

Cuban experience with local production of medicines, technology transfer and improving access to health



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Preface

This case study was led by Beatriz M. García, MSc (chemist), independent consultant on intellectual property, technology intelligence and project management. Emma Uramís (microbiologist) and Esther M. Fajardo MSc (biologist), independent consultants on the biopharmaceutical industry, including regulatory requirements and vaccines, contributed to its drafting. The work was supervised by Dr José Luis Di Fabio, Pan American Health Organization (PAHO) and World Health Organization (WHO) representative in Cuba. The study was conducted at the request of Dr Zafar Mirza of WHO.

Acknowledgements

The authors wish to thank the representatives of the Ministry of Public Health (MINSAP) and the Ministry of Higher Education of Cuba, and the directors and officers of the BioCubaFarma higher business management organization, who provided information for this case study. We would also like to acknowledge those who reviewed this document, especially Dr Agustín Lage Dávila, Director of the Center for Molecular Immunology, Dr Celeste Sánchez, Adviser, Center for State Control of Drugs, Equipment and Medical Devices, Dr Gustavo Sierra, Director of Science Policy, BioCubaFarma, and Dr Ileana Morales, Director of Science and Technology, MINSAP, who were kind enough to send us their comments and suggestions.

Executive summary

Cuba has over the years successfully managed to develop its health technology production capacity to support its national health system that is recognized worldwide for attaining universal health coverage. This is evident through health indicators that are comparable to those of highly developed countries. The level of such an achievement befits emulation by other countries that seek to establish a sustainable and competitive local pharmaceutical sector. As a result, Cuba has become a global leader in the South-South transfer of technology, helping low-income countries develop their own domestic biotech capabilities, providing technical training, and facilitating access to low-cost lifesaving drugs to combat diseases such as meningitis B and hepatitis B.

Political commitment

Owing to a particular political system, major critical success element is attributable to the government's commitment in driving the national vision for health sector development. Having identified the health needs and gaps in the health delivery system, the Cuban government developed a national strategic plan that was implemented through restructuring of the national drug industry that commenced after the revolution in 1959. Health sector was among six key strategic areas that were reformed. Implementation of these reforms was made possible through centralisation of the economic policy and by creating good trade relations with the Eastern European socialist countries.

Human development strategy

The Cuban government invested in its human resources development as the main asset for national growth and development. The creation and implementation of educational policy framework enabled access to free education that resulted in increase of the number of training teachers and institutions. Special attention was provided to medical sciences whose responsibility fell under ministry of public health to tailor the education according to public health needs. This has fostered a close relationship between students and the Cuban national health system from a theoretical and practical standpoint, strengthening the different key aspects that enhance the health system, such as primary care for the population. Cuba has shared its successful strategy for developing the education and health sectors with other developing countries especially its support for literacy campaigns in countries in the Americas, Africa and Asia and the participation of Cuban personnel in those countries.

Industrial technology development

The biotechnology sector experienced a boom in the 1980s as Cuba had established a critical mass of the qualified experts. Huge investments were committed to research and development institutions. Technology development was considered successful if it was accessible to the public and increase health coverage. Favourable incentives were made available in order to promote innovation and development of health technologies and this included adjustment of patent law based on the TRIPS flexibilities. The government of Cuba established research and development institutes that are designed to also facilitate manufacturing of the respective products (research-production centres or full cycle institutions), not only to meet local health needs but targeting export markets as well.

More recently, the Cuban government facilitated creation of BioCubaFarma as a corporate entity integrating the country's biotechnology and pharmaceutical sectors, as part of the corporate reorganization process in alignment with the Cuba's economic model. Through this corporate entity saw emergence of different business units that includes technology transfer, contract manufacturing, and establishment of joint ventures with foreign institutions. At the end of 2013, BioCubaFarma had more than 21 000 employees, 6158 of whom were university graduates. Of these, 270 had PhDs and 1079 had master's degrees covering the whole continuum of skills requirements that include technologists, biotechnologists and high-technology process specialists. The success of Cuban R&D as well as local manufacturing capacity can also be measured in the light of numerous technology transfer deals it has secured with other countries including Algeria, India, Brazil, China, South Africa, Mexico, Argentina, Vietnam and Malaysia. More so, since 1989, nine Cuban inventions have received the WIPO Gold Medal and four WIPO trophies have been awarded to innovative Cuban centres for the successful management of intellectual property.

Public health and access to health technologies

The Ministry of Public Health is mandated to implement the country's public health policy with the view of facilitating access to medicines and other health technologies. Because of the absence of the private pharmaceutical sector in Cuba, all health needs are met through public or state controlled institutions. Most of the drugs that are produced domestically are not imported in the country and the price stability is ensured through subsidies by the state and are established through the Ministry of Finance and Prices. The incentives offered helps to meet target priorities that are set as part of the annual plan for locally produced and imported drugs mentioned on the Basic Drug List. The government established a competent national regulatory authority called the Center for State Control of Drugs, Equipment and Medical Devices (CECMED) to manage and enforce national regulation and control of drugs, registration of medicines and other health technologies, regulation of clinical trials, regulation of manufacturing of drugs and API and regulation of imports among other regulatory functions.

Through the holistic approach with a long-term perspective to promoting and supporting local capacity for pharmaceutical manufacturing, Cuba has developed a good public health strategy with indicators comparable to those of industrialised countries despite limited resources. To date, local production has contributed 65% to the local health needs, drug prices are generally low compared to the income level of the Cuban population and the human development index is now comparable to that of the developed countries.

