there have been 2194 cases, the number of people affected had by 2010 decreased to 11 cases. There is no intention to highlight any political undertones in this comparison, but just to emphasize the fact that there is no way that Cuba achieved these outcomes without having wisely invested in some manufacturing and organizational capabilities. The comparison is also interesting because the United States and Cuba are the two producers of recombinant vaccines against Hepatitis B recognized by the WHO in the Americas.

Figure 4: Incidence of Acute Hepatitis B. Cuba-USA 1990-2003



Source: Delgado G et al. (2003)

²⁶Delgado et al (2003), "Vaccination strategies against hepatitis B and their Results: Cuba and the United States," *Medic Review*, available at http://www.medicc.org/publications/medicc_review/1004/pages/cuban_medical_literature.html.

The role of the biotechnology industry becomes apparent when considering that, according to a World Bank report of 2002 that, “at present, nearly 80 percent of finished pharmaceutical products used in Cuba are locally made.”²⁷ An article published in *Scientific American Worldview* in 2012 confirm this by stating that “[l]ocally produced biopharmaceuticals supply 80 percent of domestic needs and the sector.”²⁸

A paper published by *Lancet*²⁹ in 2009 assured that the “local production of diagnostics and drugs” covers “85% of the needs, including antiretrovirals and cytostatics.”³⁰ Likewise, the same *Scientific American* article of 2012 cites officials of the industry who affirm that these industries “produce 585 of the 868 essential medications registered for domestic use.” This includes a dozen vaccines, generic antiretrovirals for people with AIDS and over 40 biopharmaceuticals.³¹ This is confirmed by *Business Monitor International*, which states that from the “basic medicine list released in 2009, a total of 562 drugs were Cuban, while 307 were imported”³² (see Espicom’s data in annex 5.7 for period 2009-2011). In addition, the fact that the domestic production increased during the period 1997-2008 may help to accept that, indeed, something has been happening in Cuba in terms of drug production (see annex 5.8).

At the same time, international public opinion has begun to recognize the potential and achievements of this industry, notwithstanding ideological biases. For instance, an editorial published in 2009 by the prestigious *Nature* spoke of the Cuban biotechnology as the “developing world’s most established biotechnology industry, which has grown rapidly even though it eschewed the venture-capital funding model that rich countries consider a prerequisite.”³³ A trilateral 2013 study carried out by the World Trade Organization (WTO), the World intellectual property organization (WIPO) and the World health organization (WHO) states that “Cuba has a vibrant research-based biotechnology industry that has developed a number of innovative vaccines” and also “has numerous innovative products in the pipeline.”³⁴

²⁷ 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.

²⁸ Conner Gorry, “Biotech: The Magic Pill? Cuba's burgeoning biopharmaceutical sector helps keep the island economy afloat,” *Scientific American Worldview*, available at <http://www.saworldview.com/article/biotech-the-magic-pill>.

²⁹ The *Lancet* is one of the world’s oldest, and most prestigious general medical journals. It also has specialized journals

³⁰ Vos (2009), “The right to health in times of economic crisis: Cuba’s way,” *The Lancet*, Vol 374 November 7, p 1575-1576.

³¹ Conner Gorry, “Biotech: The Magic Pill? Cuba's burgeoning biopharmaceutical sector helps keep the island economy afloat,” *Scientific American Worldview*, 2012, available at <http://www.saworldview.com/article/biotech-the-magic-pill>.

³² Available at <http://store.businessmonitor.com/article/346369>.

³³ See “Cuba’s Biotech Boom,” *Nature* 457, 130 (8 January 2009) | doi:10.1038/457130a, available at <http://www.nature.com/nature/journal/v457/n7226/full/457130a.html>.

³⁴ Bartels H, Beyer P, Kampf R, Krattiger A, Mirza Z, Taubman A and Watal J (2013), “Promoting Access to Medical Technologies and Innovation: Intersections between public health, intellectual property and trade,” WHO, WIPO and the WTO, Geneva, p 113, available at http://www.wto.org/english/res_e/booksp_e/pamtiwhowipowtweb13_e.pdf.

Individuals such as Dr. James Larrick,³⁵ a U.S. entrepreneur, were cited in 2004 by a *Nature Biotechnology* report about the good prospects of the Cuban biopharmaceutical industry³⁶ and he confirmed in 2011 his belief that Cuba's biotechnology is clearly world-class.³⁷ Also, Professor Hudson Freeze,³⁸ Director of the Genetic Research Program at the U.S.-based U.C. San Diego, has the opinion that Cuba has become world-class in this competitive arena.³⁹

More skeptical voices, such as the German virologist and 2008 Nobel Prize winner in Physiology or Medicine, Harald zur Hausen, do not think that the Cuban biotechnology (specifically cancer research) has reached international standards. However, he acknowledges the huge progress made by the industry and believes that it has good prospects for the future.⁴⁰ A similar skepticism is shared by the American molecular biologist, and 2003 Nobel Prize winner in Chemistry, Peter Agre. Agre thinks that the question of reaching international standards is a difficult one because the prevailing trade embargo has isolated Cuba from the U.S., and clear evaluations have not been possible. He suspects that this lack of communication may have increased the skepticism that exists in the U.S. concerning Cuban biotech programs (he mentions the therapeutic cancer vaccines). That said, he is impressed by the zeal with which Cubans have advanced public health in their country and in some of the poorer countries in Africa and Latin America.⁴¹ At the same time, it is telling that even the U.S. government follows with attention the development of some Cuban cancer products.⁴²

3.2. Biopharmaceutical Trade Balance

The same 2002 World Bank report mentioned above 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”.

Likewise, *Business Monitor International* employs data from the U.N. Commodity Trade Statistics Database (UN Comtrade) to show that the Cuba Pharmaceutical Trade Balance during 2003-2006 has been improving (Figure 5). Even when some inaccuracies are revealed in the figure of 2006, the same trend is confirmed by the numbers of the Cuban Statistics Agency (ONE) for the period 2006-2009 (Figure 6).

³⁵ See his profile here:

<http://investing.businessweek.com/research/stocks/private/person.asp?personId=1368445&privcapId=19713&previousCapId=142316&previousTitle=Sofinnova%20Ventures,%20Inc>.

³⁶ Thorsteinsdóttir H et. al. (2004), “Cuba-innovation through synergy,” *Nature Biotechnology*, vol. 22, December 2004.

³⁷ Electronic communication in 2011 with the author of the present study.

³⁸ See his profile here: <http://www.sanfordburnham.org/talent/Pages/HudsonFreeze.aspx>.

³⁹ Electronic communication in 2012 with the author of the present study.

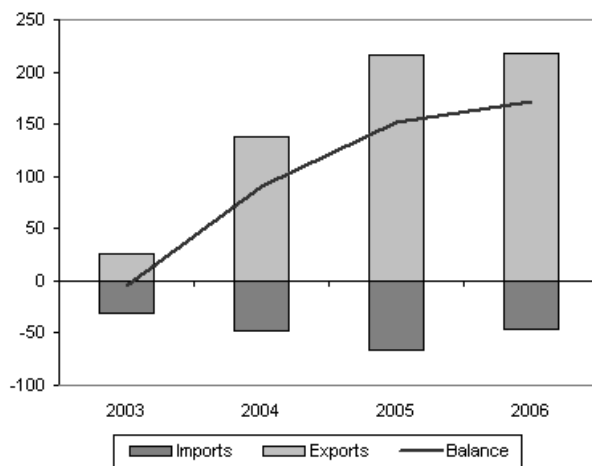
⁴⁰ Electronic communication in 2011 with the author of the present study.

⁴¹ Electronic communication in 2013 with the author of the present study.

⁴² See <http://clinicaltrials.gov/show/NCT01813253>, see also <http://clinicaltrials.gov/show/NCT00561990>.

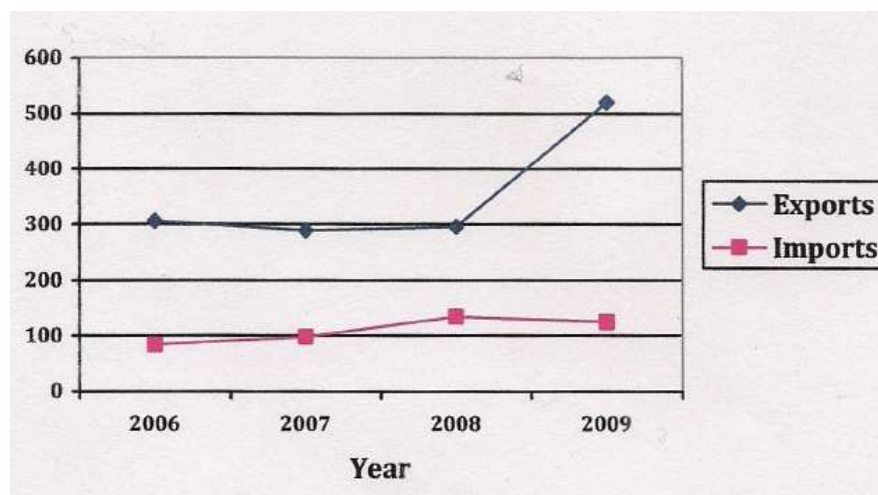
Most of the trade partners of Cuba are emerging countries that benefit from the low cost of the products. For example, “strategic alliances with Brazil, and importantly, China and India — the source of 44 percent of Cuba’s raw materials for biopharmaceutical products — contribute to enhance commercial relations.”⁴³ At the same time Cuba main-

Figure 5: Cuba Pharmaceutical Trade Balance (Million US\$)



Source: *Business Monitor International* (2010). Based on data from the UN Comtrade (public data)

Figure 6: Cuba Pharmaceuticals Foreign Trade (Million US\$)



Data Source: Cuba’s National Statistics Office (ONE) in accordance to sections and chapters of the *Standards International Trade Classification* (SITC)

⁴³ Conner Gorry, “Biotech: The Magic Pill? Cuba's burgeoning biopharmaceutical sector helps keep the island economy afloat,” *Scientific American Worldview*, 2012 available at <http://www.saworldview.com/article/biotech-the-magic-pill>.

tains a huge number of cooperative projects with these countries, which have helped to boost the prestige of the industry and have led to economies of scale, as many procedures are standardized in those countries, manufacturing plants are built, and Cuban medical doctors employed in cooperative programs utilizing industry products. It is not surprising to see that the current biggest trade partner of Cuba (Venezuela) is the same country that hosts the largest number of Cuban health professionals.

In addition, the data given by a 2011 *Espicom Business Intelligence Report* shows that during the period 1995-2010, even with fluctuation, the Cuban pharmaceutical trade balance has been positive, except for four years (Table 2). This signals that during these years, something was happening in this industry.

Table 2 Balance of Pharmaceutical Trade 1995-2010 (Thousand US\$)

Year	Raw Material	Antisera& Vaccines	Semi-finished medicaments	Retail Medicaments	Total
1995	-765	29734	-655	-11135	17179
1996	-5695	34382	-1418	-7628	19640
1997	-5071	41200	-125	-3725	32278
1998	-8251	18965	143	-15552	-4695
1999	-4510	12376	4690	-4827	7728
2000	-6648	15975	4900	-6527	7700
2001	-6820	16109	626	-9029	887
2002	-7405	23654	1070	-5820	11499
2003	-7979	25475	841	-306	18031
2004	-10782	15333	1392	-8012	-2069
2005	-6926	16336	482	-22761	-12869
2006	6761	21524	-654	-25636	1995
2007	36127	19384	-420	-21880	33212
2008	-21723	2960	-1508	-25978	-46249
2009	18894	10263	-1276	176013	203895
2010	30606	21505	-824	150512	201878

Source: *Espicom Business Intelligence* (2011) based on data from the UN Comtrade (use of data authorized by EBI)

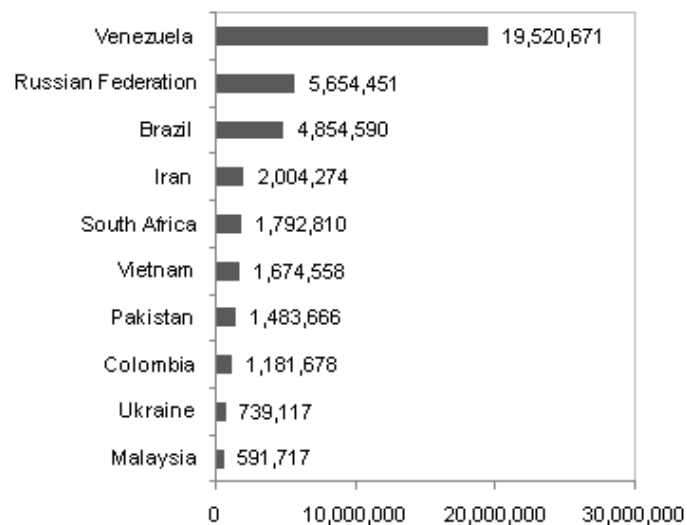
Significant is the fact that vaccines show positive balances in all the years, showing the potential reached by the industry during the period. In 2010, the surplus amounted to \$201.9 million US\$, of which \$150.6 million US\$ was accountable to retail medicaments. Raw materials, antisera, and vaccines recorded surpluses of \$30.6 million US\$ and \$21.5 million US\$. The surplus in retail medicaments during 2009 and 2010 could be an outcome of the import substitution strategy initiated by the government during the 1990s.

It should be pointed out that the data offered by *Espicom* are reverse data. As Cuba does not offer disaggregated data in relation to the pharmaceutical industry, data was

obtained by looking at other countries' imports from Cuba, which give an indication of how much activity is taking place, but, as the *Espicom* report acknowledges, tends to underestimate the level of exports.

For example, a look at the figures of 2010, shows that the aggregated export figure given by the Cuban National Statistics Office (\$491,489 US\$⁴⁴) is higher than the one obtained by *Espicom* (\$277,753 US\$). When looking at the trade balance figures of the year 2008, *Espicom* obtained a negative figure, while the figures of the Cuban Statistical office reflect a positive figure, as can be seen in the Figure 6.

Figure 7: Cuba's Top Ten Export Countries of Blood Product for Therapeutic Uses (US\$)



Source: *Business Monitor International* (2010) based on UN Comtrade, BMI Database

For example, a look at the figures of 2010, shows that the aggregated export figure given by the Cuban National Statistics Office (\$491,489 US\$⁴⁵) is higher than the one obtained by *Espicom* (\$277,753 US\$). When looking at the trade balance figures of the year 2008, *Espicom* obtained a negative figure, while the figures of the Cuban Statistical office reflect a positive figure, as can be seen in the Figure 6.

⁴⁴ The conversion is based on the official exchange rate given by the Cuban Central bank for foreign currencies and Cuban convertible Peso (CUC), which is 1. The official rate of exchange of Banco Central de Cuba is published exclusively to be used by Cuban enterprises, when registering the operations made in foreign exchange. This rate of exchange is not valid for currency purchase and selling operations between financial institutions and the population or enterprises.

⁴⁵ The conversion is based on the official exchange rate given by the Cuban Central bank for foreign currencies and Cuban convertible Peso (CUC), which is 1. The official rate of exchange of Banco Central de Cuba is published exclusively to be used by Cuban enterprises, when registering the operations made in foreign exchange. This rate of exchange is not valid for currency purchase and selling operations between financial institutions and the population or enterprises.

The point is that the numbers could be even better than the ones reflected by this report. In fact, the above mentioned article in *Scientific American Worldview* states that “Cuba’s exports of biopharmaceutical products increased fivefold between 1995 and 2010”⁴⁶ and confirms that the “sector is now the country’s second largest export earner after nickel.”

However, even if we do not possess detailed statistics on the performance of Cuban biotechnology, it is at least reasonable to assume, taking into account the above mentioned, that this industry is being to deliver cost effective products to the national health system when compared to other countries of similar and even higher income groups.

3.3. Innovative Outcomes of the Industry

At the same time, the picture becomes more intriguing when we acknowledge that several of the drugs produced and exported at lower cost by Cuba are not just generics but include a significant number of innovative drugs and vaccines. The evidence arises not only from the excellent results obtained by introducing these products into the domestic market, but also from internationally acknowledged bodies such as the WIPO Award schemes, of which Cuba makes systematic use as a means of giving public recognition to its creators and promoting the importance of innovation. This is a yearly award granted by the United Nation’s World Intellectual Property Organization to the best innovations worldwide (WIPO awards). In this work, and for the sake of the argument being made here, we will only refer to the awards given in the field of health biotechnology and other medical technologies.

For instance, Cuba is the only country in the world that has come up with an effective vaccine against meningitis B. The product was developed by the Finlay Institute, which is an organization dedicated to vaccine research and production. It is being commercialized by the company Vacunas Finlay, the commercial arm of the Institute. This vaccine (VAMENGOC- BC®)⁴⁷ was awarded in 1989 with the WIPO’s Gold Medal.⁴⁸ To date, more than 55 million vaccine doses have been administered in Cuba and 15 other countries, primarily in Latin America and the Caribbean. The product has also been patented in the European Union and in the U.S.⁴⁹

PPG, polycosanol, is a pharmaceutical derived from sugarcane wax used to reduce patient morbidity and mortality due to atherosclerotic cardiovascular disease.⁵⁰ The product was developed by the National Centre for Scientific Research (CNIC in Spanish),

⁴⁶ Conner Gorry, “Biotech: The Magic Pill? Cuba's burgeoning biopharmaceutical sector helps keep the island economy afloat,” *Scientific American Worldview*, 2012, available at <http://www.saworldview.com/article/biotech-the-magic-pill>.

⁴⁷A 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*, 2010/03/01, Online: http://www.btimes.com.my/Current_News/BTIMES/articles/vacin/Article/. See also http://wsicubaproject.org/halalvaccine_1107.cfm.

⁴⁸ <http://www.wipo.int/export/sites/www/ip-outreach/en/awards/women/pdf/cu.pdf>.

⁴⁹ See Sotolongo et al. (2009), “Cuban Meningococcal BC Vaccine: Experiences & Contributions from 20 Years of Application,” *MEDICC Review*, Fall, Vol 9, No 1 p 16-22.

⁵⁰ See: <http://www.purematters.com/herbs-supplements/p/policosanol-ppg>.

considered an incubator company within the industry,⁵¹ and is being commercialized by Laboratios DALMER S.A., the commercial arm of CNIC. The product won a WIPO Gold Medal in 1996.⁵²

Also important is the world's first synthetic vaccine (Quimi-Hib) against haemophilus influenza type b (or Hib). This particular bacterium causes nearly 50 percent of all infections, some of which lead to deafness and mental retardation, in children under the age of five worldwide.⁵³ The product was developed by the Laboratory of Synthetic Antigens,⁵⁴ a small lab which belongs to the faculty of chemistry of the University of Havana, in close cooperation with several Cuban biotech organizations and the University of Ottawa in Canada.

According to a *Chemical and Engineering News* report,⁵⁵ this is the first commercial vaccine made from a synthetic carbohydrate, which is said to be cheaper than those based on natural carbohydrates. It makes it possible to envision a new generation of carbohydrate-based vaccines.⁵⁶ The product won the WIPO Gold Medal Award in 2005 and the same year was given the Agilent Technologies Foundation Health Award (Tech Award), awarded since the year 2000 by Technical Museum of San Jose, California.⁵⁷ Cuba is saving \$2.5 million US\$ yearly with this product.

The Cuban biopharma industry has also recently developed Surfacen, which is used to treat infant respiratory distress syndrome, a frequent cause of death in premature

⁵¹ This is the first research center created after 1959 (in 1965) and is responsible for having provided professional education to many of the scientist, which were to be later the leaders of the current industry.

⁵²

<http://www.wipo.int/tools/en/gsearch.html?cx=000395567151317721298%3Aaqr59qtjbo&cof=FORID%3A11&q=wipo+awards+cuba&sa=Search#1128>.

⁵³ <http://www.globalexchange.org/countries/americas/cuba/foodAndMeds/1510.html.pdf>.

⁵⁴ This is a small but important research organization that belongs to the Faculty of Chemistry of the University of Havana. For space reasons, no further details will be provided. But in order to have an idea of its innovative potential, it can be said that this synthetic vaccine costs 12 times less than the older version. Cuba currently produces around 10 million doses a year; domestic demand is fewer than one million annually; and it is expected to reach 50 million doses a year by scaling-up production, which will further reduce the price due to economies of scale. See Gorry C (2007). The organization is depicted in violet, which represents organizations exclusively or mainly devoted to research. The other organization in violet is the Centre of Medical Genetics (a short reference to this center can be found in the section CIE below).

⁵⁵ "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>.