Abbreviations

AIDS	acquired immunodeficiency syndrome
API	active pharmaceutical ingredient
BDL	basic drug list
BRICS	Brazil, Russian Federation, India, China and South Africa
CECMED	Center for State Control of Drugs, Equipment and Medical Devices
CENCEC	National Coordinating Center for Clinical Trials
CENPALAB	National Center for Production of Laboratory Animals
CIB	Biological Research Center
CIGB	Genetic Engineering and Biotechnology Center
CIM	Center for Molecular Immunology
CITMA	Ministry of Science, Technology and Environment
CNEURO	Cuban Neurosciences Center
CNIC	National Center for Scientific Research
EMCOMED	Drug Marketing and Distribution Company
GDP	gross domestic product
GSP	generalized system of preferences
Hib	<i>Haemophilus influenzae</i> type b
HIV	human immunodeficiency virus
MES	Ministry of Higher Education
MFN	most favoured nation
MINCEX	Ministry of Foreign Trade and Foreign Investment
MINSAP	Ministry of Public Health
NSIP	National Industrial Property System
OCPI	Cuban Office of Industrial Property
PAHO	Pan American Health Organization
SUMA	Ultra Micro Analytical System
TRIPS	Agreement on Trade-Related Aspects of Intellectual Property Rights
WHO	World Health Organization
WIPO	World Intellectual Property Organization

Cuba's Experience in Domestic Production of Medicines, Technology Transfer and Improvements in Access to Health Care

Equity in access to health technologies constitutes one of the goals towards achieving universal health coverage.

The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (AMS61.21) is aimed at promoting a new conceptual approach to innovation and access to medicines, seeking a more solid and sustainable foundation for research and development, on the basis of strengthening capacities for innovation and technology transfer, as well as application and management of intellectual property rights.

Cuba, a Third World country with economic and financial limitations derived from an economic blockade that dates back over 50 years, has achieved universal, equitable access to health technologies and the consequent impact on population health. This was the result of political will by government and the state, which, from the early years of the Revolution, fomented education and health for all as inalienable rights fundamental to ensuring social and individual development.

The current transformations being carried out in the health sector are based on the premise of maintaining social achievements, with the aim of continually improving the health status of the Cuban population, raising the quality of and public satisfaction with services, and making the health system sustainable and efficient in order to guarantee its development. One factor that will contribute to reaching these goals is appropriate utilization of the results of science and innovation.

This document gathers the background, evolution, actors involved, mechanisms of interaction and results of a comprehensive, integrated system of work, as well as pathways for scientific development, all part of a state policy that has facilitated a strategy for producing health technologies (especially medicines and vaccines), concrete technology transfer and greater access to these by the Cuban population.

In the 1990s, the most critical economic and social period for Cuba, the biotechnology industry was founded. This included structures for evaluation and control that furnished the nascent industry a path to register their products, introduce and extend their use in clinical practice, and eventually market them abroad.

Cuba's medical-pharmaceutical and biotechnology industry is represented by the Executive Management Board of BioCubaFarma. This enterprise comprises a number of research/production/marketing facilities responsible for the profound innovations that led to the so-called "closed cycle" strategy that shepherds new products and technologies from research through development, production and finally use in medical practice.

Introduction and extension of these results to all services nationwide has had a definitive impact, improving both the health indicators of the Cuban population and the quality of medical services.

In the WHO's World Health Report 2013, *Research for Universal Health Coverage*, it is made quite clear that health research is not a luxury; it is, above all, fundamental for discovery, development and actions need to maintain good health. Managing research as a tool for decision-making in public health and for achieving universal coverage: this is the example Cuba has offered in this field.

A handwritten signature in black ink, appearing to be 'R. Morales Ojeda', written in a cursive style.

Dr Roberto Morales Ojeda
Minister of Public Health of the Republic of Cuba

1. Introduction

Access to medicines and other health technologies is linked closely with the right to health of all human beings (1). From this can be inferred the importance of countries possessing the political will to minimize the effects of the challenges that stand in the way of access to health, especially in developing countries.

Health technologies are all the resources used in order to meet the health needs of healthy and sick people, either individually or collectively, including medicines, medical equipment and devices, medical procedures, and the organizational models and support systems employed (1).

In the case of Cuba, the political will of the State has focused inter alia on guaranteeing access of the entire population to health. Cuba has a national health system that, in addition to providing health services, covers other activities such as research, development and innovation, and policies to train human resources and create industrial, technology and intellectual property resources (2).

1.1 Objective and scope

The purpose of this study is to compile information to show how Cuba has developed its health technology production capacity to support its national health system, recognized worldwide for attaining universal coverage and health indicators comparable to those of highly developed countries (3).

The knowledge generated will be useful for other national health authorities and will enable health policy-makers to become acquainted with the Cuban experience with local production, technology transfer and access to health technologies and to select the ideas applicable to their situation. The study explores the evolution of the legal framework for health, intellectual property and industrial policy as they relate to health technologies; it examines the following elements: political context; human resources, industrial and technological intellectual property policies; and public health resource policies.

1.2 Methodology

Various methods were used for identification, compilation, analysis and diagnosis.

After adjusting the methodology for knowledge management and generation (4) and considering the objectives and scope of this study, the methodology to be used was designed, leading to the development of a flowchart (Figure 1) and the identification and selection of the information sources and data-processing tools.