⁵⁶ The breakthrough was not the development of the vaccine itself, which was already available, but the invention of a synthetic version of the vaccine, which is substantially cheaper and much easier to manufacture than the non-synthetic vaccine currently on the market. Pharmaceutical companies currently can produce just one-fifth of the 500 million doses needed a year. With the new synthetic vaccine, Cuba alone may be able to manufacture 50 million doses a year. In: Innovation: Applying knowledge in development, UN Task force (2005) p 22.

⁵⁷ See article on website of the Santa Clara University of California, <http://www.scu.edu/sts/nexus/fall2005/StephensArticle.cfm>.

babies. The product was developed by the National Centre for Animal and Plant Health (CENSA) and won the silver medal at the 26th International Fair of Inventions Geneva in 1998 and the gold medal for best invention in the 2007 WIPO awards. This medicine allows the country to save \$3 million US\$ yearly. Before that, a foreign medicine would be imported and only employed in the most critical cases. Additionally, it had to be obtained at great expense in other countries due to the U.S. embargo on the island. Other awards include a kit for quick diagnosis of vaginitis, which received the Bronze Medal at 27th International Fair of Inventions Geneva in 1999.

For another example, Heberprot-P, is a novel and unique Cuban biomedicine for treating diabetic feet developed by the Centre for Genetic Engineering and Biotechnology (CIGB). Administered locally into chronic wounds, the product reduces the risk of amputation in diabetic foot ulcer patients, as it accelerates healing with human recombinant epidermal growth factor (hr-EGF). The product was awarded with the WIPO Award for Best Young Inventor and a WIPO gold medal at the International Inventions Fair in April of 2011.⁵⁸ Heberprot-P is already used to treat over 20 000 patients in Cuba and other nations. It has been granted patents in 15 other countries, including the U.S.A., China, and Australia, and is in clinical trials for use in others.

Other innovative products include Nimotuzumab, which was developed by the Centre of Molecular Immunology (CIM). It targets epidermal growth factor receptors, and is aimed at various epithelial cancer types, including non-small cell lung, glioma, esophageal, brain metastasis, colorectal, pancreatic, prostate, cervical, and breast cancers. The product is being commercialized by CIMAB, the commercial arm of CIM (Havana), and its partner YM BioSciences (Mississauga, Canada).⁵⁹ A more recent Cuban innovation is CimaVax-EGF, which was officially released for commercial use in September 2011 and is the world's first lung cancer vaccine. While current treatments may improve the survival rate when the cancer is caught in its early stages, the five-year survival rate for late-stage lung cancer can be less than one percent. The vaccine, called CimaVax-EGF, has also been developed by the CIM and is intended for patients with lung cancer in stages three and four who have shown no positive response to other kinds of treatment, such as chemotherapy and radiotherapy. Although the vaccine doesn't cure the disease, it might turn the cancer into a manageable, chronic disease by generating antibodies against the proteins which triggered the uncontrolled cell proliferation.⁶⁰

More than 1,000 lung cancer patients have already undergone trials in Cuba, where the vaccine is now distributed free of charge.⁶¹ In September 2012 Malaysian biopharma

⁵⁸See <http://www.woundsinternational.com/news/cuba-wins-awards-for-diabetic-foot-treatment>; see also http://heberprot-p.cigb.edu.cu/index.php?option=com_content&view=article&id=23&Itemid=60&lang=en

⁵⁹ To date, the consortium has tested Nimotuzumab in 9 842 patients in Cuba, Argentina, Brazil, Canada, China, Colombia, Germany, India, Indonesia, Japan, Malaysia, Mexico, Singapore, South Africa, South Korea, Thailand and the Philippines. Trials are also being conducted in Europe, Japan and North America. See YM Biosciences, Inc, http://www.ymbiosciences.com/products/nimotuzumab/licensee_links.php.

⁶⁰ Some preliminary results of the phase II published in 2010 showed a mean of 18.53 months survival (median, 11.47 months) in those vaccinated under 60 years old. See <http://www.cimab-sa.com/publicaciones/75649301.PDF>.

⁶¹ See <http://medicalxpress.com/news/2011-09-cuba-world-lung-cancer-vaccine.html>.

company Bioven, which has a unit in Aberdeen, Scotland, has announced the start of its pivotal Phase III trial of CimaVax-EGF in the United Kingdom.⁶² Outside of Europe, the vaccine is in the process of approval in Argentina, Brazil, Colombia, Ecuador, and Paraguay; is registered in Cuba and Peru; and is currently being tested in Canada, China, and Malaysia. Plans are under way to undertake trials in other countries in Europe and in Thailand.⁶³

The most recent innovative product is Racotumomab (Vaxira), which is CIM's second lung cancer vaccine.⁶⁴ Clinical trials carried out on some 1700 patients have shown that 24 percent of late-stage lung cancer sufferers lived for two years with Racotumomab, whereas the figure was only eight percent on chemotherapy and radiotherapy. Phase III trials are continuing in seven countries and the drug is expected to be marketed in 25 countries by 2015. The product is currently commercialized together with an Argentinean company.⁶⁵

Last but not least, WIPO's officials have confirmed that both CIGB and CIM received the WIPO Award for Innovative Enterprises in 2012.⁶⁶ That provides a further proof of the innovative potential of Cuba's life sciences industry.

4. The International Industry: The Need for Organizational Integration

In the previous section it was shown that while we cannot compare disaggregated R&D investments or yearly revenues in the case of Cuban biotech, we know, however, that its capacity meets 80 to 90 percent of domestic demand (including a significant number of innovative, world unique products). This element has contributed to substantially reduce Cuba's reliance on pharmaceutical imports and, consequently, helped to maintain country's health standards comparable to those of high income countries at a much lower cost. In addition, highly qualified officials of the industry assure that Cuban biotech works with positive cash flow,⁶⁷ which, if true, would be a privilege within the biopharma industry.

⁶² See <http://www.ihc.com/products/global-insight/industry-economic-report.aspx?id=1065971583>.

⁶³ Ibid.

⁶⁴ http://www.cim.co.cu/commercial_products.php.

⁶⁵ See <http://www.cubacontemporanea.com/en/cuban-scientists-work-lung-cancer-vaccine/>, see also <http://www.vaxira.com/new-therapeutic-vaccine-against-lung-cancer.pdf> and <http://www.ft.com/intl/cms/s/o/b75510d4-cf96-11e2-a050-00144feab7de.html#axzz2WYKHolvb>.

⁶⁶ This information has been confirmed in July 2013 by WIPO's official (email communication)

⁶⁷ Lage Dávila A (2006), "Socialism and the Knowledge Economy: Cuban Biotechnology," *Monthly Review* 58, No. 7 (December) pp53-55. Originally published as "La economía y el socialismo", *Cuba Socialista* (November 2004). Dr. Lage Dávila is the General Director of the Centre of Molecular Immunology in Havana (CIM), which is among the top 3 Cuban biotech companies. CIM is the only Cuban center whose products have been so uniquely innovative that they have been allowed to enter clinical trials in the U.S territory, even with the U.S. embargo against Cuba. Dr. Lage himself is one of the top international Cuba's scientists. He specialized in malignant transformation and cancer vaccines, fields in which he has more than 100 papers published. For these reasons, this research considers his statements as highly plausible. According to Dr. Lage, the Cuban biotech industry has been for several years providing more financial resources to the country than it consumes. He confirmed this in a recent national interview

The last assertion can sound far-fetched at first glance, but taking a closer look at the predominant business model in the worldwide industry, we can at least advance some plausible explanations for this phenomenon. It could be said, for instance, that most of the decision makers in the worldwide industry (U.S., EU-15) have not been paying much attention to the “voice of the industry.” From a sectorial perspective, the biopharmaceutical business presents some relevant features, which also happen to be its most conspicuous organizational challenges. These features can be captured in two elements: Persistent uncertainty and complex knowledge structures (Pisano 2006, McKelvey et al. 2004).

To develop an innovative drug takes years, heavy amounts of R&D, and has a significant chance of failure. As Pisano (2006) states, biopharmaceutical products are “components in a complex system” (p 42), which is a sign of the challenges faced by R&D in this industry. The process of discovering and developing a drug has four major phases: Target identification and validation,⁶⁸ lead identification and optimization,⁶⁹ preclinical phase,⁷⁰ human clinical trials (1, 2, 3),⁷¹ and regulatory approval⁷² (Pisano 2006 p 45-52). Given the lack of causal knowledge in many areas of biomedicine and the absence of high-fidelity testing models,⁷³ drug development remains a highly “iterative and inductive process” with significant levels of uncertainty involved in (*Ibid* p 53-59). One of the implications is that this process requires the integration of knowledge arising from many different fields and business areas, which raises significant challenges in terms of both the financing and the organizational mechanisms to manage and reward risk taking; i.e. institutional arrangement to assure return from intellectual property, scope of the contractual arrangements (e.g., licensing), etc.

The above mentioned has in turn, implications for the innovation strategies and business models employed by the industry. For instance, the question of whether vertical

(August 2011). You can find it here (only in Spanish) <http://www.revolucionomuerte.org/index.php/entrevistas-2/3845-las-razones-del-desarrollo-cientifico-cubano>. This assertion, however, still needs to be confirmed with hard data. This has been up to date impossible to carry out.

⁶⁸ This phase is about finding the specific biochemical pathway, receptor, protein or gene that serves as suitable point of intervention in a disease process (Pisano 2006 p 45).

⁶⁹ This phase is about finding a molecule-potential drug- that can inhibit the target.

⁷⁰ Generating data on the effectiveness of the candidate compound before testing it in humans (Pisano p 49).

⁷¹ This phase is about evaluating effectiveness in humans. It is divided in three or four phases, involving a gradually larger patient population. From these phases, the phase II (proof of concept) is considered to be the most important because it gives a more precise idea about the cost and affectivity of the product.

⁷² A regulatory agency must analyze all the information regarding the drug candidate results in trials; and further approve or disapprove it marketing application. In well-developed innovation systems, a further post-marketing surveillance is carried out by the same or several other regulatory bodies, in order to prove the pharmacological effects of the drug in a huge population.

⁷³ Having identified both the acting target behind some medical condition is no guarantee of success. Targets need to be validated and if a molecule that inhibit that target could be identified, the chance is 1-5000 that this molecule will become a commercially viable drug (Pisano 2006 p 48).

integration or alliances fit better with the need of assuring both that information flows across organizational boundaries, and that specialists in different fields cooperate. But also the question of what mechanism is most appropriate to improve the process of organizational learning in the long term, precisely in an industry with high rates of failure, plays an important role in this context.

The demonstration that these challenges remain lies in the fact that, across the 35 years of existence of modern biotechnology, the overall cash flow of the industry has been negative.⁷⁴ Even worse, the innovation rate in the industry remains very low in relation to the amount of resources invested (E&Y 2011). Over its 35 years of existence the biopharmaceutical industry has generated some 30 blockbusters (defined as at least \$ 1 billion in sales in any one year), which reflects the relatively low overall returns in terms of drug development in relation to the huge amount of funds that have been invested in the industry (Lazonick/Mazzucato 2012 p 15). The fact that small specialized biotech firms are exclusively licensing their government-funded discoveries and that most stakeholders of the industry are not being properly rewarded in relation to both the risk incurred and the amount of resources invested or that most investments are being allocated in marketing and me-too drugs on the one side and on product-less companies and stock- buyback on the other, raise important questions on the sustainability of the current set of institutional incentives in the industry.

Evidence arising from everywhere repeatedly and strongly suggests that the predominant worldwide business model is actually working against the tempo needed by the technological regime of the industry. This evidence ranges from industry reports (Ernst&Young 2008/2009/ 2010/2011/2012) through academics (e.g. Ligth et al. 2011, Ligth and Warburton 2011, Lazonick 2008/2011, Lazonick and Tulum 2011, Chang 2008, Pisano 2006, for papers exclusively on patenting issues see Bessen and Masking 2000, Boldrin and Levine 2008, Clark et. al. 2001, Shapiro 2004, Marengo et al. 2009, Cohen et al. 2000), to politicians.⁷⁵ But let us take a closer look at both history and current form of the biotech business model.

⁷⁴ Since the U.S. accounts for a large majority of the industry's revenues, the U.S. story is very similar to the global one. The industry experienced aggregate profits during the period 2008-2010 for first time in its history; mainly because, since 2008, the American branch of the sector has attained positive cash flow. This was not because of the success of its commercial leaders," but because of steep cost cutting by a broad swath of companies" due to the financial crisis (E&Y 2012 p 25). However, overall results remained negative in Europe, Canada and Australia. In 2011, American biotech net income fell, even after adjusting for the acquisitions of three large U.S.-based companies: Genzyme Corp [acquired by Sanofi-Aventis (France) in 2011] , Cephalon [acquired in 2011 by Teva (Israel)] and Talecris Biotherapeutics [taken over by Grifols (Spain) in 2011] — which collectively had revenues of US\$8.5 billion in 2010 (E&Y 2012 p 25). As the E&Y Beyond Borders report states, in an industry that has been in the red for the vast majority of its history this "decline in profitability may simply be a sign that things are indeed starting to return to normal (E&Y 2012 p 26).

⁷⁵See

<http://www.ncsl.org/IssuesResearch/Health/StateLegislaturesMagazineMarketingDrugsDeba/t/abid/13788/Default.aspx>. See also <http://keionline.org/timeline-bayh-dole>.

5. Organizational Analysis of the Cuban Biopharmaceutical Industry

5.1. Non-Firm Organizations in Cuban Biotech

The choice of non-firm organizations was made precisely because of their role within the Cuban economy. The organizational framework of the country is distinguished by the predominance (in some times absolute and overwhelming) of government-based, non-firm organizations (ministries, associations, government bodies, etc.) that have provided the most important component in Cuba's predominant non-market forms of allocation.

The Cuban biotechnology industry has not been an exception, but actually the confirmation of the rule. However, this industry has managed to show more superior outcomes than the rest of the Cuban industries.⁷⁶ This raises several questions: What did the government do right this time? 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? And most importantly, did government's non-firm organizations play a role here? These are the kinds of questions motivate this analysis.

There is almost universal consensus among Cuban scholars and practitioners on the fact that the most relevant underlying catalyst of this success is the high degree of integration between research organizations, universities, the health system and the governmental regulatory authorities. This kind of integration has been consciously fostered by the government since the very beginning of the industry; precisely pursuing the aim of ensuring organizational learning and social efficiency.⁷⁷ Of course, that is not to say that they knew exactly what they were doing, or the outcomes of their actions. Actually, innovation involves a complex process of cumulative search and experimentation in the presence of uncertainty. Indeed, many of the governmental decisions were a result of past experiences and mistakes, the most resounding being the failure of the electronic industry in Cuba. However, even in this case, government's ability to strategically allocate its resources allowed this failure to be (at least partially) compensated by redirecting these technologies into another successful branch within the biotech industry

It could be theorized that this process has not only created social efficiency in that it has activated cost-reducing mechanisms through networking effects and economies of scale and scope, but also cost-effective innovation-effects through user-innovation diffusion. "If user-innovators do not somehow also diffuse what they have done, multiple users with very similar needs will have to independently develop very similar innovations—a poor use of resources from the viewpoint of social welfare" (von Hippel

⁷⁶ For example, according to a report of the Economic Commission for Latin America and the Caribbean (ECLAE) the gross income per employee provided by the Cuban biotech industry is double that of the tourism industry; the latter seen by many as the engine of Cuban economy. See, *Estudio económico de América Latina y el Caribe* • 2009-2010, pp245-250.

⁷⁷ Of course this is not to say that they knew exactly what they were doing or the outcomes of their actions. Actually, many of the governmental decisions were a result of past experiences and mistakes. The most resounding was the failure of the electronic industry in Cuba. However, being able to strategically allocate its resources, this failure was redirected into another (at least partially) successful branch within the biotechnology. More on this later.

2005 p 9). But what kind of organization is activating all this collaboration and integration mechanisms?

In the particular case of Cuba, several ministries and government bodies have introduced government-based research programs for the promotion of indigenous technological capabilities. In fact, the development and production of pharmaceuticals in general – and biotechnological products in particular – is without doubt the most successful example of the Cuban R&D programs.⁷⁸ Over a period of 20 years or so, the Cuban government invested around \$1 billion US\$ to develop the country's first and most important science node – that of West Havana – composed of about 60 facilities related to biotechnology.

However, the existence of this phenomenon, is not limited to a strongly government-controlled (or centrally-planned) economy, but is instead common to almost all catch-up and technology policy experiences – not only in the biotech but in other high-tech industries as well.⁷⁹ For example, as already mentioned, the role played by the U.S. government's National Institutes of Health (NIH) in supporting the creation of American biotech; as well as its contribution to maintaining the US lead in this industry has been crucial (Chang 2002, Lazonick/Tulum 2011, Mazzucato 2011, Ligth/Warburton 2011). Countries such as Germany,⁸⁰ France,⁸¹ and the U.K.⁸² are also known for their government-funded research sectors (Senker in McKelvey et. al. 2004 p 112-113). In actual fact, successful examples of innovation show that state-funded labs and other non-

⁷⁸ Clark (2010), UNESCO Science Report, pp 123-131.

⁷⁹ Consider the example of institutions such as MITI in Japan, KIST and KAIS in Korea, ITRI and ERSO in Taiwan, DARPA and the National Academy Foundation in the US and so on. As mentioned in previous chapters (3 and 4) most of the most today's successful firms in the industrialized world are strongly related to these government agencies. Examples of other countries can be also found either in current or in past periods (See Chang 2002, Cimoli et al. 2009).

⁸⁰ Consider the programs of the Federal Ministry of Education and Research (BMBF: Bundesministerium für Bildung und Forschung) as executive arm of federal public R&D policies: The most renowned of these policies programs are BioRegio and BioProfile.

⁸¹ Consider the Agence Nationale de la Recherche (ANR), pôle de compétitivités, Oséo and the creation of a specific status for young innovative enterprises. Moreover, it has been created a sort of task force for health care industries called Comité Stratégique des Industries de Santé (CSIS). And last but not least, regional administrations very often offer some form of public support to biotech, through incubators or subsidies. Since 2004 research policy tries to increase finance for public research and collaborations with private companies. Due to the multiplicity of sources of funding from public institutions (CIR, pôles de compétitivité, Oséo, regions, etc.) an estimation of total public support is difficult to perform. Yet the state is clearly investing to develop biotech and other innovative industries through different schemes.

⁸² Venture capital market tends avoid the early development phases. 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. According to Mazzucato (2011) the MRC, a public funded lab in the U.K., receives annual “grant-in-aid” funding from Parliament through the Department for Business, Innovation and Skills (BIS). It works closely with the Department of Health, U.K. research councils, industry and others stakeholders to identify and respond to the U.K.'s health need.

firm organizations have been involved in the most risky phases of the research (Lazonick/Tulum 2011, Mazzucato 2011, Ligth/Warburton 2011).

If we take all this historical evidence seriously, a somewhat striking similarity (mostly for history-unaware scholars) arises from the fact that there is nothing special with the Cuban state investing and being strongly involved in biotechnology (or any other frontier technology) because everybody else has done it. However we still have different performances. Why does the American biotech industry perform differently than the European one? Why has the Cuban biotech industry achieved a pretty interesting pipeline and several innovative (and much more affordable) products while investing less than other biotech industries in both the developed and the developing world as well? As already pointed out, we should not assume a linear link between R&D investment and innovation and economic development. The difference might rather be found in the strategy and in the specific institutional-organizational setting, i.e. which institution or organization carries out what function.

Policies following sectorial development have generally been dependent on the particularity of the underlying institutional settings. Therefore, to be able to advance reasonable policy measures, it is necessary to know the specific institutions and type of organizations that shape an innovation system. But, at the same time, it is necessary to acknowledge that the aim has always been that of activating sector-specific mechanisms. Sector specificity is determined by the predominant technological regime that embodies the developmental function within the industry; i.e. learning requirements of the industry, type of technology, product cycle, markets access, etc. In other words, from a cross-country point of view, what varies is the institutional and organizational form that carries out the developmental function, not the function itself. Usually, an organization carries out more than one function simultaneously, as will be seen below.

5.2. Cuban Biotechnology: A Story of Functional Integration

The Cuban biotechnology industry has a huge cross-sectorial institutional structure, whose affiliates are parts of different ministries. Its beginnings are to be found in the early 1980s. By the end of the 1970s, Cuba had developed a well-integrated structure comprising higher education, biomedical science and the public health system. Strong investments in medical schools and in a comprehensive health system were made around the same period. This created the pool of trained specialists who became the very base of the 1981's Biological Front (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 biotechnology industries. This sort of scientific think-tank was characterized by a flexible, cooperative and collective work style, and the main idea behind its creation was to put high-quality researchers from different organizations together, in order to fill the gap between science and economy. During previous decades, the government had been able to create a critical mass of scientific, as well as number of other important institutions. However, a strong linear conception of technological development had been followed, which led to weak linkages between R&D and technological development. Practice showed that investment in R&D alone does not automatically lead to innovation. Government active policy was needed, concretely from the Council of State.

The first product obtained was Interferon (IFN- α) in 1981. Six Cuban scientists were sent to Helsinki in order to be trained in the production of interferon as developed by the Finnish Serum Institute⁸³. After they had obtained their training, a special laboratory was set up in a small house in Havana to see if they could reproduce the Finnish results and produce IFN- α in Cuba. By the end of 1981 the first interferon had been created in Cuba. In 1982, the Centre for Biological Research was created, in order to continue this work.

In 1992, after several pilot projects, the West Havana Biocluster was officially inaugurated. In subsequent periods, new facilities have been gradually included in the industry, contributing to its growing organizational complexity. The industry is currently comprised of over 300 biotechnology centers, ranging from large, modern facilities to small, modestly-equipped labs, conducting research and developing pharmaceuticals and vaccines. Foremost among these new centers is the complex of around 60 organizations, many of them located at the West Havana Biocluster,⁸⁴ employing approximately 10,000 workers and more than 7,000 scientists and engineers. Among these 60 actors, there is a relatively small group of firms that represent the core (strategic network) of the industry.

The industry can be therefore be described as a set of organizations that join their efforts, cooperate, and integrate, whenever is necessary in order to cover national public health demands and exports. That is, as a network of agents interacting in a specific industrial area under a particular institutional infrastructure."⁸⁵ This system could be considered part of a large Cuban Medicine/Public Health sectorial innovation system, that is, "a group of firms (organizations)⁸⁶ involved in developing and making a sector's products and in generating and utilizing a sector's technologies."⁸⁷

The notion of links among the firms brings us to that which this study considers the most important aspect of the organizational integration within the Cuban biotech industry: sustained and institutionalized inter- and intra-organizational collaboration. The strategy behind the Cuban biotech categorically excludes competition between

⁸³ In 1980 oncologist Richard Lee Clark, president of MD Anderson Hospital in Houston, Texas, (the first cancer hospital in the United States) travelled with a North American delegation to the island. There he met the then Cuban president, Fidel Castro, with whom he discussed his groundbreaking research on interferon, a "wonder drug" in the battle to cure cancer. Shortly after that, Clark hosted two Cuban scientists at his hospital in Houston, sharing his research and expertise. After Houston, the next stop for Cuban researchers was the Helsinki-based laboratories of Dr. Kari Cantell. Clark had visited Cantell in 1979, shortly before his trip to Cuba, and directed the Cuban scientists to seek Cantell's expertise. Cantell was the first person to isolate interferon from human cells in the 1970s. In 1981 a group of Cuban scientists headed by Manuel Limonta spent a week working with Cantell and his colleagues learning the procedure to reproduce interferon in large quantities. See "Cuba's Pharmaceutical Advantage," *NACLA Report on the Americas*, Jul-Aug, 2011 available at: http://findarticles.com/p/articles/mi_go1653/is_201107/ai_n58256857/, Bravo (1998), See also "Development within underdevelopment. New trends in Cuban Medicine," Editorial, *José Martí/ Elfos Scientae*.

⁸⁴ On a lesser scale, but by no means with less success, biotechnology has been expanded to other provinces, mainly Camaguey, Sancti Spiritus, Villa Clara, and Santiago de Cuba.

⁸⁵ See also Carlsson et al 2002.

⁸⁶ The term "institutions" was added by the author.

⁸⁷ Breschi & Malerba (1997). P. 131.

individual firms (contrary to that of Silicon Valley) and focuses on collaboration.⁸⁸ The process of linking complementary capabilities (so needed for drug development) has been actively encouraged through both explicit in-house modularity (see below in-house modularity) and different forms of cross-organizational cooperation. The almost absolute absence of commercial competition between firms may sound strange to many free-market (but also less orthodox) economists, but the fact is that historically, dynamic entrepreneurship has increasingly become collectivistic (Chang 2010, Hobday/Perini (in Cimoli et al. 2009)).

Cross-organizational cooperation

The strategic network of the West Havana Biocluster is formed by a small group of in-house modular firms (e.g. CIGB, CIM, etc.) which were until recently under the control of a specific office within the Council of State, which allowed them close ties with the country's central decision-making powers. In March 2009 the responsibility for Cuban biotechnology was transferred from the Council of State to the Ministry of Science, Technology, and Environmental Issues (CITMA). This change was in response to a governmental reorganization process initiated in 2009. More recently, in December 2012, with Decree 307 the Council of Ministers approved the creation of BioCubaFarma (Grupo de las Industrias Biotecnológica y Farmacéuticas), which represents the most significant reorganization of the industry in two decades.

BioCubaFarma is a state holding that consists of 38 companies, including the commercial branches of all research institutions of the Scientific Pole in western Havana and all companies within the Quimefa Group (see below 4.10 Holding companies). As a result, the Quimefa group has disappeared as an independent legal entity. The Quimefa Group was a state holding that represented the Cuban traditional pharmaceutical industry and was devoted to producing small molecules (chemically-based drugs) in order to save the cost of importing them into the country. It mostly produced generics and it was (so to speak) the non-biological side of the Cuban medical technologies. The biotechnological complex of western Havana and Quimefa formally belonged to different ministries, were located in different places in Havana (or outside Havana). Quimefa was supposed to follow a completely different logic.

However, in reality, it worked closely with the biotechnological part of the industry located in West Havana. Therefore, this integration, albeit noteworthy from the legal point of view, does not actually represent a significant shift in the functional conception of the industry.⁸⁹ As the visualization in Figure 8 indicates, at the time this research was being conceived, these entities were still separate legal entities, but already completely interrelated. Therefore they were represented as such.

Nor does this merge lead to any change in our analytic point of view. In fact, it corroborates the logic being followed by the present study, namely, the fact that the Cuban

⁸⁸ This insistence on cooperation and planning instead competition could sound very socialistic for many observers; however it is not a Cuban unique feature at all. In fact, "depending on the estimate, between one third and one half of international trade consist of transfers among different units within transnational corporations" (Chang 2010 p 208).

⁸⁹ BioCubaFarma does not depend on any ministry; it is a completely (government-owned) autonomous entity. But the strategic network of the industry was already working under this schema.

biopharmaceutical industry has its very foundation in a huge integration effort. While developing the visual representation, we were trying to make sense of the separation between the part of the industry devoted to small molecules (chemically-based products produced in the traditional pharmaceutical industry) and the biotechnological sector. However, in our representation (see Figure 8) it is impossible to acknowledge such a functional separation. Notice that, we always refer to the biopharmaceutical industry as one industry, precisely because it made little sense to establish that distinction between the Cuban pharmaceutical and the Cuban biotechnological production. In fact, for similar reasons, it is a distinction that is presently becoming obsolete worldwide (see E&Y 2012 pp 2-6).

The fact that the visualization was made by following relational data reveals the importance of relying on this type of information to better understand the significance of openness and long-term mutual expectation in the innovation process. This confirms the fact that micro learning dynamics, economy-wide accumulation of technological capabilities and industrial development are inextricably related (Cimoli et al. 2009). Even before the changes took place in the industry, the visualization was, somewhat semiconsciously, showing what this merge has made obvious: they have worked all together for a long time. Therefore, even though Quimefa Group no longer exists as a separate organization, we will continue with the same representation, because it was carried out assuming that this holding was already part of a huge, indivisible industry. Additionally, this organization is part of the development history of the industry and its outcomes until the present day.

At the time this clarification is being written (June 2013), the new BioCubaFarma is planning to double exports of the Cuban bio-pharmaceutical industry to more than \$1 billion per year within five years. That would total \$5.076 billion, a huge difference with respect to the previous five years, with total exports of \$2.779 billion. At the same time, the new changes are still in the process of legal accommodation. However, this should not be an obstacle for business to continue given the fact that, as already mentioned, this step toward more integration is like the ripe fruit that had to fall: a logical consequence of earlier moves. Nonetheless, we cannot talk of any significant impact yet. Having made this important digression, we can continue with the story of the strategic network.

At the beginning of the section we observed that the strategic network of the West Havana Biocluster is formed by a small group of in-house modular firms (e.g. CIGB, CIM, etc.). These firms do what industry officials call the closed cycle; and it refers to the in-house completion of all products' development phases (in our view, another word for vertical integration). However, even when each of these companies is equipped to cover the complete product development process, collaborative 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 Cuban biotechnology.

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 organizations, etc.) and orientation of investments around the population's current needs and/or export niches.

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 a knowledge producer, the biotechnology industry requires large amounts of horizontal communication and operational freedom. However, the close contact between companies and government officials 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 above mentioned, the Strategic Decision Body has the major say in the funding decision of the industry. Managers have the task of generating financial returns, but they do not alone control the generated cash flow. Instead, the export revenues go to a Council of State's account, then after deliberation of the Strategic Decision Body, are redistributed to the centers to cover operational costs⁹⁰ 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 center to another, which in turn increases the perception of common interest, collaboration and consensual culture among the employees.

Figure 8 shows a visual representation of the network of organizations that shape the biopharmaceutical industry. The color of the nodes shown in the visualization indicates the function of the organization represented. For the sake of simplicity, the flows of resources are not being represented in this figure. More detailed visualizations, with link color and direction included, can be found in the annex. The main objective of Figure 8 is showing the general idea of the industry and the relations between its agents, without getting into much detail. Note that many of the related organizations are not necessarily in regional proximity (although most of them are) to each other.⁹¹ Therefore it is functional integration, rather than regional integration, under analysis here. This study

⁹⁰ However, the way in which these resources are used (e.g. salary incentives) are decided within the centers.

⁹¹ 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 absorption capacity. As Orsenigo (2006 In: Braunerhjelm and Feldman 2006 eds.) (at least partially) concedes, knowledge flows are heavily structured by a variety of economic and social factors which in many instances do not have any clear geographical connotation. Although he acknowledges the relative importance of agglomerations, he concludes that they represent more the outcome of certain processes rather than the automatic effect of specific preconditions and agglomeration factors (p 217). Actors may be tied together closely in one relational network, but be quite distant from one another in a different relational network.

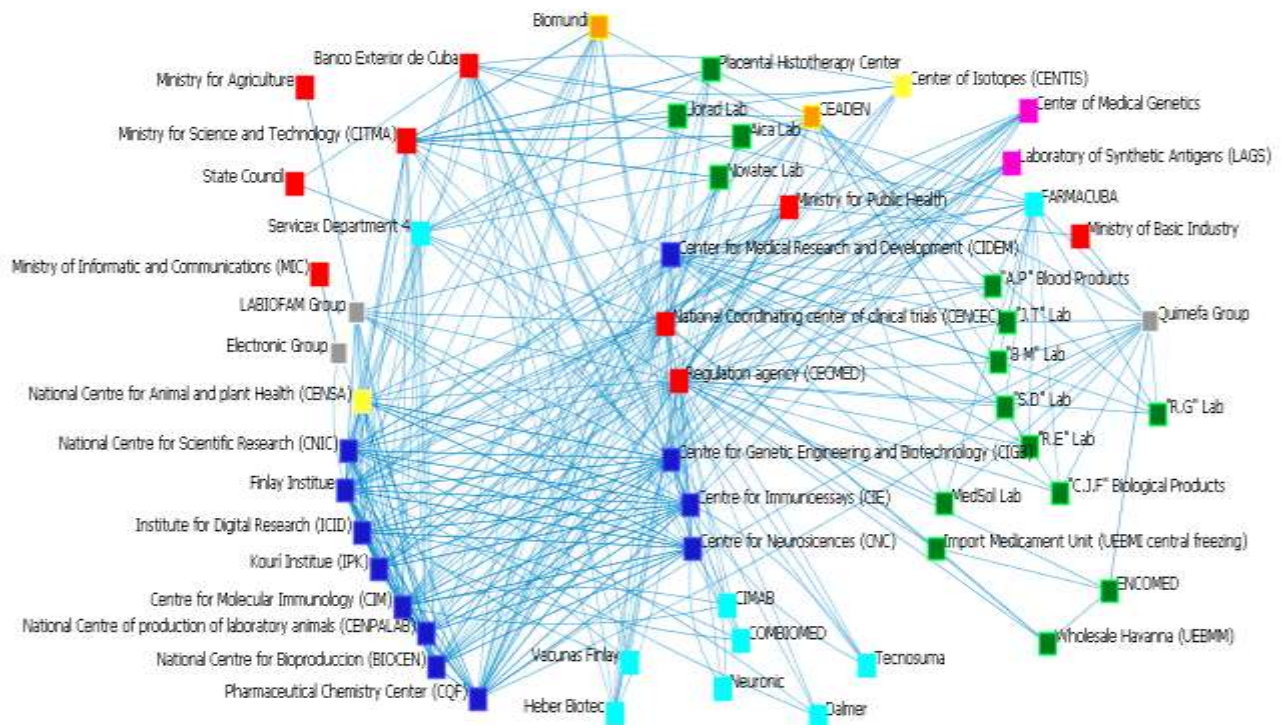
Figure 8 Cuban Biotechnology Network

Legend

- green-----** production firms, i.e. organizations, almost exclusively devoted to the manufacture of vaccines, medicaments and other products
- violet-----** organizations exclusively or mainly devoted to research.
- orange-----** organizations mostly devoted to provide high-tech services to other companies
- light blue---** trading organizations (domestic and international commercialization)
- grey-----** holding organizations of the industry
- red-----** central organizations (NFOs related to regulation, administration and legislation)
- yellow-----** research-manufacturing organization with trading license but without an autonomous commercialization unit
- dark blue--** strategic network

Cuban Biotechnology

Cuba Biopharmaceutical Industry - Network Illustration



powered by ORA, CASOS Center @ CMU

No links are represented (see annex for more detailed visualizations)
 Data: CECMED; software ORA (more detail about the software in chapter 9)

of the Cuban biotech industry focuses on 54 organizations, which have been proven, according to the collected data; to be functionally (in terms of social distance) related one another. Note, however, that we are intentionally omitting a lot of incidental data in order to focus in the most important relations from the point of view of the biopharmaceutical industry. We will make some reference to these supplementary organizations in subsequent sections. However, we will mostly refer to organizations that are included in the network visualization, as most of them have been chosen by following the periodical list elaborated by the Cuban Drug Control Agency (CECMED) which covers the organizations authorized to carry out the kind of activities they do. In addition to the CECMED's data bank, the study has employed public data offered by the companies and non-firm organizations featured in the visualization, as well as personal interviews and written communication with officials and employees, etc.

A. The Central Organizations

The **red** nodes represent the central organizations, which are non-firm organizations related to regulation, administration and legislation. Among these organizations, we can find the different ministries, the State Council and the regulation authorities of the national health system. Ministries such as Agriculture, Basic Industry (Ministry of Energy and Mines since November 2012), Informatics and Communications (Ministry of Communications since March 2013), Science and Technology (CITMA) and Public Health are displayed here. However this section focuses on two more decentralized organizations, whose functions provide them with a very central position in the Cuban biopharma ecosystem: The National Regulatory Agency (CECMED) and the National Clinical Trials Coordinating Centre (CENCEC).

These two organizations not only offer the kind of expertise that contributes to value creation, but also directly participate in the decision making process that shapes the strategic allocation of the resources. More important, for the sake of the argument being made here, is their role by establishing standard interfaces between organizations (or between activities within an organization), which allows reducing assets specifically and easily engage in long-term collaboration and organizational learning. Standards such as uniform employment policies, shared platforms and process protocols can be considered as shared standards that facilitate communication as well as knowledge transfers between heterogeneous organizations.

Shared standards and protocols make the way easier for organizational integration in that they allow organizations to efficiently exchange with multiple partners by reducing enforcement, search and monitoring costs. They provide important incentives to pursue the advantages of flexibility in an industry with a high degree of supply and demand heterogeneity, as with biotechnology. These mechanisms are at play fundamentally because of the existence of regulatory organizations of the health system (CECMED and CENCEC), which, not surprisingly, are related to almost all the organizations. These two organizations are dependencies of the Ministry for Public Health (MINSAP).

A few words about the Cuban Health System

The Cuban Public health system will not be detailed here, because it has already been extensively discussed elsewhere [see e.g. Keck / Reed 2012, Cooper et al. 2006, Richard et al. 2006, De Vos 2009, De Vos et. al. 2008 (a, b), Campion / Morrissey 2013]. However, it would be useful to point out that the Cuban health system is highly centralized in plan

preparation but highly decentralized in plan implementation. It can be conceived of as a huge and very complex network of organizations, of which the biotechnology industry is part. This research is precisely defending the point that the Cuban Biotechnology achievements could not be explainable without considering this industry being part of a broader socioeconomic development strategy, aimed primarily at finding cost-effective solutions to local health. It is the success in accomplishing this goal that has made it possible for Cuban companies to further capitalize their achievements into commercial opportunities by entering the global market as a low-cost producer of high quality products.

Cuban health ideology has been based on the fundamental principle that health protection and care is a right of all and a responsibility for the state. The Ministry of Public Health (MINSAP) controls the national health care system, which is universal and free for all Cubans resident on the island.⁹² MINSAP is in charge of carrying out the government health policy, the general regulation of the medical sector and the conduct of medical research is divided into six vice-ministries and has a further 22 national directorates. At a local level, healthcare provision is the responsibility of provincial and municipal health directorates.

Another important element of the Cuban health policy is its commitment to preventive care, which has led to the creation of a comprehensive community programs, aimed directly at neighborhoods. During the 1960s, the revolutionary government pursued the first set of strategies to transform the country's health care structures when it established a system of integrated community clinics (polyclinics); and moved to train more health personnel. The polyclinic-based system aimed at universal coverage within territorially defined districts and was the first program of the current community-based health care model. Medical care priorities were changed to the point that all graduates were expected to promote human welfare and preventative medicine, but also were expected not to engage in private practice and to perform rural service for three years.

The early municipal polyclinic model (1960s) had showed lack of integration of health care activities across disciplines, persistence of curative over preventive priorities, lack of teaching and research opportunities in primary care, and inadequate coordination of polyclinic relations with hospitals and emergency room. As a result, the polyclinic model of primary health care was corrected and expanded during the 1970s. The system focus shifted at this phase from expressed morbidity to prevention, which contributed to reduce hospitalization and emergency room utilization; and therefore to reduce the use of more expensive services and facilities. Simultaneously, professors and medical residents increased their collaboration in polyclinic activities; thus promoting opportunities for teaching and research in primary care. To further develop the focus on preventive medicine, a new holistic approach encompassing evaluation of social factors and preventive health care strategies was introduced in the 1980s: the family doctor program.

Specifically, the family doctor program was officially created in 1984. The program is based in neighborhood clinics (consultorios) staffed with a physician and a nurse. They are responsible for a number of families in the geographic area surrounding their

⁹² The government of Cuba decided that from May 1, 2010, and thereafter all foreign and also Cubans living abroad shall have a travel insurance which covers medical expenses or a policy for medical expenses with coverage in Cuba. No more free healthcare for Cubans living abroad. See <http://www.cubaminrex.cu/english/LookCuba/Articles/Others/2010/06-04.html>.

consultorio (about 1000 patients per physician in urban areas in 2013), and are more or less integrated into the community they serve. Cuba's medical faculties (currently 22), remain steadily focused on primary care, with family medicine required as the first residency for all physicians. This factor provides continuity for patients and makes it easier to advance disease prevention.

The family doctor networks play an important role by collecting community-based information about specific clinical and epidemiological patterns affecting each region. This allows the creation of comprehensive national records that help determine which health issues pose the greatest risk to society. Virtual infrastructures such as INFOMED⁹³ have contributed to the extension of the family doctor–and–nurse model of primary care, increased interdisciplinary integration of the activities of diverse health care actors, and emphasized continuous data collection, analysis, and dissemination throughout the system (Séror 2006). This information, in turn, contributes to better allocation of resources to deal with risk and channel the sector's creativity in ways that lead to more socially productive innovation. This is astoundingly similar to the patient rapprochement mechanisms included in the new holistic approach envisioned by the new business model Pharma 3.0 (see above Section 3).