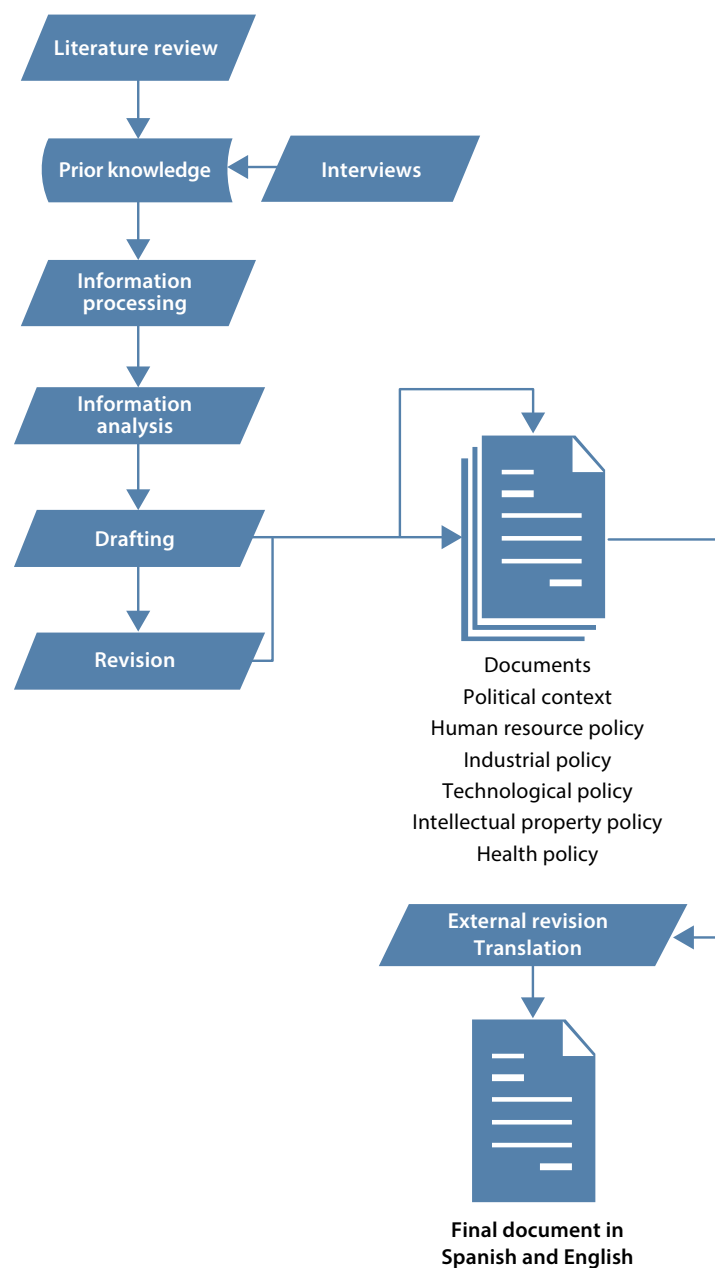
The information compiled was obtained from databases (patent and non-patent), grey literature and interviews. The following websites were consulted:

- Google (<https://www.google.co.uk>)
- Google Scholar (<http://scholar.google.es/>)
- Infomed (<http://www.sld.cu/>)
- Microsoft Academic Search (<http://academic.research.microsoft.com/>)
- National Statistics Office (<http://www.one.cu/>)

- Pan American Health Organization (<http://www.paho.org/>)
- PatentScope (<http://patentscope.wipo.int/search/en/search.jsf>)
- PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>)
- Scirus (<http://www.scirus.com/>) (inactive since 2014)
- United States Patent and Trademark Office (<http://www.uspto.gov/patents/process/search/>)
- World Health Organization (<http://www.who.int/>)
- World Intellectual Property Organization (<http://www.wipo.int/portal/en/>).

The elements to be included in each section of the document were analysed, determining their scope and the respective output indicators in each case.

Figure 1. Methodological flowchart



2. Political context

This section provides the most relevant background on the development and consolidation of Cuba's biopharmaceutical industry.

Cuba has had a tradition of training doctors and, to a lesser extent, pharmacists (5). Several Cuban doctors are renowned for their scientific achievements, chief among them Dr Carlos J. Finlay (6). Before the 1959 Revolution, Cuba had nascent experience in the manufacture of pharmaceutical and biological products, since it had several private pharmaceutical laboratories (both domestic and foreign-owned, including Abbott and Squibb) and state entities that at different times produced vaccines (rabies, smallpox, typhoid, tuberculosis) and therapeutic sera (5).

Development of the national drug industry began after the Revolution, owing to the priority accorded by the new Cuban Government to the health of the population, one of the six major problems identified in the country (the other problems being land distribution, industrialization, housing, unemployment and education) (7). The State created a legal framework to underpin the political, economic and social transformations necessary to promote equity, access to services and intersectoral development. Significant among these laws is the right of all Cuban people to free education and health care (5).

The economic blockade by the United States of America has been an obstacle to procuring the resources necessary for developing different sectors of Cuba (8–13). At the same time, however, it has stimulated the search for alternatives to implement the Cuban Government's plans, as seen in the following examples:

- Centralization of Cuba's economic policy has led to decisions that promote the development of different sectors, with education and health always a priority.
- Full opening in 1960 to the market of the Eastern European socialist countries enabled Cuba to obtain oil, food, medicines, vaccines, farming equipment, factories, transportation, many staple items, and military equipment and supplies for its army. These economic relationships were vital for Cuba and lasted until the collapse of the socialist bloc in 1990 (14).
- Establishment of a single political party has permitted the continuity of the Cuban Government's programmes conceived from the outset.

2.1 Education sector

Human resources are a country's main asset for growth and development. This understanding has been present in Cuba since 1959, when major steps were taken in the education sector, such as the creation of new classrooms at the different educational levels, the training of new teachers, and the Literacy Campaign, which proclaimed Cuba "free of illiteracy" in 1961 (5,15). An extensive scholarship programme for all levels of education was subsequently created, enabling young people from poor families to continue their studies to university level free of charge (15). Academic institutions have been essential in training the human resources required for the development of different sectors, including health and the biopharmaceutical industry.

2.2 Health sector

In the early years of the Cuban Government, major changes were made in the health sector, especially in three areas: the extension of state institutions charged with public health care; the creation of a rural health system; and the reorientation of medical education and health research to respond to the population's needs (16). From the outset, the strategy was to develop prevention. Health activities to fight infectious diseases were carried out nationwide, among them the national polio vaccination campaign; this activity, held annually since 1962, has eliminated polio in Cuba, an achievement officially recognized by the Pan American Health Organization (PAHO) and the World Health Organization (WHO) (17). In 1966, the first health science institutes were created, housed in specialized hospitals (5).¹ Health was conceived as a fully integrated national system (18,19).

The political will to implement a national health system under the economic constraints of a developing and blockaded country forced the Cuban Government to take steps such as the training of competent human resources and the manufacture of the medicines and supplies needed to guarantee health services at different levels.