In fact, as the 2012 report *Beyond Borders* points out, future talks in the industry will be about the “need to engage with patients by identifying relevant populations... developing ongoing relationships with them and collecting their data with their informed consent. This has the potential to enable better outcomes through an increased focus on prevention and health management...” (E&Y 2012 p. 6). In turn, to have databases with comprehensive patient information would allow for appropriate individuals to “quickly and easily be enrolled once a suitable [clinical] trial comes along”, making it “possible to

⁹³ The information requirements of the Cuban national health care system continued to increase in complexity with the emergence of institutional networks and continuing emphasis on education and research. All of these factors contributed to further development of telecommunications infrastructures to support health care information, communication, and service delivery. These infrastructures reduced institutional health care costs in difficult economic conditions. INFOMED was founded in 1992 as the Cuban National Health Care Telecommunications Network and Information Portal. The virtual infrastructure maintained through INFOMED includes the Virtual Library (Biblioteca Virtual en Salud, BVS) and Virtual University (Universidad Virtual), the Health Information Observatory (Vigilancia en Salud), and key ministerial structures accessible through the portal. Specialized networks connect provincial information centers, research institutes, hospitals, and institutions of higher education (including community level), but also foster communication and interaction with the international scientific community. The Virtual Library integrates access to Cuban electronic publications in medicine and public health as well as important US, Latin American, and international publication initiatives. Medline and the U.S. National Library of Medicine offer subscribed English language bibliographic databases while SCIELO, the Latin American Scientific Electronic Library Online, initiated in Brazil, offers medical journals by country of publication (Brazil, Chile, Cuba, Costa Rica, Spain, and Venezuela) in English, Spanish, and Portuguese. Technical personnel at both the national and provincial network nodes are specialized in network management, the Linux operating system, and system security. While MINSAP is largely responsible for hierarchical control, INFOMED is the vehicle for horizontal communication and coordination throughout the health care system. In 2002, INFOMED was awarded the Stockholm Challenge Prize in the health category for life-improving information technologies (see Séror 2006) see also <http://www.stockholmchallenge.org/project/data/infomed-health-information-network-cuba>).

substantially speed up clinical trial enrolment [and thus to save money]" (Ibid). Nothing could be closer to the approach employed by the Cuban health system since the 1980s. The commitment of the Cuban government towards prevention, integration and collaboration is nothing else than the expression of its financial constraints.

In the 1960s, the government acquired private local producers, and foreign producers reduced imports and closed their plants. The domestic industry was underdeveloped. Foreign subsidiaries controlled 50 percent of the market, importers accounted for a further 20 percent and local production was accountable for the remaining 30 percent (Espicom 2011). In the 1970s, and in order to minimize the impact of the US blockade, the first investments were made in pharmaceutical production plants. These efforts were complemented by purchasing drugs in both Western and Eastern Europe.

Following the collapse of the Soviet Union, East European supplies as well as the hard currency to purchase drugs in Western Europe dried up. Cuba's public health financing experienced a dramatic reduction, from over \$250 million a year in the late 1980s to \$65 million in 1993, only rising slowly to around \$160 million in late 1990s. As a consequence, imported pharmaceuticals represented around 52 percent of Cuba's public health expenditure. As a result, the government implemented a program for import substitution and domestic production of drugs, encompassing a total of 422 pharmaceuticals at a cost of \$75 million.⁹⁴ At the same time, further investment continued to be made in health biotechnology.

However, the foundation of innovation is not only to be found in R&D investments alone. In the Cuban case, it has been more important the openness underlying the government strategy; namely the intentionality to integrate national research and innovation policy. That is, the ability to recognize the need to create standards tools (such as the abovementioned INFOMED) that foster inter-organizational exchange of research and ideas. Indeed, visions such as Pharma 3.0; or the experience of the biopharmaceutical industry worldwide are telling us that integration efforts will not be successful if industry and health system continue to be seen as separate entities (Olson/ Downey 2013). In this respect, as several authors point out, it needs to be emphasized that Cuban organizational innovations such as the family doctor program "represents the first international effort to provide family medicine universally... as part of an integrated national health system." (Eckstein 2003 p 131).

The Cuban health system – Its universal access and coverage, as well as statistical records – has provided a formidable backbone for research, enabling massive informed-consent participation in clinical trials of new medications and vaccines, as well as longitudinal studies on conditions such as chronic vascular diseases and cancer. It helps explain why massive vaccine campaigns can be carried out effectively and rapidly. The case of the vaccine against meningitis B, developed by the Finlay Institute, is an example of this (see below Finlay Institute). In fact, we argue that the integration of biotech and health system has been the foundation of the success of the government's long-term strategy. This strategy has, so far, created the best (maybe the only) example in Cuba of a sectorial system that has proved capable of assimilating the best technology, improving upon it; and organizing the linkages between science, technology and markets necessary to generate higher quality, lower cost products; and necessary for the exploitation of new technological trajectories.

⁹⁴ <http://www.pugwash.org/reports/ees/ees8e.htm>.

Of course, there is no room for romanticizing here. The Cuban healthcare system is not a perfect system. Particularly in the last decade some critics have tried to raise issues such as material shortages and inefficiencies, authoritarian methods in the doctor-patient relationship, ideological bias of the system, etc. Without completely undermining all the critiques,⁹⁵ it needs to be pointed out that the objective of this research is not to criticize the Cuban health system. Instead, our main point is to highlight the good performance of the system in relation to the economic conditions of the country.

In this respect, it is clear that given factors such as the developing country condition of Cuba (in terms of basic infrastructure such as roads, housing, plumbing, and sanitation), the additional shortages imposed by the American embargo and the starting material conditions⁹⁶ of the Cuban health system, the performance of the country's health system should have been far worse than it is. The evidence is found in many countries of the region, which, even with more GDP/per capita and better starting conditions do not perform necessarily better. That is what we do want to explain. In addition, most of the critics (not all of them) tend to show the same ideological bias they are intended to criticize.⁹⁷

⁹⁵ Several problems of the Cuban health system have become apparent in the two last decades: the physical deterioration of facilities and the serious supply shortages caused by the economic crisis in Cuba in the early 1990s, the growing public dissatisfaction related to service instability, wait times, physician absence because of administrative duties, new teaching responsibilities or international cooperation abroad, or the growing costs of the health care. In order to address these issues, a general reorganization of primary care was launched in 2008, followed by a complete reform (currently under way) of the health system in 2010, mainly but by no means exclusively for economic reasons. For example, according to official figures, during the first decade of the new millennium, the health care budget did not decrease. Another delicate problem to be addressed is the material living and working conditions of health professionals. It is well known that the majority of Cuban physicians who have neither served internationally nor have the benefit of supplementary income sources—such as family assistance or remittances—generally experience economic constraints similar to those of other workers in the country (professional or otherwise). These situations, although not exclusive to Cuba, are infrequent in other countries, where professions with significant social recognition—medicine, nursing and rehabilitation specialists, among others—frequently constitute a strata with an income advantage. See Iniguez (2013), “Overview of Evolving Changes in Cuba’s Health Services,” *MEDICC Review*, Vol 15, No 2, April, available at http://www.medicc.org/mediccreview/articles/mr_305.pdf.

⁹⁶ Cuban physicians were highly trained and well respected, but nearly half of them left for the United States when the new government set about drastically reforming the health sector. Thus, from 1959 through 1967, when accumulated expertise was most needed, the island of six million people lost 3000 of its 6300 physicians and found itself with just 16 professors of medicine and a single medical school. See <http://www.saludthefilm.net/ns/cuba-health-system.html>.

⁹⁷ For example see <http://www.miscelaneasdecuba.net/media/pdf/Article-Hirschfeld-Press.pdf>. In this critique, the American anthropologist Katherine Hirschfeld makes a libertarian (and quasi post-modernistic) critique of the system in that she blames the centralized system of all the problems without engaging in any serious debate in this direction. For example, if the centralized system and Marxist ideology are the problem, why do the countries of the region do not perform better? She cites the examples of the Soviet Union and communist China (and suggests that Cuba also does it) as countries that systematically manipulate statistics in order to advance a political agenda. However, apart from the fact that, in the case of Cuba, the contrary has been proven by specialized articles in prestigious journals, the author does not even mention (see

National Regulatory Agency (CECMED)

The task of any drug regulatory agency is overseeing and regulating the medicines market place in order to ensure that manufacturing and distribution are to be made in compliance with international standards (GMP⁹⁸, GCP⁹⁹, GLP¹⁰⁰). The Cuban National Drug Regulatory Agency (CECMED) was created in 1989 by Resolution No. 73 of the Ministry for Public Health as the as a project of the Science and Technique division of this ministry; and was subsequently upgraded as the Cuban National Regulatory Authority. Its main purpose was to centralize and develop all the procedures in relation to the control of medicaments and diagnostic kits. Cuba's medication regulatory agency guarantees protection of the public health through a sanitary control and regulatory system, ensuring

<http://www.thelancet.com/journals/lancet/article/PIIS0140673606684225/fulltext>

doi:10.1016/S0140-6736(06)68422-5), is this only true for socialist countries? Could we say for example that China is manipulating something when they affirm they are growing economically? Without denying that some manipulation can exist, the facts stand by themselves. The collapse of the Soviet Union speaks for itself. Last but not least, she too does not engage in any serious discussion of the real impact of the American embargo on the island.

While these sorts of one-size-fits-all critiques do not stand by themselves, it needs to be acknowledged that problems exist and that a debate about them should be welcomed (see for example the harsh critique contained in a letter to President Raul Castro; written by a team of medical surgeons of a Havana hospital <http://www.cubainformacion.tv/index.php/manipulacion-mediatica/45829-medios-tergiversan-y-anaden-parrafos-a-carta-de-medicos-del-hospital-calixto-garcia-al-gobierno-cubano-leer-verdadera-carta> (Original letter Spanish). However, to highlight the point of the ideological bias of many of the critics, here you can see a manipulated version of the letter, which was evidently made following political objectives rather than objectivity (<http://www.elmundo.es/blogs/elmundo/habaname/2012/09/25/sos-del-servicio-de-cirugia-general-del.html>) (manipulated version in Spanish).

⁹⁸ Good manufacturing practices (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product. The main risks are: 1) unexpected contamination of products, causing damage to health or even death, 2) wrong labels on containers, leading to the patient getting the wrong medicine, 3) not enough or too much active ingredient, resulting in ineffective treatment or adverse effects. See <http://apps.who.int/medicinedocs/en/d/Js6160e/11.html>.

⁹⁹ Good clinical practices (GCP) refers to a standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented. See <http://apps.who.int/medicinedocs/pdf/whozip13e/whozip13e.pdf>.

¹⁰⁰ The notion of Good Laboratory Practices (GLP) is defined in the OECD Principles as “a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.” The purpose of the Principles of Good Laboratory Practice is to promote the development of quality test data and provide a tool to ensure a sound approach to the management of laboratory studies, including conduct, reporting and archiving.

The position of GLP studies within the drug development process is specific to the second stage. See <http://www.who.int/tdr/publications/documents/glp-handbook.pdf>.

that drugs and diagnostics, imported or locally manufactured, are safe, effective and of acceptable quality.¹⁰¹ CECMED is also responsible for approving the Clinical Trials and authorizing marketing, post-marketing and licensing activities.

The effectiveness of these factors allowed the pre-qualification of the Hepatitis B vaccine by the World Health Organization (WHO).¹⁰² In fact, the prestige won by CECMED has allowed it to co-operate with the WHO, pre-qualifying products for the treatment of AIDS, malaria and tuberculosis. It has also directly contributed as expert force to develop the regulatory systems of several countries in Asia, Africa and Latin America. The performance of CECMED and its compliance to international standards is also regularly evaluated for the WHO.

CECMED's most important regulatory functions include drug registration (marketing authorizations), renewal and variation of registered products; and the lot release for vaccines and biological products. It also comprises authorization, inspections and regulatory control of clinical trials; as well as regulatory inspections and granting of licenses in such areas as manufacturing, distribution, imports and exports. That is, CECMED has the power to provide or withdraw the operation license (in case of not meeting the required standards) of virtually all the organizations involved in core activities of the industry (manufacturing, trading, domestic distribution), which, by virtue of the characteristics of the Cuban industry, are themselves well connected to each other. This function makes it probably the most influential organization within the industry.

In addition, this influence allows CECMED to spread and obtain information quickly. The regulatory function of CECMED makes it imperative for this organization to be able to constantly transmit, evaluate and retransmit the requirements for manufacturing permissions, certifications and marketing. The faster good quality information can be spread, the faster and the more productive the rest of the system will function. Likewise, CECMED's multifunctional nature imposes the obligation to constantly identify staff qualification necessities; or to integrate new regulatory capabilities. For example; in 2011, the National Control Centre for Medical Devices (CCEEM) was integrated into CECMED.

At the same time, and responding to the institutionalized cooperation ethos within the industry, CECMED works to integrate approaches with several of the most important companies such as the Molecular Immunology Centre (CIM) and the Genetic Engineering and Biotechnology Centre (CIGB), in close collaboration with CENCEC, to conduct clinical trials in compliance with commonly established criteria and procedures, and to speed the registration process of the products.

Another important factor shaping the performance of CECMED is its emphasis on post-marketing surveillance, including Adverse Events Following Immunization (AEFI). This function became a central objective of CECMED in the year 2000; and particularly after 2005, when a WHO assessment on the Institutional Development of CECMED was completed. However, the most important element here is the cooperation of CECMED

¹⁰¹ Equivalent of the American FDA.

¹⁰² 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/.

with other organizations in order to improve its regulatory performance. For example, there is a National Coordinating Pharmacovigilance Unit that coordinates the National Monitoring System of adverse reactions suspicions produced by drugs.

In addition, the internal organization of CECMED was modified in 2005; in conformity with the benchmark revisions made by a WHO's capacity building program (together with other international regulatory bodies) in order to strengthen the performance of the national regulatory agencies across the world (Pérez /Sanchez 2008). The organizational changes carried out by CECMED included the creation of a national laboratory in charge of physical-chemical-microbiological and biological analysis, as well as the creation of specialized departments in such fields as pharmaceutical inspection. There is also the Quality Division of the former Quimefa (this division has been now integrated into the state holding BioCubaFarma), which oversees the quality of the national industry products. Both CECMED and this division maintain surveillance systems. Every month, the data is analyzed and cross referenced based on the product, batch, manufacturer, place of report, etc., and, this way, the two systems feedback themselves. A monthly meeting is also held to check the results of the systems. All this information is sent to the post-marketing system of CECMED. These work division and collaboration process have allowed minimizing the amount of risky products in the domestic markets. It also gives strong credibility to the Cuban products overseas.

The lack of cooperation and compatibility in the surveillance process is one of the problems faced by the industry worldwide. Consider the example of the US Food and Drug Administration (FDA), by far the best known, and one of the most prestigious drug regulation agencies in the world. According to Light (ed.) (2010), the ability to assess the safety of products after marketing approval of this organization has been increasingly compromised as a result of the deregulation and the influence of pharmaceutical companies.

Despite the new safety initiatives of 2007,¹⁰³ serious problems remain. For instance, many agency information databases are incompatible with each other; and it has, as a result of the chronic under-funding,¹⁰⁴ too few inspectors to monitor the quality of active ingredients (Ibid pp 57-59). Additionally, drug safety has not been given its own organizational division. In fact, the control of side effects "still rests with the division that approved the drug". Many decisions are taken without consulting epidemiology safety specialists. At the same time the agency remains partially funded by the industry it regulates.¹⁰⁵

¹⁰³ We are referring to the Food and Drug Administration Amendment Act passed by the US Congress in 2007. This Act gave the agency new regulatory power, more money and more safety-related mandates (Light ed. 2010 p 57).

¹⁰⁴ According to Light (ed. 2010)) budget cuts of FDA started under President Carter. President Reagan increased the trend by issuing an Executive Anti-regulation Order. In many aspects, industry was left to regulate itself (pp 52-53). Other institutional changes, such as the weakening of the once –legendary federal pension system, has made it more difficult to retain well-trained regulatory scientists, which flow continuously to the industry (Ibid).

¹⁰⁵ Industry financing became law in 1992 under the Prescription Drug User Fee Act, which allowed companies to pay for each new drug application. These fees would provide funds to the FDA. In return, the industry required that 90% of reviews be completed in less time. It also prohibited the use of fees for any post-marketing drug safety activities. An estimated of twenty million US citizens were exposed to drugs approved under this Act that were then withdrawn soon

All these elements have, according Light (ed. 2010), seriously affected the autonomy of FDA and its ability to assess rigorous post-marketing surveillances. In fact, prescription drugs have become the fourth-leading cause of death in the U.S.¹⁰⁶

Likewise, lack of standardization of the new drug application data submitted to FDA has serious implications for FDA reviewers. The applications have extremely variable and unpredictable formats and content, which limits reviewers' ability to address in-depth questions and late-emerging issues in a timely manner. It also impedes timely safety analysis to inform risk evaluation and mitigation strategy decisions, and limits the ability to transition to more standardized benefit–risk assessments (Olson /Downey 2013). In fact, when referring to these limitations, Ron Fitzmartin, senior advisor in the Office of Planning and Informatics at FDA's Center for Drug Evaluation and Research (CDER) recognizes that “[i]t is unbelievable that in 2012 we are still saying that” (Ibid p 55).

National Clinical Trials Coordinating Centre (CENCEC)

The National Coordinating Centre of Clinical Trials (**CENCEC**) was created in 1991, and it is the first Clinical Research Organization (CRO) created in Latin America. Its main objective is designing and executing clinical trials of Cuban products requiring evaluation before entering national and international markets.

The fulfilment of these functions demands frequent review and adaptation of the CENCEC to international trends in contractual clinical trial research; in order to help the Cuban organization(s) to keep up to date. This needs to be done as quickly and effectively as possible; for that reason, this organization possesses a coordinated network of clinical trials at the national level, supported by a specialized staff in each of the provinces of the country for the conduction of these studies.

The structure of CENCEC's site network reflects the non-rivalry ethos of the industry and represents an important organizational innovation, together with the fact that no other country has a national network for clinical trials.¹⁰⁷ Also, it should be recalled that the usual scenario in the worldwide industry is that of CROs and academic medical centers competing head to head for the opportunity to enroll patients in clinical trials.

Corporate sponsors have been able to dictate the terms of participation in the trial and academic researchers may have little or no input into trial design, no access to the raw data, and limited participation in data interpretation terms.¹⁰⁸ The competition for scarce trial sites and the desperate need for product differentiation as a result of shrinking pipelines (expressed in trials with too many endpoints) raises the expenses for recruiting

after for their severe adverse effects. Corporate fees went from one-tenth of total FDA funding to more than half (Light ed. 2010 pp 54-56).

¹⁰⁶ See

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm>.

¹⁰⁷ See Pascual et al (2011).

¹⁰⁸ Davidov et al, Sponsorship, authorship and accountability, CMAJ • September 18, 2001; 165 (6), <http://www.cmaj.ca/content/165/6/786.long>, See also Light (2010 p16).

trial sites,¹⁰⁹ which in turn leads to more clinical trial work being outsourced.¹¹⁰ The fact that there are a great number of sites worldwide, but not all with the adequate requirements for safety and data collection, has raised concern over product quality.¹¹¹

The peculiarity of the Cuban CRO (CENCEC) is that it works together with academic medical centers. CENCEC's National Clinical Trial Sites Network is composed of hospitals throughout the country. This Network has functional units in the country's medical universities, with more than 30 professionals who divide their time between academic responsibilities and leadership of clinical trials. These clinical studies are conducted using the services of teaching hospitals attached to the medical universities in each territory.

To enhance the Network's effectiveness, sub-centers have been set up in three provinces and coordinating groups in nine provinces, all methodologically subordinated to the CENCEC. Each is responsible for coordination, quality assurance and training of clinical research personnel in its jurisdiction. This relatively high centralization makes possible economies of scale in administration when carrying out the clinical trials and multi-center trials.

For the multi-center trials network be able to work properly, CENCEC provides centralized protocol guidelines of clinical trials (particularly for Phase III) that are to be followed in multi-center trials by clinical sites across the country. The Sites Network helps speed patient recruitment, product development and subsequent approval; but also contributes to researchers' knowledge and skills in conducting clinical trials.

CENCEC also has to work closely with the drug regulatory agency CECMED and at the same time with the sponsoring firms, in order to have the clinical trials approved. A company (sponsor) presents its pre-clinical information to CENCEC, in order to prepare the clinical trial for a given product. Then the CENCEC prepares, together with the interested sponsor, a technical report, which is sent to CECMED for approval.

CECMED (just as FDA in the U.S. and EMA in Europe, or other drug regulatory agencies do) evaluates, then determines, if the clinical trial project is in compliance with good clinical practice guidelines (GCP). If the report gets approved, the clinical trial can be carried out. However, in order to increase the probabilities for this to happen, and in

¹⁰⁹ According to an article quoting data of a Cutting Edge Information survey states that the average per-patient trial costs across all therapeutic areas rose in Phase I from \$15 023 in 2008 to \$21,883 in 2011. In Phase II, the cost rose from \$21 009 to \$36 070. In Phase IIIa, the cost increased from \$25 280 to \$47 523 and in Phase IIIb, cost jumped from \$25 707 to \$47 095. Finally, Phase IV expenses rose from \$13 011 to \$17 042. The article can be found in <http://www.pharmalot.com/2011/07/clinical-trial-costs-for-each-patient-rose-rapidly/>.