2.2.1 Manufacture of pharmaceuticals²

In 1960, foreign and domestically owned pharmaceutical companies were nationalized, and some 15 of them were placed under the Consolidated Pharmaceutical Company. This company was initially to become the Medical Pharmaceutical Industry and was placed under the Ministry of Public Health (MINSAP); it was later renamed the Chemical Pharmaceutical Corporate Group and placed under the Ministry of Basic Industry. The raw materials used were procured primarily from socialist countries (14). The importance of pharmaceutical production to support the country's developing health programmes began to be recognized, along with the need for standardized, centralized quality control. Centralized quality control and pharmaceutical laboratories located in the country's capital were created for chemical, microbiological and biological control (5). Later, with the development of a national pharmaceutical industry, a state agency to guarantee the quality of all medicines (domestically produced and imported) used in the country was required: the Center for State Control of Drugs, Equipment and Medical Devices (CECMED) was established in 1989 (20).³

2.2.2 Production of biologicals and diagnostic reagents⁴

Vaccine production took place at the Finlay Institute,⁵ which produced the smallpox vaccine and later the typhoid, tetanus, rabies and tuberculosis vaccines (5). Because of their high

1 In 1966, eight institutes were founded: Endocrinology; Cardiology and Cardiovascular Surgery; Neurology and Neurosurgery; Oncology and Radiobiology; Gastroenterology; Angiology; Haematology (now Haematology and Immunology); and Nephrology. Later, the Institute of Occupational Medicine and the Institute of Nutrition were created. The Institute of Hygiene, founded in 1943, was restructured as the National Institute of Hygiene, Epidemiology and Microbiology and has played a major role in research and the diagnosis of diseases and epidemic outbreaks over the years.

2 Source: interview with Dr Epifanio Selman, September 2013.

3 In 2011 the Regulatory Bureau for Health Protection, the Center for State Control of Drugs and the Center for State Control of Medical Equipment merged under the current name Center for State Control of Drugs, Equipment and Medical Devices.

4 Source: interview with Dr Mario Álvarez, September 2013.

5 Founded in 1927, the Finlay Institute's original purpose was to prepare physicians for health service management. In 1934, it took over production of the smallpox vaccine.

costs in the international market and the demand in the health services, the institute began production of human blood products (albumin and normal immunoglobulin) in the 1970s, using raw material from voluntary blood donations by the population.⁶ The institute also produced culture media and bacterial antisera for microbiological diagnosis. Production did not cover the domestic need for some products, however, which had to be imported, mainly from socialist countries.

2.2.3 Biotechnology development in Cuba

The initial years after 1959 witnessed a shift in the concept of science and scientific institutions towards a focus on activities related to economic and social development and solution of the problems that were hindering this development (5). This was evidenced in the founding of the National Center for Scientific Research (CNIC) in 1965, the first of the scientific institutions built by the new Cuban Government. For many years, CNIC was considered a national centre of excellence for chemical and biological research and for the training of high-level human resources in the sciences (5).

By the 1980s, Cuba had sufficient human resources with expertise in biomedical research acquired at institutions that had produced results in scientific and clinical areas, many of whom had completed graduate studies or training abroad (5).

Biotechnology was born in the late 1970s in California and came to Cuba in the 1980s (21). In Cuba, products were developed to solve pressing health problems, unlike in other countries, where commercial interests prevailed (22). The first Cuban biotechnology product obtained was human leukocyte interferon alfa in 1981, produced by the Biological Research Center (CIB) created for that purpose (23), marking the launch of the Cuban biotechnology strategy (24–26).

The next novel biotechnology product produced was the meningitis B vaccine to battle an epidemic that had begun in 1980 and for which the world had no vaccine. This epidemic was considered Cuba's major health problem at the time (26–28).

In 1986, the Genetic Engineering and Biotechnology Center (CIGB) was created, producing new products to solve health problems of the Cuban people; these products include recombinant interferons (alfa and beta), the hepatitis B vaccine, streptokinase, erythropoietin and epidermal growth factor, a key component of the product Heberprot-P (29).⁷ The biotechnology products obtained in the 1980s, and other countries' interest in acquiring them, revealed Cuba's potential to generate novel products, which, in addition to solving national health problems, could turn into a source of income for Cuba.

Subsequent Cuban biotechnology development occurred in a complex historical and economic context, the economic crisis of 1989–1995 (known as the "Special Period") caused by the collapse of the Eastern European socialist countries and the intensification of the economic blockade (13,30–32). The will to continue the biotechnology development

6 To boost production volume, blood product manufacture was moved to a new plant in the 1980s. This was critical for meeting domestic demand, since with the global emergence of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), Cuba had banned imports of blood products to prevent introduction of the disease by this route.

7 Heberprot-P was registered in Cuba in 2006 and included in the Basic Drug List and approved for sale in 2007. It has since been registered in 15 other countries, permitting treatment of more than 100 000 people with diabetes.

begun in preceding years was maintained, now with the vision of linking biotechnology and its products to the economy. In the period 1990–1996, several institutions were completed, including the Molecular Immunology Center (CIM). The total investment in biotechnology was US\$ 1 billion (19,24).

Cuba's main biotechnology centres are located west of Havana. They were initially placed directly under the control of the State Council (26) and later the Ministry of Science, Technology and Environment (CITMA). This complex of centres was part of the West Havana Scientific Pole, which also included centres under agencies such as MINSAP and the Ministry of Higher Education (MES), resulting in intersectoral work. From a strategic and scientific standpoint, these centres were part of the vanguard scientific community, tasked with addressing urgent public health issues and other needs of the country (24).

Marketing biotechnology products in the initial stages of the 1990s required the creation of business entities in some centres of the Scientific Pole to implement the last phase of a closed cycle (research–development–manufacture–marketing).⁸ The advantage of this strategy is that the full cycle of each product is under the same management (33), making it possible to track the product's history. Feeding back marketing information to the production group on a product's performance in social practice is extremely useful for better understanding and, if necessary, improving a product.

Conditions were created for the production and marketing of new products generated by the young biotechnology institutions. The State centralized and financed the process and directly oversaw these institutions. MINSAP, the main consumer of the products manufactured by these centres, was at all times closely connected with this activity through its various entities.

In 2012, as part of the economic and social transformations taking place in Cuba (34), the higher business management organization BioCubaFarma was established as an umbrella agency for all pharmaceutical and biotechnological drug-manufacturing centres (35). The biotechnology industry has human resources with a high level of scientific and technical expertise attained through sound professional training and years of experience, internationally renowned centres, and products of proven efficacy (several with patents in many markets) included in the basic drug list (BDL) of Cuba and registered in different countries.

2.3 Maintenance, development and coherence of policies designed to ensure access to health technologies

The benefits of the development policy pursued by the Cuban Government since 1959 can be seen in the evolution of Cuba's health and education indicators, summarized in Tables 1 and 2. The Cuban strategy effectively reduced health risks during the crisis of the Special Period, demonstrating that in times of socioeconomic hardship, a well-conceived health policy can play an important role in maintaining the well-being of the population. Education rates have also improved significantly, especially in higher education: the graduation rate in the twenty-first century has tripled from that of the 1990s.

⁸ The first attempts at commercial activities began in late 1983. Sales were directed to Latin American and socialist countries. This activity was undertaken in partnership with the CIMEX Corporation (a Cuban state marketing firm), and the Heber Biotec SA trading company was born. Market research was done for the products available for distribution at that stage. An economics culture was gradually created, which had significant repercussions for marketing activities and other institutional activities related to finance (23).

Table 1. Evolution of general health indicators (selected years)^a

Indicators	1958	1960	1970	1980	1990 ^b	1995	2000	2010	2011
Child mortality (per 1000 live births) ^c	>60.0	42.0	38.7	19.6	10.7	9.4	7.2	4.5	4.9
Mortality in children aged <5 years (per 1000 live births)		42.4	43.8	24.3	13.2	12.5	9.1	5.7	6.0
Children with low birth weight (%)				9.7	7.6	7.9	6.1	5.4	5.3
Maternal mortality (per 100 000 live births)		120.1	70.5	52.6	31.6	32.6	34.1	43.1	40.6
Hospital deliveries (%)		63.0	91.5	98.5	99.8	99.8	99.7	99.9	99.9
Inhabitants per physician	6286		1389	638	276	193	169	147	143
Inhabitants per dentist	27 052		6256	2667	1532	1200	1128	925	878

^a Compiled from references (3,18,36).

^b 1990–1995 were the most difficult years of the Special Period and the worst economic crisis in Cuba since 1959 (3,13,30,31).

^c In 2013, child mortality reached its lowest point of 4.2 per 1000 live births (3,37).

Table 2. Evolution of general education indicators (selected years)^a

Academic year	Schools (n)	Teaching staff (n)	Initial enrolment (n)	Graduates (n)	Higher education (per 10 000 inhabitants)
1958–59	7679	22 798	811 345	26 693	3
1959–60	10 623	30 793	1 240 898	29 179	–
1970–71	35 582	116 787	2 345 188	135 774	41
1980–81	15 857	213 159	3 213 014	636 496	156
1991–92	12 702	232 626	2 416 367	459 046	209
1995–96	12 263	202 153	2 173 885	383 788	111
1999–2000	12 175	195 917	2 285 641	475 863	106
2004–05	12 327	252 484	2 650 271	558 746	322
2007–08	12 323	289 279	3 081 117	639 691	662

^a Compiled from reference (15).

Cuba has shared its successful strategy for developing the education and health sectors with other developing countries. An example is its support for literacy campaigns in countries in the Americas, Africa and Asia, the training of human health resources, the participation of Cuban personnel in health activities, and the presence of Cuban health technologies in those countries.

Likewise, the Cuban experience in developing its biopharmaceutical industry has been transferred to other developing countries.

3. Human resources policy

Training human resources has a major impact on a country's development, and most especially on health and access by the population to health technologies. Since the closing decades of the twentieth century, the existence of human capital has been key for the new technologies, especially in the case of biopharmaceutical and health technology development (33).

In Cuba, the State has paid special attention to educational policy, which is supported by a legal framework based on the Constitution of the Republic of Cuba, which refers to education in several sections, clearly states in Article 51 that "everyone has the right to education" and establishes free education in Article 39 (38).

The promotion of education has enabled Cuba to move in 50 years from a country with an illiteracy rate of over 23% and a low level of schooling to a country with worldwide recognition for the quality of its human resources (15).

3.1 Background

The Cuban Population and Housing Census of 1953 reported a figure of 1 032 849 people aged 10 years and over who could not read or write, a situation that had worsened by the late 1950s. The eradication of illiteracy (707 212 previously illiterate adults became literate) and the creation of the national education system promoted the first educational changes and the Comprehensive Education Reform (15).

In 1961, the General Nationalization of Education Law was enacted (39), establishing State responsibility for providing free educational services. This was supplemented in subsequent years with the universalization of primary education and programmes to grade six and grade nine for people who had recently become literate; this led to schooling higher than the ninth grade of general education for almost the entire population of Cuba.

The 1960s were remarkable for the preparation of middle-school students. An example of this was the creation of two types of high school for pre-university studies – one with a plan for rigorous and intensive study in the basic sciences, and another whose mission was to prepare students for a degree in the medical sciences. The University of Havana, closed since 1956, was reopened; the University Reform (1962) was implemented, and new universities were established throughout Cuba. This, together with other actions, contributed to quickly training a large pool of professionals for the different branches of science and technology, who have played an important role in Cuba's biotechnology industry.

In the context of the economic, political, ideological and cultural changes of the 1960s, higher education played a key role in the social transformation of Cuba and in building the emergent national science (40).

Social relevance and commitment to society have been embraced as core values of the new institutional framework for universities and science, and scientific institutions were created under the universities, a notable example being CNIC (26).