According to the article The Cutting Edge surveyed 21 drug makers, 12 biotech companies, nine device makers and 23 contract research organizations. The survey can be found in <http://www.cuttingedgeinfo.com/research/clinical-development/trial-operations/>.

¹¹⁰ For Phase I trials, 58 percent are now outsourced, compared with 35 percent in 2008. In Phase II, the figure is 63 percent, up from 36 percent. In Phase IIIb, 54 percent are outsourced versus 46 percent, and in Phase IV, 51 percent are now outsourced, compared with 43 percent three years ago (Ibid).

Risk proliferation syndrome has made prescription drugs the fourth-leading cause of death in the US (Ligth 2010, ed.).

¹¹¹ See <http://ipsnews.net/news.asp?idnews=40472>.

contrast with the current international practice, the CENCEC combines the efforts of both sponsoring companies and CECMED to review and refine trials designs. Additionally, it provides both advice on preparation of clinical reports for submission to the drug regulatory agency and guidance on clinical product evaluation strategies. Indeed, the CENCEC acts as knowledge bridge between different organizations, as well as between them and the Drug Regulatory agency. The resulting data are put to disposition of other companies through the health-system-based electronic network.

These elements pose the two government-based NFOs among the most influential organizations within the industry. By virtue of their functions, these two government entities are associated with many types of knowledge and resources. Both count on specialized departments and workforces in constant contact with themselves and with the industry (domestic and abroad) in order to stay up to date with the latest technical and procedural information.

This in turn makes it possible for the industry to count on the most actualized regulations and operational standards, for an effective organizational integration (in form of intra-industry and inter-sectorial collaboration) to be able to take place. These two NFOs are at the core of the industrial policy followed by the government. As above noted, they are organizationally subordinated to the Ministry for Public Health, which has a priority status for the Cuban government.

The fact that Cuban regulators are fully government-funded may also explain the good functioning of the industry. Light/Lexchin (2012) propose that the EMA and other regulatory agencies should be fully financed “with public funds, rather than relying on industry generated user fees, to end industry’s capture of its regulator” (p 4). Contrary to the conventional notions, recent research shows that countries with more stringent regulation have actually contributed to a more innovative and competitive pharmaceutical industry. “This is because exacting regulatory requirements force companies to be more selective in the compounds that they aim to bring to market” (Munos 2009 p 964). By making research more demanding, stringent regulatory requirements “promote the emergence of an industry that is research intensive, innovative, dominated by few companies and profitable” (Ibid).

The crucial role of regulators as catalyzers of innovation has also been acknowledged by Pharma 3.0. The most important feature of this holistic approach is the capacity of a diverse set of stakeholders to be open and learn by connecting diverse data sets that allow the creation of common pools of information. These networks could bring together genetic data from patients, claims data from payers, data on failed clinical trials from life sciences companies, insights from disease foundations, etc. (E&Y 2012 p 6).

However, the pooling from data raises the question about standards because the absence of standards undermines the ability to collectively analyze the shared information. It is in this point where it becomes apparent the need of engaging regulators in the making of regulatory regimes that allow different assets and insights to be gathered in real time through more flexible approaches. That means that stakeholders and regulators will need to work together in order be able to encourage new approaches to R&D and clinical trial design. Developing standards will play a crucial role in accelerating the creation of promising R&D tools (e.g. biomarkers and disease models) and can help make drug R&D to be more productive and efficient across the breadth of the ecosystem (Ibid). As discussed above, this is something CENCEC and CECMED have been doing for a long time.

However, “aligning interests in the development of data standards and the sharing of data is not easy” (Olson/Downey (2013 p 45). The search for common interests “requires identifying common values and integrating them into the research enterprise”. Communication and transparency can help identify and spread these common values while also building public trust. It is our contention that in this point Cuba’s life sciences industry has developed a truly comparative advantage. We argue that the story of Cuban biopharmaceutical industry provides a remarkable example of how openness and integration can save significant time and cost. While the lack of information on the Cuban biotech prevent us to provide more accurate data, it would be impossible, without relying in integration, to explain how a country with such constrained resources can produce a huge number of affordable drugs to tackle diseases that run rampant in low- and middle-income countries. According to the WHO¹¹², the industry has more than 90 new products are currently [2013] being investigated in more than 60 clinical trials” in several countries.

B. Firms as Research Spin-Offs

The beginnings of the Cuban biotech industry are found in the early 1980’s. However, the foundation was laid much earlier. Most Cuban biotechnology research centers emerged from already existing centers, as the Cuban state had been investing in scientific research since the 1960s. The main organization created then was the National Centre for Scientific Research (CNIC) in July 1965. CNIC has reciprocal linkages with all organizations of the strategic network. This research-production firm was originally a non-firm entity staffed by a small group of physicians that had graduated just a few years ago, who answered the government call to dedicate themselves to biomedical research. The institution was also staffed by chemists and engineers of different specialties¹¹³. Many of today’s “brains” in the industry received their first scientific training in this organization.

Just as with KAIS in South Korea, the main goal of CNIC in its first years was to increase knowledge of “basic sciences” (mathematics, physics, chemistry, biology) of young medical graduates, and initiate them into research tasks. It was a postgraduate school complementing existing universities and colleges, producing the high-level scientists. To that effect, a series of courses and practices taught by Cuban and foreign professors was organized. After taking these courses, several young researchers won graduate scholarships to study in Western and Eastern European countries¹¹⁴. However,

¹¹² See http://www.who.int/features/2013/cuba_biotechnology/en/.

¹¹³ http://resultados.redciencia.cu/historia/periodo_5_4_en.php.

¹¹⁴ 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 organizations 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 learning capabilities and in-house research effort was required to absorb and to translate the acquired knowledge into innovative world-class products. This is quite consistent with many other catch-up experiences where foreign students, apprentices or broker agents played a central role. Mazzoleni and Nelson (2009) mention the cases of Taiwan, South Korea and Japan and Brazil (see Mazzoleni and Nelson 2009 in: Cimoli et al eds. 2009). We could also add the case of China and India (Ibid). This is nothing different from the industrial, trade and technology policies on behalf of the wool manufacturing industry carried out by Britain from XVI century on (See Chang 2003 p19-24). We could also

an important difference is that KAIS (just as KIST) was much more mission-oriented than CNIC. The Korean organization interacted since the beginning with the industry; while CNIC remained more rooted in basic science and had little contact with industry.

In a few years, and thanks to huge investment in research equipment, CNIC turned out to be the national "center of excellence" for chemical and biological experimental research. In the biological field, special importance was attained by the microbiology, micro-organism genetics and neurophysiology laboratories but also by bio-chemistry and computer sciences, from where important working teams and research centers arose in the eighties. Similar to other countries' experiences ¹¹⁵, this multi-disciplinary organization is considered to be the incubator ¹¹⁶ for the rest of Cuban scientific institutions today; and was established to promote the development of research and training activities in frontier fields.

The success of this spin-off business model was based on elements such as the provision of a costless physical environment to the new firms, which were subsequently helped to grow by sharing support services, such as the availability of secretarial help, a receptionist, and access to copiers and professional services, including acquisition of financial resources, business planning, and legal and accounting ties to international research partners and marketing support.

CNIC functioned as a focal point for access to the broad spectrum of available business services and provided the point of contact for entry into various technology programs. The good results are consistent with the international practice that asserts that incubated companies have a dramatically higher rate of survival than the average spin-off¹¹⁷. Even when the incubator model has experienced transformation in some countries (such as the US) that made it more expensive for small firms to grow¹¹⁸, the Cuban industry remain to the sharing model as a basic paramount. However, the focal role of

mention the role played by Samuel Slater in the development of the textile industry in the United States(see <http://www.woonsocket.org/slaterhist.htm>) or the role played by Peter Beuth as head of the department of trade and industry in the Prussian Ministry of Finance when setting up the Gewerbeinstitut (Craft Institute) in 1820 (see Chang 2002 pp32-35). When going back in the timeline, we find the role played by the French Jesuits priest Francois Xavier d'Entrecolles by revealing the Chinese technique of manufacturing porcelain (Rowe W/ Brook, T 2009, pp. 368), and mercury (see Barnes L, 2005, p.101). Many other examples of this kind can be found in these and other countries, but the point is that technology transfer, be it in form of licensing, joint ventures or reverse engineering, has always been part of a good emulation strategy.

¹¹⁵ KIST during the 1970s in Korea, IRI in Italy.

¹¹⁶ Finland, for instance, is typical of countries that locate incubators to nurture startup firms near universities that host biotechnology centers of excellence, See: Senker et. al. (2000), "European exploitation of biotechnology—do government policies help?," *Nature Biotechnology*, Vol. 18, June. Other examples are to be found in Cimoli et al. (2009) and in Mazucatto 2011).

¹¹⁷ U.S.-based Incubator managers report that somewhere between 80 and 90 percent of companies that have incubated with them are still in existence after five years. This figure vividly contrasts with the Small Business Administration (SBA) statistic that finds that only 50 percent of start-ups survive their first five years. These figures are less surprising when one considers that nine of ten companies fail because of management deficiencies, and that 90 percent of these deficiencies could have been foreseen. See Zablocki EM (2007).

¹¹⁸ Today, however, most incubators prefer the company-centered approach, charging market rates for rent and offering services as the value-added benefit of locating in the incubator (Ibid).

CNIC has been gradually assumed by other organizations within the industry. From its beginnings as an essentially non-firm organization between the 1960s and the 1980s, it has thereafter adopted the form and function of a typical company of the strategic network, by focusing on developing products and integrating a trading arm into its structure.

C. Strategic Network Organizations

As already suggested, most of the firms of the strategic network of the Cuban biotech industry (represented by the **dark blue** nodes in Figure 8) were former departments or divisions of CNIC. This strategic network is formed by a small group of in-house modular firms (see below in-house modularity), which were until 2009 under the control of the Council of State, then work under supervision of CITMA for a short period and now are part of BioCubaFarma, a state holding created in December of 2012 as part of the economic reforms carried out by Raúl Castro.

This nodes group also includes the Centre for Medical Research and Development (CIDEM), which does not directly belong to the strategic network, but offers services (e.g. microbiologic, biologic and toxicological studies) to the centers of the strategic network and to the medical-pharmaceutical (small drugs) sub-network. Its main establishments can carry out processes such as Chemical & Microbiological Control, Chemical Research or the manufacturing of Cytostatic medicaments.

However, this organization plays a more important role in the chemical-pharmaceutical branch by producing and commercializing mostly generics and synthetic products.¹¹⁹ Its main function is still conducting research aimed at supporting different national or sectorial programs directed at import substitution. Founded under Resolution No. 148/1992, CIDEM (Spanish: Centro de Investigación y Desarrollo de Medicamentos) is Ministry for Public Health's (MINSAP) scientific and technical arm.

By taking a look at the ego network or (sphere of influence) arising from the subgroup formed by the in-house modular facilities of the industry (see visualization 2 in the annex) one can see that it covers a big portion of the network. This is consistent with the fact that these facilities represent the core of the industry and exchanges resources with most of the network actors and with almost all the actor of their subgroup.¹²⁰

The linking level within the strategic network is very significant. One reason for this could be that many of these organizations were created from the same incubator, which makes it more probable that those scientists that worked together previously will tend to keep collaborating. However, had an encouraging institutional setting not been there, this close collaboration would hardly have taken place.

Indeed, it is the government decision of creating expedited channels of cooperation (e.g. through absence of exclusive licensing, regular meetings, state ownership of the patents and facilities, no competition ethos of the industry, etc.) among the in-house integrated firms the reason of the high level of linkages among them. Nevertheless, the

¹¹⁹ CIDEM develops antiretrovirals, cytostatic medicines, immunosuppressants such as oral cyclosporines, homeopathic medicines, bacterial endotoxins marketed under the ENDORETO brand, pharmaceutical forms of aloe vera & *Plectranthus amboinicus*, and antihistamines & antiasthmatics.

¹²⁰ Note that the node(s) selected in the visualization will be represented (and henceforth) within a circle.

fact remains that having belonged to the same incubator (CNIC) provided an environment of dynamism and flexibility, which improves the prospects for knowledge sharing and learning.

In-House Modularity

In-house modularity is a definition¹²¹ employed here to describe the governance structure of the core firms (strategic network) of Cuban biotech. The companies of the strategic network of the Cuban biotech industry are *in-house modular* because they are *vertically* integrated firms working under a *horizontal* and non-linear regime (not to confuse with horizontal integration). This concept applies to both intra- and inter-organizational levels and conceives the core firms within the Cuban biotech industry as networks integrated within a wider network of organizations, even when subjected to formal hierarchical control.¹²²

As already discussed, vertical integration means that companies of the strategic network are organized so that research, development, production, marketing, and follow-up evaluations for a given product are carried out within the same administrative unit. Cuban industry officials call this structure the *closed cycle*, which could, in fact, be identified with the notion of a *vertical integrated firm*, in that it refers to the in-house completion of all the product's development phases. However, the term could also be associated synonymously vertical/hierarchical/linear which is employed by a good part of the literature on production networks and value chains (See e.g. Gerefi 2005, Thomson 2003, Williamson 1975).

However, practical evidence shows that vertical and horizontal relations are interlinked in a much more complex way (Coe et al. 2011). That also strongly applies to Cuban biotech. For example, research, pharmaceutical development, pre-clinical and clinical studies, regulatory and intellectual property issues, manufacturing, negotiations, and commercial tasks for the development of Heberprot-P ® (treatment of diabetic's foot) were coordinated by the 'Heberprot-P ® task force. The task force belonged to a product management team, directly subordinated to the General Direction with constant intensive interventions of all institutional directions (research, development, regulatory

¹²¹ In Cárdenas-O'Farrill (2009) the same concept was introduced as "in-house integration". Henceforth it will be used as in-house modularity.

¹²² For example, while Heber Biotec is the trading arm of the Center of Genetic Engineering and Biotechnology (CIGB), it is also involved in the commercialization of products of other organizations without marketing capabilities. That is, Heber Biotec has not only specialized in CIGB products (although vertically integrated within CIGB), but it is also flexible enough to go beyond CIGB product configuration. In contrast to the typical alliances and other short term contracts that take place in the worldwide biotech industry, Heber Biotec has an institutionalized long term commitment to other companies that lack in-house capabilities, which allows more flexibility (modular-like behavior) while at the same time strengthening mutual commitment (more characteristic of vertical integration). This also allows employees to develop firm-specific knowledge (but still highly combinable with other firms' knowledge stock) and loyalty sense, so important in industries such as the biotechnology.

affairs, etc.). That is why the term closed cycle is being substituted with a more encompassing one.¹²³

Closed cycle as vertical integration could also be associated with the traditional purpose that Williamson (1975) reserves for this kind of structure, namely the reduction of transaction costs. However, other authors suggest that in addition to the cost factor, the *accumulation of capabilities* at the firm and industry levels, essentially expressed in form of shared languages, routines and coordination is a central element that explains the vertical scope of firms (Malerba et al. 2006, Schilling 2001 p). In order to avoid confusion between the common definition of vertically integrated companies on the one hand and the actual non-linear and dynamic nature of vertical integration, in-house modularity will be used instead.

On the other hand, the notion of horizontal regimes has been usually linked to the flexibility given by modular forms of production (modularity) as opposed to hierarchies (see e.g. Miles et. al. 1997). In management science modularity basically refers to the property of some production/organizational systems to be decomposed into independent modules and then further recombined (Schilling 2000, Schilling/Steensma 2001). This process increases the flexibility in the end product by allowing a variety of possible configurations to be assembled, thus increasing the opportunity costs of those producers that stay in a single configuration. Products can be made increasingly modular by adopting a standardized interface that makes the product compatible with other firms' components.¹²⁴ This process is influenced by factors such as heterogeneity of inputs and demand¹²⁵ and utilized by the semiconductor industry, as well as the automobile, computer and software industries.

However, the very notions of market and hierarchy as distinct and clearly distinguishable categories is problematic because it tends to obscure the fact, that in practice, the configuration of the system of production and distribution is far more complex and dynamic than is usually assumed (for further discussion see Coe et al. 2008). There are industries, with high heterogeneity in inputs and demand, whose characteristics however, make it very difficult for them to work under a modular regime, because most of their underlying technologies are hard to codify. As above discussed, this is the case of biotechnology, where to develop a product requires constant interaction between the agents involved in the process, thus making a shared experience a critical asset (Pisano 2006 149-152). This element might at least partly explain why the most successful companies in the industry have been integrated under the FIPCO model.

¹²³ That is also considering that many industry officials (and academic experts) tend to use the term, partly unaware of its possible theoretical implications, while ironically trying to express the same notion covered by the term in-house modularity.

¹²⁴ Visible consequences of this process are phenomena such as large-scale downsizing and outsourcing, which have conquered the industrial landscape of the last three decades in both developed and developing countries. A very detailed discussion on the subject can be found in Lazonic (2008).

¹²⁵ The inputs into a product system include both the technological options available to achieve particular functions and the resources and capabilities of the firms involved in the production process. Heterogeneity in these inputs will increase the value to be obtained through modular product configurations (Schilling 2000).

At the same time, the high levels of input and demand heterogeneity shown by the biopharmaceutical sector signal the possibilities of knowledge recombination (and thus innovation) that could be obtained if the system were able to exploit the potential offered by modularity. In fact, in the worldwide industry certain institutional incentives have made R&D companies, universities and public research organizations within the industry more prone to try to profit from these conditions by generating proprietary knowledge and exclusively licensing it via short-term based alliances. However, the output of this trend toward industry disintegration has so far been very disappointing as a business model, perhaps, precisely because the need for integration has not been sufficiently heard.

In this context, the Cuban biotech industry has been organized in such a way that the components of its vertically integrated (and most important) companies also have the ability to take advantage of the gains of modularity while successfully dealing with the strong pressures for integration of the industry. For example, the product HEBERKINASA®, employed in emergency rooms in case of acute myocardial infarction, was produced by CIGB’s facilities for more than 15 years. After effectiveness was demonstrated; and emergency departments became more acquainted with the product, it was decided to transfer the technology package to BIOCEN (see below D). However, CIGB does not have to worry about losing the capabilities acquired during those 15 years because there is no mutual blocking between these organizations. That is, openness and collaboration are constantly encouraged.

Through the existence of NFO-based technical and organizational *standard interfaces*, vertically integrated firms (such as CIGB, CIM, Finlay Institute, etc. see below) do not become knowledge fortresses unable to interact with the rest of the industry. Rather, they have become the most important innovation agents within the Cuban biopharmaceutical complex. Indeed, these companies have developed in-house competences in most of the technological knowledge of the specific markets they compete in, which puts them in a better position to design communication standards with the rest of the participants. NFO-based standard interfaces allow specific assets to become less specific thus facilitating knowledge exchanges between heterogeneous organizations.

Indeed, when it comes to disruptive innovation, some *de facto* industry standards usually precede the existence of voluntary and consensual standards. That applies more than ever to the biomedical sector, where, among a number of issues, many researchers and practitioners also stress the important role of regulators by creating the standards that will allow clinical trial data to be shared. Shared clinical data is expected to contribute to innovation by allowing available data to be reused at no cost, thus increasing the chances for new drugs to be developed (Olson /Downey 2013 eds.). However, standardization of such complex data as those produced by clinical trials is needed upfront. The rules for collaborative expert input and consensus need to be established by regulators along with standard development organizations (usually NFOs). This, in turn, requires political will.

For example the European Medicines Agency (EMA), the NFO which regulates drugs and biologicals in Europe, has very recently taken the position that clinical trial data will no longer be considered commercial confidential information (Ibid p 58). EMA’s officials recognize that this measure puts many people from industry “outside their comfort zones” (Ibid). However, they also acknowledge it has to be done because the industry is moving toward a new model of openness in which data are made available for others to reanalyze and combine with other data. In fact, Light/Lexchin (2012) observes that EMA “does

Europe a disservice by approving 74 percent of all new applications based on trials designed by the companies, while keeping data about efficacy and safety secret” (p 2). Consensual standards make it much easier to engage in broad-based cooperative projects, but people and organizations need the right incentives to contribute (if not always voluntarily) their data. This context demands for regulators to issue the corresponding upfront standard.

These standards can take the form of technological interfaces and organizational interfaces such as process protocols, uniform employment policies, and shared platforms such as regular meetings of institutional directors, the creation of inter-institutional task teams for specific projects, non-exclusivity licensing¹²⁶ within the industry and other forms of cross-organizational cooperation. Most of the products of Cuban biotech have been developed as a result of the cooperation between several organizations.