3.2 Human resources

The training of human resources in general, and especially in health, has relied on the political will and determination of Cuba (41,42). The human capital developed over the course of more than six decades has been critical to achieving health indicators similar to those of highly developed countries (3) and the development of Cuba's biopharmaceutical industry.

3.3 Cuban higher education

At the beginning of the 2013–14 school year (43):

- Cuban higher education had about 58 000 educators. Of the full-time professors, 24% are full or associate professors and half have a master's degree or PhD.
- Total preliminary enrolment was over 205 000 students. Enrolment in the day programme totalled 142 000 (70%), 52% of which corresponded to medical sciences, 18% to technical sciences, 10% to educational sciences, 6.5% to social sciences and humanities, and 4.4% to economics.
- Universities under the MES had a strong full-time faculty of more than 12 000 teachers, 24% of whom hold PhDs and 49% master's degrees. About 40% were full or associate professors. The faculty also had more than 6000 part-time professors.

To date, Cuban higher education has consisted of universities assigned to different agencies, among them MES, MINSAP, the Ministry of Education, and the National Institute of Sports, Physical Education and Recreation (44). In order to improve the quality of higher education, all universities, with the exception of those that teach medical sciences (which will remain under MINSAP), are gradually being integrated (45).

The Cuban higher education system is made up of 68 institutions of higher education, including 3150 municipal university venues (46). Ninety-four undergraduate programmes with an overall duration of five years are offered, covering all fields of knowledge.

Table 3 shows the total number of graduates in some fields that are highly important for institutions linked to the biopharmaceutical industry.

Table 3. Cumulative series of university graduates^a

Chemical engineering	13 576
Biomedical engineering	237
Mathematics	1565
Physics	1524
Chemistry	3913
Biochemistry	2941
Biology	3673
Microbiology	1198
Foods	1516
Pharmaceutical sciences	5228

^a Compiled from information provided by MES, 30 October 2012.

3.3.1 Higher education in the Ministry of Public Health

The decision to put medical sciences education under MINSAP has led to a better education of human resources in the field of health (Table 4). This experience, unique in the world, has fostered a close relationship between students and the Cuban national health system from a theoretical and practical standpoint, strengthening the different key aspects that enhance the health system, such as primary care for the population. In 2013, there were 481 960 health workers (70.3% female), corresponding to 6.6% of Cuba's working-age population. There is a rate of 133 inhabitants per doctor and 732 inhabitants per dentist (3).

Table 4. Higher education graduates in Cuba, 2009–13^a

Medicine	34 251
Dentistry	6289
Graduate nurses	27 610
Health technicians	58 502
Psychology	1947

^a Compiled from reference (3).

In the early 1960s, there was only one medical school in Cuba (47). This situation has changed radically, in terms of both the number of universities and schools of medical science and the diversity of degrees related directly to health (Table 5). Cuba also has the National School of Public Health, the Latin American School of Medicine, and the National Center for the Training of Health Technicians and Professionals (3).

Table 5. Numbers of medical education centres in Cuba, 2013^a

Universities of medical sciences	13
Schools of medical sciences	25
Schools of dentistry	4
Schools of nursing	4
Schools of health technology	4
Centres affiliated with medical sciences	26
Centres affiliated with municipal universities	76

^a Compiled from reference (3).

Specialization and ongoing training of the human capital linked to the national health system has allowed for a significant number (15 219) of master's degrees in biomedical sciences (about 50 master's degree programmes, some of which are taught in different provinces) and PhDs in biomedical sciences, including doctorates of medicine, health, dentistry, nursing and medical education. In the period 2010–13, a total of 230 health professionals were awarded a PhD degree (3).⁹

9 Source: MES National Doctorate Commission, 27 April 2014.

Trained in the field of health for over half a century, Cuban human resources have been present in dozens of countries, in many cases responding to natural disasters and epidemics and aiding inaccessible communities. In 2013, 55 000 Cuban health personnel were working in 66 countries (3).

As part of the export of Cuban medical services, an integrated strategy has been developed for promotion and marketing inside and outside the country. This strategy includes medical care abroad and for foreign patients in Cuba, academic services inside and outside Cuba, and other health services (48).

3.4 Human resources and the Cuban biopharmaceutical industry

Since 1959, Cuba has invested significant financial resources in the training of human resources and science and technology development. This has influenced the achievements of the Cuban pharmaceutical industry and the population's access to health technologies.

At the end of 2013, BioCubaFarma had more than 21 000 employees, 6158 of whom were university graduates. Of these, 270 had PhDs and 1079 had master's degrees. Table 6 shows the scientific and teaching categories occupied by the human resources of BioCubaFarma. To this should be added a large number of specialists with scientific production degrees, including technologists, biotechnologists and high-technology process specialists, who represent valuable human capital for both scientific development and the production aspect of the industry.¹⁰

Table 6. BioCubaFarma human resources by scientific and teaching category^a

Category	<i>n</i>
Scientific	
Full researcher	136
Associate researcher	213
Adjunct researcher	268
Research candidate	120
Teaching	
Full professor	260
Associate professor	39
Assistant professor	31
Instructor	107

^a Compiled from information provided by BioCubaFarma, 29 December 2013.

¹⁰ Source: BioCubaFarma, 29 December 2013.

Despite the achievements to date, ongoing personnel training continues, and connections are made with universities, given their great scientific potential, which in the coming years should support the institutions of the Cuban biotechnology industry through postgraduate training and the development of research lines.¹¹

The training of human resources is one of the key variables in the development of the biotechnology industry (49). Human resources are “the main capital of these organizations” and there is ongoing training “based on the demand for knowledge” (33).

¹¹ An example of this is the signing in 2013 of the first Framework Agreement for University–Enterprise Cooperation between the University of Havana and CIM to improve collaboration between the two institutions.

4. Technology policy

Genesis of the Cuban biotechnology centres began in the 1980s, when Cuba now had highly qualified experts with experience in medical and non-medical specialties working at MINSAP health institutes, hospitals, research institutes, universities and production centres. Thus, perhaps unintentionally, Cuba took its first steps towards entering the knowledge economy with high-technology ventures (33,50).

In Cuba, health technology is considered appropriate “when it is accessible to the population in a particular country or region [and] it increases health coverage as efficiently as possible with the resources available ... because appropriate technology (at least in our case) has a greater dose of justice than economics” (51). Under this premise, the main research and development institutions for health products (such as medicines, equipment and computer systems) were created not for commercial ends but to respond to urgent needs of the national health system, which, due to the economic blockade, could not be met by purchasing products in the international markets (9,10,13).

The blockade has also interfered with the development of these institutions, which require high-technology equipment, state-of-the-art technologies and good-quality raw materials and reagents. This has compelled Cuba to purchase them at higher prices, thus increasing expenses (9,10,13).

Cuba made a US\$ 1 billion investment in these institutions (24), which employ the full-cycle system – that is, they not only conduct research and develop technologies but also manufacture and market their products (24,25,52,53).

Since each centre emerged from the need for specific products, its facilities were designed to manufacture its respective products. With time and new product requirements, the centres embraced new products that could be adapted to their existing production platform or created new conditions for their assimilation. An important strategy for optimal use of the facilities is the complementarity or synergy between these centres – they collaborate with each other, each contributing what its product manufacturing facilities are capable of (54). Table 7 summarizes the principal research and production centres and their main activities. These centres were part of the West Havana Scientific Pole, now under BioCubaFarma (26,33,35,53). The sections below discuss the origins of these institutions and the products that drove their development.

Table 7. Scientific production centres at the core of BioCubaFarma^a

Centre	Foundation date	Main activity	Business entity
National Center for Scientific Research	1965	Medicines based on natural products, biomaterials, diagnostic media and equipment for rapid microbiological diagnosis, ozone therapy procedures, molecular genetics, genetic engineering	Laboratorios Dalmer SA
National Center for Production of Laboratory Animals	1982	Production and marketing of laboratory, domestic, productive and exotic animal species and lines and their respective feeds	–
Genetic Engineering and Biotechnology Center	1986	Biopharmaceutical products obtained through genetic engineering	Heber Biotec SA
Immunoassay Center	1987	Production of equipment and reagent kits for diagnosis, blood certification, mass screening for infectious diseases, pre- and postnatal diagnoses of congenital diseases and some types of cancer; leading centre in the field of diagnostic technologies for population health	Tecnosuma SA
Finlay Institute	1991	Bacterial vaccines – whole inactivated cells, outer-membrane vesicles, capsular polysaccharides, toxoids	Vacunas Finlay SA
National Bioproducts Center	1992	Formulation, filling, lyophilization, inspection and packing services for small-volume parenterals, microbiology culture media, some allergens	Heber Biotec SA
Molecular Immunology Center	1994	Biotechnology products for cancer (diagnostic, biopharmaceuticals, monoclonal antibodies, therapeutic vaccines) and immune system diseases	CIMAB SA
Cuban Neuroscience Center	2005 ^b	High-technology medical equipment and software systems for diagnosis and treatment of nervous system disorders	Neuronic SA

^a Compiled from references (5,24–26,35,55–67).

^b As an independent centre.

4.1 National Center for Scientific Research (CNIC)

Opened in 1965, this was the first Cuban scientific centre built after 1959 (5). Its training of human resources in scientific research has been recognized nationally and internationally.¹²

Initially, CNIC's research topics varied with the country's needs, but today most of its research and products are related directly or indirectly to health (55). Its leading product is Ateromixol (PPG),¹³ a natural product whose active ingredient is policosanol, a mixture of higher aliphatic primary alcohols extracted from sugar-cane used to lower cholesterol (26). Another natural product developed by CNIC is Abexol, an antioxidant obtained from beeswax (56).

CNIC developed and markets the DIRAMIC system for rapid microbiological diagnosis.¹⁴ CNIC researchers produced the attenuated strain of *Vibrio cholerae* 638 (El Tor Ogawa), modified through genetic engineering to eliminate its toxicity and used in the vaccine candidate produced and under clinical evaluation by the Finlay Institute (68).

Another of CNIC's research–production lines is the use of ozone for various purposes, accumulating experience in the use of ozone to treat various diseases.

4.2 Biological Research Center (CIB)

The first experience that marked the research–development–production–marketing strategy was the obtaining of leukocyte interferon alfa in 1981, using technology developed in Finland (23,69). The main interest in this product was its potential use as an anti-tumour agent to treat different types of cancer (23,54), due to the increased mortality of cancer in Cuba (70).¹⁵ Its first mass applications, however, were in 1981 during an epidemic of dengue hemorrhagic fever that affected thousands of people, mainly children, and later in an outbreak of hemorrhagic conjunctivitis (23). Development and initial production activities took place in a house that was turned into a laboratory with the conditions required for production on a pilot scale. To increase production capacity, CIB was built; this centre was the predecessor of CIGB, into which CIB staff and production were ultimately subsumed.

4.3 Genetic Engineering and Biotechnology Center (CIGB)

This centre was opened in 1986 as the flagship institute of Cuban biotechnology (23,24). CIGB developed the recombinant vaccine against hepatitis B, natural and recombinant interferons (alfa and beta), transfer factor and recombinant epidermal growth factor in the 1980s. The hepatitis B vaccine was a high-priority product because it was needed for the national immunization programme (28). With the launch of vaccine administration in 1991, Cuba was able to meet the WHO recommendation that all member countries introduce this vaccine into their immunization programmes (24,71). Other products then appeared in response to the needs of the Cuban national health system to provide care for the population: recombinant biopharmaceuticals, such as streptokinase, the first recombinant product of its kind to hit the world market (5) for the treatment of acute myocardial infarction

12 The directors and several scientists at current biotechnology centres come from CNIC.

13 Awarded the WIPO gold medal in 1996.

14 Awarded the WIPO gold medal in 2007.

15 In 1977–76, the crude cancer mortality rate in Cuba was 100.34 per 100 000 inhabitants; in 1980–86, this had increased to 113.63.