Notice that the term *vertically integrated* will continue to be used when referring to cases others than Cuban biotech. Among other reasons in order to show that very often what is meant as “vertical integrated” in traditional sense (hierarchical, resulting from market failure) could actually be defined as “in-house modular”. Even if organized as a formal hierarchies, Cuban biotech firms cannot be understood as hierarchical and linear structures only designed as a result of market failure, but as in-house modular structures which are crucial for product and process innovation. Below is a summary of the role of these organizations in the existence of the Cuban biotech industry.

Centre for Genetic Engineering and Biotechnology (CIGB)

The CIGB is the Cuba's biotechnology leading research-production organization. This in-house modular company has 20 years of experience in the production of recombinant biopharmaceutical molecules such as interferon, Hepatitis B vaccine, Synthetic Haemophilus influenza type b vaccine, Tetra- and Penta-valent combined vaccines, streptokinase, epidermal growth factor formulated in different forms, monoclonal antibodies and other products, which are already producing a positive impact on public health in Cuba and a positive cash flow from sales to more than 50 countries¹²⁷. Many of these products have been certified by the World Health Organization (WTO), e.g. the Hepatitis B vaccine. This is by far the most innovative company of the industry. CIGB operates 12 manufacturing plants and as of 2011, had six operational licenses.

The beginnings of the genetic engineering in Cuba date back to 1977. At that time, researchers of the Microorganism Genetic Department (MGD)¹²⁸ of the CNIC were working on the genetics of microorganisms and molecular biology. In 1981 the Biological

¹²⁶ The firms still retain their proprietary technologies (patents, secrecy, etc.) but these technologies work within an open standards-based production system, so that companies can reap the gains of compatibility with a wide range of complementary knowledge while still retaining the rent-generating potential of their proprietary component. Different technologies can coexist more peacefully because they are made compatible.

¹²⁷ <http://gndp.cigb.edu.cu/index.html#>. A complete list of the product in which CIGB has been involved can be found in <http://www.heber-biotec.com/Ingles/default.htm>.

¹²⁸ A significant part of the work was actually being doing by Dr. Luis Herrera, the then head of the department and current president of CIGB. According to Bravo (1998), there was actually a different group working molecular biology, but the book also acknowledges that Herrera was also an expert in this field.

Front was created, in order to obtain leukocytes interferon (a group of proteins with antiviral properties). As early as 1978, researchers at the MGD knew about the possibility of recombination.¹²⁹

Production of interferon (IFN) obtained from human leukocytes began to take place as early as 1981 in a small lab staffed with a group of workers of the CNIC. But at the same time, there was increasing interest in obtaining the recombinant IFN because it had soon become evident that the demand for the product couldn't be met with the leukocytes obtained from the country's blood banks. Consequently, it was decided to produce it by genetic engineering, which would provide in the long term a much cheaper method; since it allowed mass cultivation and purification from bacterial cultures.¹³⁰

Then, parallel to the production of IFN leukocytes, which was being created in a separated lab, a lab for obtaining IFN recombinant was set up. Afterwards, both groups started to work together forming the Genetic Engineering group. After learning that the recombinant IFN had been already obtained by Tamaguchi in Japan and Weissman at Hoffman-La Roche labs, the Centre for Biological Research (CIB) in 1982 was created and the group began to work in that direction. The IFN beta (1983), alpha (1986) and gamma (1988) were created shortly after the pioneers in the field. Further government investment led to the creation of the CIGB.

In 1981, UNIDO (United Nations Industrial Development Organization) decided to create a center of excellence for the transfer of biotechnology to developing countries. Cuba applied for the vacancy, but it was awarded to India. The Cuban Government then decided to create its own center. On July 1, 1986, the (CIGB) was inaugurated, and CIB became a division of it.

This vast research-productive complex has about 1400 staff workers, including 550 scientists and engineers work in more than 50 research and development projects. It is staffed with state of the art equipment in several fields including the most recent technologies (genomics, proteomics, etc). The project portfolio of CIGB is covered by more than 70 inventions intellectually protected by more than 1900 patent application worldwide. CIGB has published 680 peer-reviewed papers in scientific journals (from

¹²⁹ Recombinant technology was discovered by Cohen and Boyer around 1975 (1972-1973 first papers and 1974 application for patents). The first drug using recombinant technology was insulin, manufactured by Genentech (which had been founded by Boyer and the venture capitalist Swanson) and licensed by Elli Lilly.

¹³⁰ The difference is that the leukocyte IFN contains different types of IFN's. The recombinant version allows obtaining a purified IFN type, which makes its production more economical. The possibility of recombinant IFN had been expressed by Pestka, of Roche Institute in 1978. Genentech labs and several other were simultaneously trying to be the first obtaining it, but it was finally obtained by first by Taniguchi, a Japanese and then by Weissman Lab at Biogen, the competitor of Genentech. A couple of months later, the Pestka lab cloned interferon cDNA for both IFN-a and -b on the same plate and then contracted with Genentech. After that, Genentech did not expand the deal with Hoffmann-La Roche and the IFN gamma was obtained in collaboration with Boeringer Ingelheim and other Japanese partners. See David V. Goeddel, Ph.D., "Scientist at Genentech, CEO at Tularik," an oral history conducted in 2001 and 2002 by Sally Smith Hughes for the Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 2003, see also Fitzgerald- Bocarsly P(1997), The History of Interferon: An Interview with Sid Pestka, at: <http://www.isicr.org/newsletter/isicr4.2.pdf>.

1986 to 2006) and they have been cited in more than 3000 papers.¹³¹ The hepatitis B vaccine manufactured at the CIGB has reduced the incidence of this infectious disease in Cuba from 376 cases in 1991 to eradication in 2000, it has been on the WHO's list of vaccines purchased by UNO from 2001. \$220 million worth of vaccine were sold in 10 years and 100 million doses have been used.¹³² This vaccine was first obtained in 1986 by employing recombinant methods, quite Avant-garde at the time.¹³³ CIGB's manufacturing plant N° 1 is devoted to the production process of the recombinant Hepatitis B surface antigen, which is also the API for the vaccines HEBERBIOVAC-HB®, TRIVAC-HB®, and HEBERPENTA®.

As is the case with most of the in-house modular facilities, the CIGB engages in reciprocal resource exchange with the rest of the organizations of its subgroup. For example, the manufacturing plant N° 4 has to do with the production of new pharmaceutical products derived from the results of the CIGB's biomedical research activity. The first lots for clinical trials are manufactured in this facility, operating under clean room conditions. It is also intended and designed to perform contract manufacturing operations, according to commercial agreements with partners. At the same time, lots of APIs for clinical trials of CIM's lung cancer vaccine have been also manufactured in this production facility. In turn, plant N° 10 is a review and packaging facility for products manufactured in Plant N° 4 and other products that can be processed in this productive area.

On the other side, a relatively exclusive relation arises with organizations outside the subgroup. This is obviously due to the fact that the CIGB is the research-production organization that most exploits economies of scale and scope by collaborating with other facilities (within and outside the strategic network).

A relative recent example is the collaborative relation established with the small Laboratory of Synthetic Antigens (LAGS), which belong to the University of Havana and had no manufacturing capabilities to scale-up the first worldwide synthetic vaccine anti-*Haemophilus influenzae* type b Quimi-Hib® for clinical trials; developed by them. Large-scale production was made possible by the CIGB's staff, a few months after the vaccine discovery. The pharmaceutical facility Plant N° 3 is devoted to the manufacture of the API of the vaccine in accordance with regulatory requirements of CECMED. The vaccine's API

¹³¹ <http://gndp.cigb.edu.cu/index.html#>.

¹³² Ibid.

¹³³ The hepatitis B virus was discovered in 1965 by Nobel Prize winner Baruch Blumberg. Four years after discovering the hepatitis B virus, the first hepatitis B vaccine was developed, which was initially a heat-treated form of the virus. In 1981, the FDA approved a more sophisticated plasma-derived hepatitis B vaccine for human use. Merck Pharmaceuticals manufactured this plasma vaccine as "Heptavax," which was the first commercial hepatitis B virus vaccine. Dr. Saul Krugman played a significant role in this research. See http://www.hepb.org/professionals/hepatitis_b_vaccine.htm. See also http://library.med.nyu.edu/library/eresources/featured_collections/krugman/index.html. In 1986, Chiron developed the technology to obtain genetically engineered (or DNA recombinant) hepatitis B, which was licensed to Merck (according to an article of the *New York Times* In: <http://www.nytimes.com/1986/10/13/business/biotechnology-spotlight-now-shines-on-chiron.html>). The Cuban recombinant vaccine was also developed in 1986 at CIGB, which illustrates how the biotech industry of Cuba was right at the forefront of the technological frontier.

is from two primary raw materials, supplied to the CIGB by Vacunas Finlay, S.A, the trade arm of Finlay Institute).

Centre for Neurosciences

Another example of research spin-off resulting from CNIC is Cuba's Centre for Neurosciences (CNC). The origins of the organization date back to 1966, when a small Neurophysiology unit was created in CNIC in order to introduce the application of quantitative and automated methods for the analysis of the brain's electric activity. Concretely, the objective was to develop computerized equipment to analyze electrical brain signals, and eventually create instruments for early diagnosis of neurological, psychiatric, and development disorders.¹³⁴

In 1969 neurophysiology unit's researchers had access for first time to a CAT-400C¹³⁵ computer, donated by U.S. scientists, for computerized evaluation of brain disorders. During the early 1970s, Cuban brain's researchers also collaborated with US colleagues on developing one of the earliest methods for computerized (also called quantitative) electroencephalogram (qEEG) analysis or neurometrics.¹³⁶ At the same time, the development of the first Cuban midrange¹³⁷ computer in 1970 (see below ICID) allowed both experimenting with and exploring the potential of endogenous technology. This

¹³⁴ At the time, there were only five research groups in the world who shared those same objectives. See Reeds/Torres (2008), *Riding the Brainwaves of Cuban Science: Interview with Pedro Valdés Sosa, Vice Director for Research and Director of Neuroinformatics Cuban Neuroscience Centre, Havana, MEDICC Review, Spring, Vol 10, No 2.*

¹³⁵ The Computer of Average Transients (CAT) was invented in 1960 by the Austrian-born musician, scientist and inventor Manfred Clynes with the objective of measuring brain electrical activity. This machine, one of the first special purpose digital computers, was used around the world and greatly furthered brain research.

¹³⁶ Neurometrics is the science of measuring and interpreting brainwave frequencies. The term was coined after a homonymous foundational paper was published in 1977 by *Science*. This paper happened to be the result of the close collaboration between Dr. Erwin Roy John (1924-2009), a world renowned American neuroscientist and pioneer in the field of Neurometrics; and other scientist, including Dr. Pedro Valdés-Sosa, pioneer of the field in Cuba and founder (and current director general) of the Cuban Neuroscience Centre. In fact Dr. Valdés is registered as co-author of this foundational paper, which, as in the case of other disciplines within the Cuban biopharma, gives an idea of how cutting edge was the knowledge that many Cuban scientists were dealing with at that time. Actually, they were not only catching up, but co-pioneers in many fields (see the paper John ER et. al (1977), "Neurometrics," *Science* 24 June 1977, Vol. 196 no. 4297 pp. 1393-1410, DOI: 10.1126/science.867036, available under <http://www.sciencemag.org/content/196/4297/1393.citation>). At the same time, the mentoring role and long-term collaboration of Dr. John with young Cuban scientists at that time (and thereafter) has gained recognition among Cuba's neuroscientists and policymakers (see <http://www.ecnsweb.com/roy-john.html>).

¹³⁷ A contemporary term for "minicomputer", which is the kind of computer developed during the 1960s, whose size ranges between the big mainframe and the microcomputers. The Americans recognized UM1-NX, produced at the Leningrad Electromechanical Plant (LEMZ) from 1963, as the world's first mini-computer. In a review of Soviet computers published in *Control Engineering*, (no. 5, 1966) with the title "Desktop Model," the UM1-NX was described as "remarkable" for its size and low energy consumption (see <http://web.archive.org/web/20080804025916/http://sovietcomputing.com/node/49>). However they were unable to keep the pace after the microprocessor revolution.

made it possible for Neurophysiology unit's researchers to develop in 1972, in close collaboration with the Ministry of Public Health, the first prototype of the MEDICID-01, the first Cuban computerized EEG system.

The research activity of this small division took a different level when MEDICID-03, the first Cuban digital diagnosis equipment and the first exportable item (to Mexico) was developed in 1982, which led to the creation of a full department of computational Neurosciences,¹³⁸ still subordinated to CNIC. The main purpose of the department was to improve this technology, made mostly of Cuban-designed and Cuban-manufactured hardware,¹³⁹ and to introduce it in to the national health system. This laid the foundation for the development of a national neuroscience diagnostic network in the 1980s, which, in turn, enabled the center to launch in 1991 one of the world's first national programs for early detection of hearing loss (Valdés/Obrador 2009). In 1992 Cuba became the world's first country to systematically introduce the use of quantitative electroencephalogram (qEEG) in a public health system. In 1990 MEDICID-3E became the first Cuban qEEG equipment registered in France and Switzerland (Ibid).

Since the 1980s, five generations of this equipment have been designed and produced, expanding functional capabilities along different lines under the Neuronic trademark. In 1990 the Council of State created the Centre for Neurosciences as a Research-production facility, but still as a department of the CNIC. Structurally, the CNC was composed by a mixture of the previous department and a division of the Institute for Digital Research (ICID). In 2005 CNC was registered officially as an autonomous Research-Production-Trading facility.

Cuba's Centre for Neurosciences electroencephalography and electromyography equipment is being exported to over 20 countries in North America, Asia, Africa, Europe and Latin America under the Neuronic trademark.¹⁴⁰ The Spanish subsidiary (located at Saragossa) of this Cuban company has earned the European Union's certification for sale in Europe and won in 2009 the National Exporter Award for the volume of goods commercialized.¹⁴¹

Institute for Digital Research (ICID)

It is worth mentioning that the existence of a branch within the Cuban biotech industry devoted to medical equipment is closely related to the attempt to develop an electronic industry. The electronic industry in Cuba dates back to the 60s when the CNIC was created. In 1962 the Department of Automation and Electronics was created in the Cuban Ministry of Industry, which explicitly aimed at the development of electronics and

¹³⁸ The takeoff of the Cuban neuroscience is inextricably linked to the design and building of the country's first micro-computer (PC) in 1970 – when it was very difficult for Cuba to access this kind of technology (Ibid).

¹³⁹ During the 80's, applications of these devices to the biological sciences were frequent and several computer programs were written or adapted to allow such applications. See Pons et al. (2007), "Computational Biology in Cuba: An Opportunity to Promote Science in a Developing Country, *Plos Computational Biology*, Vol 3, Issue 11, e277, pp 2047-2051, November

¹⁴⁰ Riding the Brainwaves of Cuban Science, MEDICC Review, Spring 2008, Vol. 10, No. 2

¹⁴¹ "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.

computing in Cuba. In 1965, the University of Havana acquired a second generation¹⁴² computer Elliott 803¹⁴³ for information processing. This equipment was purchased as part of the scientific equipment for CNIC, which, as above noted, was created in 1965. In 1968 an agreement with the French government was reached for the purchase of two SEA 400 second generation computers that were destined to process the information for the population census of 1970. By virtue of the same agreement with the French government, near a dozen of IRIS10 third generation computers were purchased in 1972.¹⁴⁴

The first Cuban mini (or midrange)-computer in 1970 was manufactured by ICID (Institute for Digital Research). This government owned company had been created in 1969 with the aim of developing an electronic and computing industry in Cuba, precisely when the industry was emerging in the rest of the world.¹⁴⁵ This was about the same time the first generation of biomedical researchers was being trained at CNIC. The muster equipment, from which the Cuban computer was developed, was provided as a donation by Dr. Erwin Roy John of New York University¹⁴⁶ (a PDP-8 L/I model¹⁴⁷), which was surprised to see how the Cubans had managed to reverse engineering the computer in 18 months.¹⁴⁸ This computer (second generation) was developed under the name of CID 201

¹⁴² The second computer generation is based on transistors and diodes, which substituted the vacuum tubes of the first generation. The third is based on integrated circuits (miniaturized transistors placed on silicon chips called semiconductors) and the fourth is based on microprocessors (thousands of integrated circuits built on a single silicon chip). A fifth generation based on artificial intelligence (human intelligence being simulated by a machine) was started by the MITI in Japan during the 1980s without success.

¹⁴³ This was a small, medium speed digital computer manufactured by the British company Elliott Brothers in the 1960s. See <http://www.ourcomputerheritage.org/wp/upload/CCS-E3X1.pdf>.

¹⁴⁴ See Lopez et al. in Impagliazzo ed (2008), *History of Computing and Education*, Springer pp57-74.

¹⁴⁵ During the academic period 1970-71, the University of Havana introduced undergraduate programs in Computing Science and computing engineering, only five years after the creation of the first world's computing science department at Stanford University (Ibid p 68).

¹⁴⁶ See Reeds/Torres (2008).

¹⁴⁷ PDP-8 was the first commercially successful Western minicomputer manufactured by Digital Equipment Corporation DEC in the 1960s and introduced in 1965. It is generally recognized as the most important small computer of the 1960's. It was the least expensive parallel general purpose computer on the market, the first computer sold on a retail basis, and the first parallel general purpose digital computer sold in a table-top configuration (see <http://www.pdp8.net/>). After the advent of the microprocessor, minicomputer leading manufacturers (except IBM) collapsed or merged. DEC was sold to Compaq in 1998.

¹⁴⁸ This is nothing different from the kind of emulation strategy which led, for example, to Brazilian engineers, trained at both Instituto Tecnológico da Aeronáutica and MIT, to develop the Brazilian aircraft industry in 1969 under the roof of Embraer, a government-owned company. The Korean semiconductor industry developed in 1975 in collaboration between the Semiconductor Technology Development Centre (STDC) and Goldstar to produce bipolar integrated circuit (IC) through reverse engineering. The case of the Taiwan's semiconductor industry is also illustrative. Companies such as Taiwan Semiconductor Manufacturing Corp which resulted from a joint venture with Phillips, were created to produce VLSI chips (see Mazzoleni/Nelson in Cimoli et al. eds. 2009).

A¹⁴⁹ and in 1971 was started its serial production. Having no access to U.S. system (because of the U.S. embargo) and facing software incompatibilities (with French computers) was a real challenge for the developers of the first Cuban computers. For that reason the first domestic software (LEAL 201) was created in 1971 employing as reference the French Auto-code Elliot 803-Mark III.

In 1972 the first line of Cuban video terminals, CID 702, was developed. In 1973 the CID 300, the first Cuban third generation minicomputer, was developed, compatible with the operating system of the PDP-11 model (the successor of PDP-8), which began serial production in 1978. However, the Cuban overall hardware production fell behind shortly thereafter, when Cuba introduced the Soviet-based labor division system.

According to some scholars, the main reason high-tech development during the 1970s fell behind was to be found in the obsolescence of devices built in the former Soviet bloc and a strong dependence on components from the same market, which hindered Cuba's national hardware production (Pons et al. 2007). After the development of CID 300, Cuba became part of the Intergovernmental Council Committee, which was the CMEA¹⁵⁰ body aimed at the computing development. The purchase of French computers stopped and Cuba specialized in video-terminals and keyboards, which were exported mostly to Soviet Union. Training programs and methodologies were changed as a result of this situation, with catastrophic consequences for the Cuban industry. The biotechnology industry did not suffer the same fate because it remained catching-up to keep abreast of the countries that were at the technological frontier. A lesson to be learned for future industrial policies programs.

Nevertheless, and thanks to the brokering function played by CNIC, an important stage was reached in 1982, when the computerized system for brain research MEDICID was developed. As mentioned above, since the 1970s, research on advanced medical equipment and applications was taking place within the CNIC. The current ICID and the Centre of Neurosciences were actually integrated into one department within the CNIC. Afterward, the development of complex medical equipment and automated systems became the specialization of ICID. Subsequently, a number of medical applications have been developed by ICID for the Cuban Health System. Some of them are being currently exported via COMBIOMED,¹⁵¹ ICID's trading agency. ICID is today part of the strategic network of the Cuban biotech industry.

However, even when the most important value contribution to ICID products proceed from the ability to combine high tech equipment in a new, creative way, the fact remains

¹⁴⁹ The computer was designed by the talented engineer Orlando Ramos, head of the Centre. The prototype was called CID 301. The letter "A" was included to identify the serial model.

¹⁵⁰ The Council of mutual economic assistance (also called Comecon, 1949–1991), was an economic organization under hegemony of Soviet Union comprising the countries of the Eastern bloc along with several others countries of socialist orientation elsewhere in the world. Cuba was accepted in 1972 as a full member. The Comecon was the Eastern Bloc's reply to the formation of the OECD in Western Europe. See Library of the US Congress Country Study: Appendix B -- THE COUNCIL FOR MUTUAL ECONOMIC ASSISTANCE available in: http://memory.loc.gov/frd/cs/germany_east/gx_appnb.html.

¹⁵¹ Currently, COMBIOMED commercializes ICID products to Angola, Algeria, Bolivia, Brazil, Colombia, Chile, Ecuador, Spain, France, Ghana, Mexico, Peru, Ukraine, R. Dominican Rep., Russia, Venezuela and Vietnam See <http://www.combiomed.sld.cu/>.

that, if a hardware industry had been developed, important value gains could have been made. In contrast, most of the high tech components are being imported, which represents an outflow of resources.

Centre for Immunoassay (CIE)

The cooperation between the biochemistry and micro-organism genetics divisions of CNIC accounted for the emergence of the first generation of Cuban molecular geneticists. During the 1980´s CNIC developed the procedures needed to obtain polycosanol (known as PPG), the production of which became a small industrial branch in the country. CNIC carried out some synthesis works, though it focused on chemical analysis. For that purpose, it introduced in Cuba the techniques of mass spectrometry, nuclear magnetic resonance, atomic absorption, ultracentrifugation, automatic analysis, as well as many others.¹⁵²

As a complement, CNIC also created repairing and manufacturing workshops and started to develop lab instrument manufacturing, including some equipment for medical use. This work line of CNIC was the starting point for creating, in the eighties, an institution specialized in designing and producing clinical diagnosing equipment: the Centre for Immunoassay.¹⁵³

In 1987 the Centre for Immunoassay (CIE) was created as another of CNIC´s research spin-offs. Its foremost purpose was to develop enzymatic tests (screening methods) for pregnant women, in order to timely detect birth malformations. The main motivation to develop this method started in 1975, when researchers of both the Clinical Diagnosis and the Biochemical Immunology divisions (Immunochemistry group) at CNIC and researchers of the Centre for Medical Genetics¹⁵⁴ of the Ministry for Health (first

¹⁵² http://resultados.redciencia.cu/historia/periodo_5_5_en.php.

¹⁵³ Immunoassay is a biochemical test to identify the concentration of a certain substance within a mixture of substances.

¹⁵⁴ This is basically a basic/applied research organization, which is also devoted to human resources training, and health services in the area of medical genetics. The National Medical Genetics Center was created in 2003 and it belongs to the Higher Institute of Medical Sciences of Havana and the Western Havana Scientific Pole. As the national reference center for medical genetics, it also coordinates the national medical genetics network that operates at all levels of care, beginning in the community polyclinic, where patients are referred by their family doctor, in order to detect, study and keep registries of genetic diseases and congenital malformations in their coverage areas. Genetic risk detection, community-level follow-up of screening and diagnostic programs genetic counseling, and research on the causes and prevalence of genetic diseases and/or the role of genetic risk factors in common diseases are very important tools for prevention. These programs include neonatal screening and prenatal screening for maternal serum alpha-fetoprotein (MSAFP), sickle cell anemia risk, and fetal chromosome abnormalities. A national registry of families with multiple members affected by common diseases—such as asthma, high blood pressure, ischemic heart disease, diabetes mellitus, dementia, depression, schizophrenia, bipolar disorder, cancer, alcohol addiction, and mental retardation—has been kept since 2004 as part of a study on the role of genetic factors in the origin of these conditions. In 2009, over 43,000 families had been included in this registry. These services are voluntary and free of charge. The National Medical Genetics Center is also responsible for undergraduate and postgraduate training, research, and introduction of new technologies in the field [see Marcheco

separately and short thereafter as a team) became interested in the field of diagnostic methods. The Cuban Immunochemistry group knew that prenatal diagnosis by using radio-immunologic methods had been developed in England in 1979. However the expense and hazards of preparing and handling the radioactive antigen¹⁵⁵ influenced the decision to do it by using immunochemistry, a method with which they had been working since the mid-1970s¹⁵⁶ and which was considered avant-garde at the time.¹⁵⁷

With the development of personal computers during the 1980s, experimentation with fully automated systems for micro-analytical methods using immunochemistry methods increased worldwide. During this period a method called ELISA¹⁵⁸ was being increasingly employed, but it had also proven too expensive to be used in large-scale screening.

Cuba's government objective was to be able to cover the whole population of pregnant women, or, in other words, to carry out mass screening. For that reason, a system using a smaller quantity of reagents was developed. Even while the principle was the same as ELISA, this new system required major changes in the kind of reagent and technology (new automated procedures) employed. The new reagent UMELISA AFP was introduced

(2009)]. It is represented in the visualization of fig 8.8 as violet node. The other violet node is LAGS, which belong Faculty of Chemistry of the University of Havana.

¹⁵⁵ This does not mean that radio-immunoassay (RIA) had not been developed in Cuba. In 1988 the Centre of Isotopes (CENTIS) was created (its current facilities in 1995) with the aim of developing, manufacturing and commercializing products such as radiopharmaceuticals, radiosotopic generators and; conventional and radioisotopic diagnostic reagents, which are suitable for medical and agricultural purposes, as well as for genetic engineering and biotechnology.

¹⁵⁶ See Bravo (1998).

¹⁵⁷ Evolution of diagnostic tests began in the 1940s with colorimetric measurements of the enzymes and metabolites found in biological fluids using classical chemistry methods and agglutination reactions. In the 1950s, the radio-immunoassay (RIA) was developed by Rosalyn Yalow and Solomon Berson. This group was later awarded the Nobel Prize in 1977 for developing an RIA to detect and measure blood glucose levels in diabetic patients. In the 1960s, immunoassay technology was enhanced by replacing radio-isotopes with enzymes for color generation. The use of enzymes eliminates the use of radioactive materials; and has faster reaction times, higher specificity to the target molecule, and longer shelf-lives compared to RIAs. Although immunoassay techniques were first described in the 1950s, they were not readily applied outside of clinical laboratories until the advent of economical automated plate-reading systems and personal computers to analyze data. See <http://www.immunochemistry.com/what-history-immunoassays>.

¹⁵⁸ Enzyme-linked immunosorbent assay. Engvall and Perlmann of at Stockholm University in Sweden, and Anton Schuurs and Bauke van Weemen in the Netherlands independently published their first paper on ELISA in 1971. Among the first commercial manufacturers of fully automated systems are firms such as Boehringer-Mannheim (Germany), Abbott (United States), and Organon Teknika (The Netherlands). Across the years Enzyme immunoassay (EIA) and enzyme-linked immunosorbent assay (ELISA), as non-radioactive variants of immunoassays, have become household names for medical laboratories, manufacturers of in vitro diagnostic products, regulatory bodies, and external quality assessment and proficiency-testing organizations. See Lequin (2005).

in 1982 in the National health System to develop an economical alpha-fetoprotein screening test for fetal malformations¹⁵⁹.

The resultant product packet of CIE has been called SUMA® (ultra-micro- analytic system) technology, which offers significant cost savings and other advantages. A decade after the creation of CIE, each analysis costs 30-50 percent less, making mass-screening possible. This leads to prevention, which is, in contrast to curative medicine, the principle of the Cuban health system. Other products affirming the same principle are e.g., a glucometer developed for diabetic patients and specially designed for tropical climates, which is being provided to the Cuban public health system at 60 percent of the international price. CIE stopped receiving a budget from the government at the beginning of the 1990s. Since then, it finances its own R&D, as well as production, through sales and exports.

SUMA is the CIE's product insignia and it is currently being commercialized by CIE's trading agency Tecnosuma Internacional S.A. International subsidiaries are to be found in Brazil, Mexico, Argentina and China. For several years Tecnosuma has been given the national award as the best exporter.¹⁶⁰

SUMA technology applications cover the whole health system, comprising all the municipalities. It includes such country-wide programs as the maternal-infant program, the epidemiological surveillance program and blood control programs. Part of the export-profits obtained by Tecnosuma and Neuronic are employed to finance and coordinate a huge country-wide network of laboratories to carry out the diagnosis of prenatal and perinatal care malformations. For example, in 2008, CIE grossed \$22 million US\$ that were re-invested in new 42 laboratories in 2008 and another 64 in 2009. As a result, some municipalities now have three labs. This process moves the technology closer to the community, therefore creating more room for the innovative and cost-reducing potentials arising from the user-producer links¹⁶¹ and economies of scale. This technology has played a significant role in the prevention and reduction of the infant mortality in the country. In 2011, CIE's worker productivity was 22 times higher than the national average productivity. Its director is now Vice-President of BioCubaFarma.

¹⁵⁹ Since then, 28 diagnostic tests have been developed, as well as 16 generations of equipment to screen for conditions ranging from congenital hypothyroidism and phenylketonuria (PKU) in newborns, to HIV, hepatitis and dengue. See Reed (2009).

¹⁶⁰ See website of Centre for the promotion of Cuba foreign trade and investments (CEPEC) <http://www.cepec.cu/premioexportador.php>.

¹⁶¹ The user-centered innovation process is in sharp contrast to the traditional model, in which products and services are developed by manufacturers in a closed way, the manufacturers using patents, copyrights, and other protections to prevent imitators from free riding on their innovation investments. In this traditional model, a user's only role is to have needs, which manufacturers then identify and fill by designing and producing new products (See Von Hippel (2005), *Democratizing innovation*, MIT Press. A vivid example of this is the CIE, which dispose of a network of 181 laboratories located in all the country's municipalities, in order to receive accurate information about genetic and environmental factors. This information will be then used as start point for the development of new products. Another 55 laboratories are located in research institutions and armed forces health facilities. See Reed (2009).

National Centre for Animal and Plant Health (CENSA)

Given the increasing necessity to find solutions to the problems of livestock in the country, the CNIC's Animal Health division was created in January 1969. In addition to the research in this field, this division also provided postgraduate training and highly specialized services to other companies in the country. For example, this division played a crucial role in during the epidemics of swine fever in 1971 and 1980.

In 1976 this division started to work as an independent administrative unit and on September 1, 1980, CENSA was officially inaugurated. On June 15, 1981, research objectives were expanded to the field of plant protection, fighting against diseases and pests from Cuba's main crops: sugar cane, citrus, coffee and tobacco. In 1991, the activity scope was extended to the production of drugs, vaccines and diagnostic kits for humans. These products, along with the ones devoted to animal and plant use, are to be commercialized under C-KURE trademark. Since 2007, CENSA works by annual objectives¹⁶² in previously defined priority fields for the middle and long terms.

CENSA is identified by a **yellow node** in Figure 8, which also represents a research-manufacturing organization with have been given (by CECMED) trading license. But, in contrast to the in-house modular companies, its commercialization unit does not have operation autonomy. That means, for example, the unit cannot engage as an independent entity in joint ventures with international partners. However the fact that it has an export-import license reveals a quality that differentiates it from other organizations within the industry, which also have internal commercialization departments, but no license. The other yellow node represents the Centre of Isotopes (CENTIS).

Centre for Molecular Immunology (CIM)

Other non-firm organizations (besides the original CNIC) have incubated successful companies. This is the case of CIM, which is part, along with the CIGB, of the most innovative and leading exporter core of the Cuban biotech industry. In 2011, CIM has three operational licenses for three manufacturing plants.

Although many of its leading researchers also received training in the CNIC, most of them were originally trained in 1970 at the Institute of Oncology and Radiobiology, which belonged to the Ministry of Health. Furthermore, many of the institute's graduates worked there, acquiring decisive experience in pioneering fields such as the production of monoclonal antibodies to combat different types of malignant tumors.

In 1989 the institute was considered a reference in monoclonal antibodies and started to receive further support from the government (specifically from Academy of Sciences). In 1990 it was decided to create an independent facility specialized in monoclonal antibodies. The CIM was completed and opened in 1994 as a spin-off of the Institute of Oncology. At the moment of its birth, CIM already had a lot of research and production experience¹⁶³ that accelerated its successful international engagement. To mention an example, in 2008 the Cuban cancer vaccine programmer was the largest outside of the USA, including eight therapeutic vaccines, six of which were already undergoing clinical

¹⁶² In 1995, a process of Organization Change started; based on the adoption of the Strategic Planning and Direction by Objectives. In 1996 the main strategic document up to 2000 was written and adopted, reviewed and adapted later up to 2007 (See website of CENSA: <http://www.censa.edu.cu/index.php>).

¹⁶³ See <http://www.cimab-sa.com/index.php?action=desarrollo>.

testing¹⁶⁴. During the period 2008-2010, the number of clinical trials in the area of Oncology represented the 59.9 percent (106) of the overall trial number. The second therapeutic area was infectious diseases, at 10.7 percent (19).

The institute also introduced the production of recombinant Epidermal Growth Factor (EPG), when researchers had hypothesized that it could be useful in the diagnosis of breast cancer. Until the end of the 1980s and early 1990s the institute had to rely on a very long process of obtaining EPG from the urine of pregnant women. For that reason, they contacted the CIGB; which by then had already been created, and discussed the possibility of producing a recombinant version of the product through genetic engineering. The effort was successful and today the CIGB continue to produce EPG for curing of burns and other wounds.

Finlay Institute

The Finlay Institute, created officially in 1991, is along with the CIGB and CIM (with whom it regularly cooperates), among the most important: a research-production organization, dedicated to the development of vaccines. It is a start-up company formed by workers of several organizations. Its antecedents are to be found in the early 1980s, when Cuba was hit by a severe epidemic of meningitis. While vaccines against the types A and C were already available in the world market, there was no vaccine for the type B, which rose frighteningly in Cuba during the period 1982-1984. At that time, to solve this problem was considered the first priority of the health system.

To have an idea of the magnitude of the crisis, we need to point out that from 1916 to 1975; meningococcal disease took an endemic form, with 10 to 40 sporadic cases annually. However, in May 1976, an epidemic began as household outbreaks with general incidence increasing by 50 percent (from 0.4 to 0.8 per 10^5 population). In 1978, the incidence increased to 1.5 per 10^5 population, and in 1979 reached 5.6 per 10^5 population. During 1983 and 1984, meningococcal disease reached a general incidence of 14.4 per 10^5 population, but in specific age groups – such as infants under one year – it was extraordinarily high, surpassing 120 per 10^5 population (Sotolongo et al. 2007).

In order to seek a solution, the government created in 1983 a team of 15 researchers from members of different staffs. The group started to work in an ad-hoc department created in the National Centre for Bioproduction (BIOCEN), another research-production organization of the strategic network. After nearly six years of basic research, as well as pharmacological, preclinical, and clinical trials, followed by phased scaling up of the manufacturing process, researchers and technicians produced a vaccine candidate.

After the safety and efficacy of the product was demonstrated, the national regulatory authority -CECMEC- licensed the vaccine for use in Cuba. It was introduced as a nationwide vaccination campaign in 1989-90 on 3 million infants, children and adolescents aged 3 months to 24 years. It is currently administered in a routine 2-dose vaccination schedule at 3 months and 5 months of age, which resulted in a sharp and sustained decline in the incidence of the disease reaching 0.2 per 10^5 in 2006¹⁶⁵ and 0.08 per 10^5 population in 2008 (Sotolongo 2009). VA-MENGOC-BC® is the first

¹⁶⁴ Lage (2008).

¹⁶⁵ http://www.who.int/vaccine_research/diseases/soa_bacterial/en/index1.html#Vaccines%20against%20group%20B%20meningococci.

world's commercially available vaccine against serogroup B meningococcus, protected by three patents in 20 countries.¹⁶⁶

An interesting thing is that the time it took to develop the vaccine was less than the average time for vaccine products (biological or synthetic), which is circa 10-15 years.¹⁶⁷ One possible explanation could be the close relationships between the different organizations of the industry. For example, the research team was composed of two workers¹⁶⁸ that belonged to the C.J.F Biological Products (see visualization Figure 8), a manufacturing company that belonged to the medical-pharmaceutical (currently the producer of injectable medicaments) and the rest belonged to the CNIC. Other organizations such as CIGB also collaborated. Last but not least, as the workers of the industry acknowledge, is the financial commitment showed by the government in these issues, especially for the process of scale-up required by the last stages of the trial. Likewise, the fact of having a very high rate of patient enrolment, made simple by the very inclusive and highly networked Health System, is also mentioned. The Finlay Institute has three operational licenses as of 2011.

D. Other research-production organizations

Other research-production organizations in the strategic network of the industry are the Kouri Institute (IPK), the National Centre for production of Laboratory animals (CENPALAB), the National Centre of Bioproduction (BIOCEN) and the Pharmaceutical Chemistry Centre (CQF). The IPK Institute of Tropical Medicine is the successor of the one created in 1937, and was re-founded in 1979 by expanding its focus in order to protect the Cuban population from the so-called tropical diseases, cooperate with other developing countries in combating these diseases, and contribute to developing medical sciences in general, particularly microbiology, parasitology, epidemiology, and tropical

¹⁶⁶ In January 2013 Novartis has received approval from the European Union to market its Bexsero against Meningitis B. However, Reuter wrongly states that this vaccine is the first against the condition, which is not strictly true. See <http://www.reuters.com/article/2013/01/22/us-novartis-europe-meningitis-idUSBRE9oLo7D20130122>. In fact, the Cuban vaccine has been employed for more than two decades in Cuba and other countries with impressive results. In fact, in 1999 the Cuban vaccine caught the attention of the pharmaceutical company, SmithKline Beecham (now Glaxo SmithKline), which subsequently reached an agreement with the Finlay Institute to market the vaccine globally. Given the size of the U.S. market, there was obvious interest in being able to market the vaccine in the U.S. Although the initial U.S. government response was negative, SmithKline Beecham managed to galvanize enough scientific and medical support to demonstrate that the Finlay vaccine was the only option available on the market. After two years of negotiations, SmithKline Beecham received a license from the U.S. Treasury Department allowing them to finalize the deal with Finlay and bring the vaccine to the U.S. market, providing these vaccines were produced in SmithKline Beecham facilities. However, the political confrontation between Cuba and the U.S has prevented the vaccine from seeing widespread use in the U.S.

¹⁶⁷ <http://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation>.

¹⁶⁸ One of these two workers was in fact Concepción Campa, who was later elected the head of the group and is today one of the most internationally acclaimed Cuban scientists. After getting her biochemistry degree, she started work in CJF Biological products in the department of quality control. See Bravo (1998).

medicine. New laboratories and several other divisions have been subsequently included.¹⁶⁹ In 1993, IPK moved to new, enlarged and modernized facilities and was officially opened in 1994.

The IPK belongs to the Ministry of Public Health and it is basically dedicated to research and services. This includes the validation of vaccines or other products requiring clinical trials, field studies, among other similar activities. But it is also equipped for the production (at request) of cultures, biological reagents or raw materials needed by the industry. For example, this organization carried out the Epidemiological assessment of the effectiveness of the antimeningococcal vaccine (see Finlay Institute) in 1991 and 2000. It also contributed to the commercial scale production and demonstration of the innocuousness and the effectiveness of the recombinant vaccine against hepatitis B (see above CIGB). The institute also has developed a broad network of international collaboration and has become a world reference for infectious diseases.¹⁷⁰

CENPALAB is an organization created in 1982 with the aim of producing and commercializing laboratory animals. Here are carried out experimental toxicology analyses that are part of the pre-clinical phase of the process of clinical trials. This is, before vaccines or medical products are to be tested in humans. CENPALAB covers the whole domestic demand and it develops research on diagnostic resources to assess the levels of pathogen agents in animals. Certainly, it also plays a very important role in the Cuban agricultural and veterinary sciences.

BIOCEN is another important research-production organization of the Cuban biotechnology industry, officially opened in August, 1992. This institution, however, is much more focused on developing manufacturing capabilities for vaccines and medicaments developed by the industry. For example, the production and packing operations of the hepatitis B vaccine, developed at CIGB, were carried out in BIOCEN. However BIOCEN has also developed its own products and components. In recent years, the organization's researchers obtained a novel group of anti-anemia tonics of natural origin and high efficiency (Trofin¹⁷¹ being the most successful). It has also developed and manufactured the active component of several cancer vaccines designed at the Centre for Molecular Immunology.

The CQF belongs to the Ministry of Public Health and was developed to carry out scientific-technical research directed towards obtaining bioactive substances for the formulation of medicines for human use. It is a Teaching Unit of the Ministry of Public Health, the University of Havana and the University of Medical Sciences and it has built an impressive international (more than 40 institutes and organizations from 20 countries) and national collaboration network with almost all the research and health centers in the country.¹⁷²

The CQF has developed several medicaments for the medical-pharmaceutical (small molecule) sector as well as software applications for the biotech industry.¹⁷³ According to

¹⁶⁹ <http://www.ipk.sld.cu/indice1.htm>.

¹⁷⁰ See <http://www.ipk.sld.cu/indice1.htm>, see also http://www.paho.org/english/dd/pin/Number17_article4_4.htm, see also Guzmán (2005).

¹⁷¹ <http://www.biocen.cu/producto/trofin/indicetr.htm>.

¹⁷² <http://www.cqf.sld.cu/ingles/relaciones/relaciones.htm>.

¹⁷³ <http://www.cqf.sld.cu/ingles/productos/productos.htm>.

the UNESCO Science report of 2010, this organization was the number one in the Cuba's top 20 S&T research organizations measured in terms of items such as the number of prizes awarded by the Cuban Academy of Sciences over 1997–2006, on the basis of the number of papers published and the socio-economic benefit of the research results

E. Manufacturing companies

The green nodes of the Figure 8 represent production firms, i.e. organizations, almost exclusively devoted to the manufacture of vaccines, medicaments and other products. Among these firms we find a group of firms that are closely linked to the biopharma companies: The Novatec Lab,¹⁷⁴ the Llorad Lab,¹⁷⁵ the Aica Lab¹⁷⁶ and the Placental Histotherapy Centre (PHC) products are commercialized throughout institutions of the strategic network. The value of their contributions resides primarily on their specialization in the preparation and bottling of certain injectable medications. This process also includes technologies for the aseptic filling and packaging of the products. The rest of the value (R&D, commercializing, import of raw materials and laboratory reagents, quality assessment, clinical trials, etc.) is distributed among other organizations.

An important distinction must be made in the case of the PHC, which, in addition to manufacturing, also carries out high quality research and is well known for R&D focused on searching for new medicines and other products from human placenta.¹⁷⁷ This center provides also clinical services such as computerized clinical assessment and digital photography to estimate the duration of the treatment and the required amount of drugs, training on the use of placenta products for each case, etc.

The rest of the green nodes are exclusively devoted to the production of generics and other medicaments. They are related to the medical-pharmaceutical side of the industry, which focuses mostly on the production of small molecules (rather than biologic) drugs. For instance, we could mention the Reinaldo Gutiérrez Lab (R.G Lab.) which researches, produces and distributes pharmaceuticals. In 2011, the company had two operational licenses for the production of oral contraceptives and pressurized aerosols.

The MedSol Lab focuses on the production of solid forms. In 2011, the company had two operational licenses for the production of finished products. Around 90 percent of total production serves the domestic market, while the remainder is exported mainly to Latin America. Also worth mentioning is the Roberto Escudero Lab (R.E Lab), which manufactures pharmaceutical semisolid products and had in 2011 three operational licenses for the production of creams & ointments, suppositories and powders; and the 8 de Marzo Lab (8.M Lab), which specializes in the production of beta lactamic antibiotics

¹⁷⁴ Laboratorios NOVATEC produces oral solid products in tablet and capsule presentations. The company supplies about 38 products to the industry. In 2011, NOVATEC was processing its operational license for the production of tablets, coated tablets and capsules.

¹⁷⁵ In 2011, LIORAD lab had two operational licenses for the production of dental anesthetic products and liquid injectables, respectively.

¹⁷⁶ In 2011, AICA Lab had an operational license for the production of injectables.

¹⁷⁷ The director, Professor Dr. Carlos Miyares Cao, has a well-known international prestige for having discovered the only medicines in the world for the effective treatment of Vitiligo, Psoriasis and Alopecia. See website <http://www.histoterapia-placentaria.cu/ingles.htm>.

and penicillins and had in 2011 two operational licenses for the production of cephalosporins & penicillins and sterile cephalosporanic powder, respectively.

CECMED continuously re-evaluates the bioavailability and bioequivalence requirements of the domestically produced pharmaceuticals (mostly generics), in order for them to keep up to date with international requirements (WTO, FDA, EMA, etc.). The most recent were published under Decree No. 18/2007 in February 2007.

Also within this area, we have included four organizations that do not classify in any specific group, but that are strongly related to the production units. It is essentially a group of organizations devoted to the national distribution of pharmaceutical products. These are the Wholesale Havana, the Import Medicament Unit, and ENCOMED.

ENCOMED is an umbrella organization that belongs to the Ministry of Basic Industry and contains 15 wholesale drugstores across the country (one per province). These drugstores are in charge of the domestic distribution chain of pharmaceuticals, and are represented in the visualization by Wholesale Havana, given that we are using Havana a reference point. Early in 2011, CECMED reported 26 wholesalers with an operational license across the country, and most of them were involved in the distribution of human pharmaceuticals. One of the few exceptions was CIMAB, the trading arm of CIM, which has also been given license for wholesaling biopharmaceuticals. The distributions will be carried out according to previous planning on the need of each province. The Import Medicament Unit is in charge of distributing drugs and vaccines which have been imported and the ones imported that require especial temperature conditions.

F. High value service companies

The **orange** nodes of the Figure 8 identify organizations mostly devoted to provide sophisticated services to other companies in the industry. In this category there are two organizations: Biomundi¹⁷⁸ and CEADEN. The first one is a business intelligence consulting organization that belongs to the Ministry of Science, Technology and Environment (CITMA) and provides services on strategic profiles, market and tendency studies and carries out the implantation of Intelligence Systems. It is a useful tool for the biotechnology sector, mainly for technological surveying and prospective.

The second orange node represents the Centre for technological and nuclear applications (CEADEN), which also belongs to CITMA. This organization was created in 1987 with the aim of providing engineering and technical consultancy to the biopharma complex and to other sectors in the country. The biggest share of its clientele is composed of organizations of Cuban biopharma. Most of the industry's equipment and system tools made of stainless steel are welded, assembled and further monitored by staff of CEADEN.

Although represented by yellow nodes, given its characteristics (see above CENSA), the Centre of isotopes (CENTIS) also provides high value services to the industry. For example, it provides phamaco-kinetics and bio-distribution studies with radio-labelled compounds to evaluate the absorption, distribution, metabolism and excretion of current and potential new drugs in biological models. It also provides service of calibration of specialized instruments and centralized measurements services for different

¹⁷⁸ For the sake of simplicity; the visualization only displays the links of Biomundi to the Ministry of Technology (CITMA) and to the holding QUIMEFA, which represent the relation of this center to both the biotech and chemical firms respectively.

radioimmunoassays reagents. CENTIS has also been given licenses to export medicaments and to import active pharmaceutical ingredients (APIs).

G. Trading companies

The light blue nodes of the Figure 8 represent the trading organizations, which is one of the most important groups of firms within the Cuban biotech. This group of companies is in charge of the domestic and international commercialization of the products created by the biopharmaceutical complex. The group of nodes located in the bottom part of the visualization in Figure 8 represents the trading agencies of the strategic network's research-production centers. The majority of these commercial arms were created in order to complete the product production cycle, which integrates basic and applied research, experimental development, engineering design and production. The most relevant example is Heber Biotec, which is the most important trading company within Cuban biotech. This company has been given license to export pharmaceuticals, biologics and active pharmaceutical ingredients APIs, both biotechnology-based and chemically synthesized). It has been also given the exclusive marketing rights of to the Placental Histotherapy Centre and to the pharmaceutical laboratories Novatec, Aica and Liorad.

CECMED also gave export licenses in 2011 to CIMAB (the trading arm of CIM) to export biopharmaceuticals and other medicaments for the treatment of cancer. Vacunas Finlay, the trading arm of Finlay Institute, was given license for biopharmaceuticals, especially vaccines and immunoglobulins. Laboratorios DALMER, the trading arm of CNIC, is allowed to export APIs and human pharmaceuticals.

One of the greatest contributions of these firms is realized by establishing partnership for joint development and out-licensing¹⁷⁹ around the world, which leaves a greater margin for scale-up, economies of scale, and cost-reduction of clinical trials. In a survey among developing countries engaged in South-North entrepreneurial collaboration in the health biotechnology,¹⁸⁰ published by *Nature Biotechnology* in 2009, it is shown that Cuba is engaged in the highest number of such collaborations (10.5 per firm in each region). It is the only country, of the surveyed list that has an equal percentage of firms involved in North and South collaboration.

Other important trading organizations of the biopharma complex are Servicex 4 and FARMACUBA. Servicex is the import service office of the Cuban Council of State (legislative government). It is composed of several departments of which Servicex

¹⁷⁹ This strategy is part of a coordinated and targeted alliance-building policy, in which the Cuban firms remain with the strategic control of their R&D assets. Consequently, neither equity purchase nor sharing of Cuban tangible asset property will be included in any agreement. In contrast, a highly financierized form of exclusive IP-based, R&D outsourcing has become the dominant practice among biotech firms worldwide. See e.g. CIGB's Negotiation Policy at <http://gndp.cigb.edu.cu/index.html#>.

¹⁸⁰ The surveyed firms worked in the health biotech sector in six developing countries—Brazil, China, Cuba, Egypt, India and South Africa. These countries were selected on the basis of their position as southern leaders in the field, as identified through previous research on health biotech in developing countries. The survey followed a broad definition of 'collaboration', considering it to be any work jointly undertaken by firms and organizations in developed and developing countries that contributes to the production of knowledge, products or services in health biotech. See Melon et al. (2009), [A survey of South-North health biotech collaboration](#), *Nature Biotechnology* 27, 229 - 232 (2009).

Department 4 is in charge of importing diagnostic kits and reagents exclusively for the biotechnology industry. FARMACUBA is in charge of the whole importing-exporting activities of the medical-pharmaceutical complex. In 2001 the national pharmaceutical industry (until then under MINSAP) was re-organized under the Ministry of Basic Industry (MINBAS and Ministry of Energy and Mines since November 2012) in order to increase pharmaceutical exports. Since then, FARMACUBA was solely responsible for importing and exporting for QUIMEFA (until its dissolution in December 2012). FARMACUBA´s trading activity mainly has to do with the small molecules drugs and reagents of the national chemical and pharmaceutical consortium Quimefa Group (now part of BioCubaFarma), which is the holding covering the medical-pharmaceutical industry (see next section).

FARMACUBA also supports CENCEC´s planning and distribution program of supplies across its entire national network of clinical sites. CENCEC projects availability and demand for medical resources and supplies at each clinical site. These are acquired centrally by the Centre and distributed through the certified clinical trial supply distribution service of FARMACUBA´s national distribution channel.¹⁸¹

H. Holding companies

The grey nodes represent the holding organizations of the industry. The creation of new holding companies (corporations), “corporaciones” during the 1990s represented an entrepreneurial innovation in the Cuban context. The holdings are all owned by the state but they were also allowed to control their own finances, borrow on the international financial markets for their own account, import its supplies, keep foreign exchange, establish joint ventures, and hire foreign managers (only for the tourism industry). The economy began to take this configuration to face the crisis of the 1990s by giving more autonomy and at the same time keeping the organizational integration. In the visualization three of the most important holdings of the Cuban biopharma complex are represented.

The Labiofam Entrepreneurial Group, which belongs to the Ministry of Agriculture, maintains a broad product portfolio that ranges from biolarvicides, natural products and foodstuff, homeopathic medication, to household cleaning products. The Group has an industrial plant for the manufacture of plastic containers and it has several research laboratories where biopharmaceutical medicaments are developed in conjunction with other organizations such as CIGB. Labiofam products are commercialized in over 35 countries by its trading arm Labiofam S.A.¹⁸²

The other holding company was the Quimefa Group (now part of BioCubaFarma), which belonged to the Ministry of basic Industry (MINBAS). It was created essentially to improve exports and to substitute imports, a program begun in 1991. Until 2000 IMEFA (in Spanish Industria Médico-Farmacéutica), a division of the Ministry of Public health (MINSAP) was in charge of producing the small molecules drugs needed by the National Health System, mostly of the generics. However in 2001 most generic pharmaceutical production was shifted to MINBAS, which had created the QUIMEFA group as part of the Union Química, a division of MINBAS end of 2000. QUIMEFA absorbed all operations of IMEFA aiming at operations efficiencies and increasing exports. According to official

¹⁸¹ See Pascual et al (2011).

¹⁸² <http://www.labiofamcuba.com/en>.

figures, during the period 2008-09, Quimefa has saved the Cuban economy over \$2.5 million, when it began to manufacture 16 products that were previously imported.¹⁸³

A careful national monitoring of demand is carried out in Cuba. According to the National Health Program, MINSAP is to gather information (through its extensive communal network) and to present an estimate of the possible national demand. Before producing a medicine, its therapeutic value and economic feasibility is tested, i.e. whether it is more expensive to produce or import it. This is carried out in close collaboration with ENCOMED, the distribution company of the QUIMEFA Group and QUIMEFA. From this the national demand and possible imports are determined. Imports and exports are carried out by FARMACUBA, the trading arm of QUIMEFA.

In actual fact, the frontiers between QUIMEFA and the Biotech-based Western Biocluster are hard to define, as they continuously work together. This was confirmed when in December 2012 both entities were officially merged into BioCubaFarma, a state holding that will continue with the work they were doing before.

However, as mentioned above, this does not alter the analytic point of view of this research whatsoever. On the contrary, it is a confirmation of the point being made by the present study, namely, the huge organizational integration on which the existence of this industry is based. In fact, in our representation (see Figure 8) it is impossible to establish a functional distinction, as both entities were very interlinked. The fact that the visualization was made by following relational data reveals the importance of relying on this type of information to better understand the significance of knowledge sharing in the innovation process. Even before the changes took place, the visualization was, somewhat inadvertently, showing what this merge has made obvious. For example, according to a 2011 report of Espicom Business Intelligence,¹⁸⁴ QUIMEFA and the Biotech-based Western Biocluster were collaborating to renew a quarter of the national list of essential medicaments. QUIMEFA's 2007-2012 production program included 73 products, 31 of which were going to replace imported products and 42 new products.

The last holding company is the Electronic Group (EG), which belongs to the Ministry of Informatics and Communications (MIC).¹⁸⁵ The holding is composed of fifteen facilities focused in import substitution and exports. The main bond of the group is to be found in the Institute for Digital Research (ICID), which belong to EG.

Conclusions: The State as a Central Linking Agent

In this paper we have seen that the Cuban biopharmaceutical industry is a sophisticated network of multifunctional organizations, where NFOs play crucial incubating and brokering roles by allowing open flows of knowledge and resources across the boundaries of heterogeneous organizations. Openness helps to reduce the inherent uncertainty in the innovation process and to build long-term expectations among the diverse agents involved in the system. This process creates an opportunity to build collective pools of knowledge that may contribute to reduce the cost of innovation and therefore to encourage risk taking; knowledge recombination and experimentation.

This is particularly relevant in a branch such as the biopharmaceuticals, where much of these collective pools are governed by a strong tacit component needed to be learned

¹⁸³ <http://www.cubaminrex.cu/english/LookCuba/Articles/Economy/2009/0810.html>.

¹⁸⁴ http://www.espicom.com/Prodcats2.nsf/Product_ID_Lookup/00000336?OpenDocument.

¹⁸⁵ Since March 2013 Ministry for Communications (Decree Law 308).

and not easily movable. This type of knowledge is acquired largely through association with other people, which means also the integration of different disciplines and learning cultures. This requires the continuous creation of standard interfaces and protocols that encourage these people to engage in that kind of learning (e.g. regulatory frameworks and other shared platforms). The lack of integration (given the lack of government involvement) may lead to higher costs and to a halt in the innovation process, which are some of the big challenges that the conventional innovation model in medical technologies is facing today.

At the sector level, NFOs continue to have an impact on early-stage drug development worldwide (although this has often been neglected). However they also play an important role in subsequent stages of the innovation process within the industry. For example, government regulatory agencies (such as CECMED and CENCEC) control the quality of health products, which determine whether a product is ready to be marketed and, if so, how quickly. Additionally, the governments play a crucial role in the delivery phase of health products because they often are usually the main purchasers of health products and they usually organize the distribution and delivery of such products. Government-based NFOs also provide key R&D inputs, help to form companies' R&D priorities, and influence how health products are procured and disseminated.

The Cuban biopharmaceutical industry is embedded in an institutional system that encourages collaboration, and as a paramount rule, excludes rivalry. This element makes it easier for small specialized firms to have a sustainable existence along with the core companies of the industry. In other words, it builds a mechanism to assure good ideas not to be lost. This, in turn, allows the system to simultaneously profit from the advantages of the functional hierarchy provided by the vertical integration and the flexibility of the modular production system (what I call in-house modularity).

Even when the pervasive lack of data makes it difficult to establish an accurate picture of the innovative outcomes of Cuba's biotechnology industry, the available evidence of its achievements in this field seems to be unequivocal: the industry capacity meets 80 to 90 percent of domestic demand (including a significant number of innovative, unique products). This explains the affordable inland sale prices, most of them being the result of a less expensive home-grown production that can be covered by export revenues. This element has contributed to substantially reducing Cuba's reliance on pharmaceutical imports and consequently, helped to maintain country's health standards at a level comparable to those of high income countries, for a much lower cost.

For example we saw how CIE is financially independent since 1991. Part of the export-profits obtained by Tecnosuma (CIE marketing-arm) and Neuronic (CNC marketing-arm) are employed to finance and coordinate a huge country-wide network of laboratories to carry out the diagnosis of prenatal and perinatal care malformations. In this way, Cubans have access to sophisticated medical services that otherwise they would not have been able to enjoy. The government would not have been able to afford all these services with subsidies alone. No way.

Still while more accurate metrics are needed, it is not implausible to assume the existence of important cost and innovation effects resulting from economies of scales and scope, as well as user-producer interactions along the value chain. The openness encouraged by the creation of shared standards and protocols, and shared manufacturing or commercialization capabilities are commonplace in the Cuban health biotechnology

industry and play a paramount role in its performance. All the products of this industry have been developed in collaboration.

The paper calls also attention to the role played by the state in the innovation-led growth. The case of Cuban biotech, which is the confirmation of a robust body of cross-country historic evidence, shows that to ignore the role of government could be part of the innovation sustainability problem that this industry (and other industries) faces in a good part of the world today. However this must not be taken as a straightforward conclusion. The state has only the potential to promote development. The state is an ensemble of capacities that offer unequal chances to different forces within and outside the state.

The realization of these capacities depends on complex interdependencies between the state, the political system; and the rest of the society. The fact that a government fulfil a developmental function in a sector does not mean that it is developmental in others. Nor should be overlooked the fact that these developmental attempts do not always succeed. However, that something went wrong once does not mean that it should not be attempted again, because all entrepreneurial visions (private or public) run the danger to fail. In fact, these phenomena are often present in all attempts of technological and organizational innovation (private or public).

Otherwise, in a perfect predictable world, it would not make any sense talking about entrepreneurship, which necessarily supposes the existence of bounded rationality, information asymmetries and uncertainty. Therefore, it is not about rejecting the state as an economic actor, because as ultimate guarantor of property (and other rights) it has the function to provide a framework for the economy to properly work. It is more about how to improve the ability to build societal devices that make it possible for the state to create consensus between the different visions that exist in the society. That is, for example, to improve the ability of creating opportunities through institution building or of pooling risks through conflict management.

Indeed, what has made the Cuban state (at least in the case of biopharma industry) capable of qualified action is its long-term conception, the will to invest both in technological and organizational capabilities in which the rest of the agents (private or not) would not be willing to invest. The most obvious example is the universal education and the universal health system, but by no means the only ones. It had also the ability to provide insurance mechanisms that encouraged people's investment in assets with limited mobility and without a guaranteed return. This was made by being a provider of patient capital, e.g. financing long term-training and investing in cutting age facilities, guaranteeing a job, social protection and a second chance for everyone, guaranteeing expedite access to government funds and to policy decision makers, etc. By doing this it has created space for experimentation and for risk-taking.

The Cuban biotech case also shows that the collective ability to mobilize resources can be more important than the amount of R&D invested (of course, provided there exists a financial commitment of the stakeholders). Otherwise we could not explain how innovative products are being produced at such a low cost. Innovation is definitely a collective process. We see that government-based NFOs (particularly the regulation agencies) have played a central role in shaping this collective ability.

This contrasts with the kind of capabilities developed by the neo-liberal state, which have been shown by the historic evidence to be a failure everywhere. Essentially, this kind of state failed to manage conflicts properly. Because its advocates lacked a theory of

innovation that explained the conditions under which risk-taking leads to innovation, and because they failed to understand the implications of the collective and cumulative nature of innovation, they have had the tendency to encourage institutions that disrupt the very ability of most stakeholders to commit their resources in certain investments (e.g. dismantling social security systems, institutionalizing job and income instability or by outsourcing useful capabilities).

In addition, the neo-liberal state has been made it easier for certain agents to position along the chain of innovation, and has allowed them to extract rather to add value to the economy (e.g. legal manipulation of stock markets, financial and labor market deregulations, lower tax rates, etc.). This, as reality has shown, is not likely to make the innovation process sustainable or even possible because it does not promote organizational integration and therefore no long term expectations among the agent involved in the process. However to dismiss the state is not an option, but to reform it. It is necessary to retake the debate about the role that governments should play in order to boost innovation and economic development.

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