(72); granulocyte colony stimulating factor for neutropenia; human epidermal growth factor, whose commercial formulation, Heberprot-P, is unique for its effective treatment of diabetic foot ulcers (29); and vaccines, such as the pentavalent vaccine Heberpenta, which protects against diphtheria, tetanus, pertussis (whole inactivated *Bordetella pertussis* cells), hepatitis B and *Haemophilus influenzae* type b (Hib) infection (59); this last component was obtained synthetically as a world first (73). CIGB also produces the vaccines against hepatitis B and Hib as monovaccines.

In addition, CIGB does research and production for the agricultural sector.

CIGB was a pioneer in technology transfer for some of its products and joint production with companies from other countries. CIGB has been issued several important patents. Its production facilities are subject to periodic inspections by CECMED and the national regulatory authorities of the countries that buy its products. In the specific case of the recombinant hepatitis B vaccine, the facilities have been inspected by WHO.

4.4 Immunoassay Center (CIE)

The Immunoassay Center originated in CNIC. Its first product was the Ultra Micro Analytical System (SUMA), consisting of equipment and reagents for mass prenatal screening for congenital malformations through quantification of alpha-fetoprotein in the serum of pregnant women (51,74). The centre developed other reagent kits for the diagnosis of congenital hypothyroidism and phenylketonuria in newborns and later for congenital adrenal hyperplasia, biotinidase deficiency and galactosemia. CIE's products are used in the maternal-child programme implemented throughout Cuba, and in the diagnosis of HIV/AIDS, hepatitis B and hepatitis C for blood donation certification and epidemiological surveillance (60,74). More recently, diagnostic kits for prostate cancer (PSA antigen), colon cancer (haemoglobin in faeces) and chronic kidney disease through the detection of microalbuminuria have been introduced. The Immunoassay Center also produces the SUMAsensor tropical glucometer for blood glucose monitoring by people with diabetes, a videocolposcope for early detection of cervical cancer, a stereotactic frame for minimal access brain surgery, other equipment used in hospitals and polyclinics such as spectrophotometers, and parts used in SUMA equipment such as the plate reader (fluorometer), plate washer and multipipette for simultaneous application of samples and reagents. The computer systems used in all Immunoassay Center equipment are also developed at the centre. There is a network of SUMA laboratories throughout Cuba, to which the centre regularly provides technical assistance (60,74).

4.5 Finlay Institute

This started out as the National Center for Development of the Meningococcal Vaccine. In 1991 it was officially opened as the new Finlay Institute, a centre for research-production of sera and vaccines (5). It obtained the vaccine against meningococcal meningitis B to deal with the epidemic that was considered Cuba's main health problem in 1980 (27). This was the world's first vaccine against *Neisseria meningitidis* type B, and it successfully controlled the epidemic in Cuba and outbreaks in Brazil, Argentina, Colombia and Uruguay. The formulation also contains purified serogroup C polysaccharide and protects against the two serogroups (hence the trade name VA-MENGOC-BC¹⁶) (27). The institute also obtained

16 This was the first Cuban biotechnology product awarded the WIPO gold medal, in 1989.

a trivalent leptospirosis vaccine from inactivated cells (*canicola canicola*, *pomona mozdok* and *icterohaemorrhagiae copenhageni* serovars) to combat the leptospirosis outbreaks during the Special Period and natural disasters such as the hurricanes that have hit Cuba and Central America in recent years (75). Other products from the Finlay Institute are the purified Vi polysaccharide typhoid vaccine, the tetanus monovaccine, a combination vaccines of tetanus toxoid with diphtheria toxoid for pediatric and adult use, and a diphtheria–tetanus vaccine with inactivated suspensions of *B. pertussis* (DTP or triple bacterial vaccine) (62). The meningococcal AC vaccine requested by WHO for African countries was obtained in conjunction with Brazil (76). The Finlay Institute supplies CIGB with purified concentrated antigens of diphtheria and tetanus toxoids and inactivated suspensions of *B. pertussis* for production of the pentavalent vaccine Heberpenta, and outer-membrane vesicles of *N. meningitidis* B to CIM as an adjuvant in cancer products. Its current research includes the development of new vaccine adjuvants based on outer-membrane vesicles of *N. meningitidis* B and clinical trials of an oral vaccine candidate for cholera consisting of a live attenuated strain of *V. cholerae* (68). Its production facilities have been inspected by the national regulatory authorities of the countries that buy its products.

4.6 National Bioproducts Center (BIOCEN)¹⁷

This was initially intended as a major centre for the production of bacterial and viral vaccines, microbiology culture media and diagnostic reagents. This was being done by the former Finlay Institute, but its facilities were not adequate for increasing production volumes. Many of the centre's founding personnel came from the former Finlay Institute. The economic crisis of the 1990s changed the initial plans: the National Bioproducts Center opened in 1992 as a centre with service facilities for filling, lyophilization, inspection and packaging of small-volume parenterals. It currently carries out aseptic processing of products made by CIGB and some other centres on request. It also produces more than 50 different types of culture media for microbiological use, some allergens, and a natural product for the treatment of anaemia (26,63). The Quality Management System has been certified by Lloyd's Register Quality Assurance and the Oficina Nacional de Normalización (National Standardization Office) according to ISO 9001:2000.

4.7 Molecular Immunology Center (CIM)

This is the youngest of the major Cuban biotechnology centres. Built during the years of the Special Period and opened in 1994 (26,64), it originated with a group of researchers from the Institute of Oncology and Radiobiology, who achieved significant results in obtaining monoclonal antibodies and in research on tumour markers, particularly epidermal growth factor. The centre was given priority due to the importance of cancer as a health problem in Cuba and the novelty of the approaches for addressing it, supported by several scientific publications with novel results (77). Its main products are used in the treatment of cancer: two therapeutic vaccines for non-small-cell lung cancer are noteworthy – CIMAvax EGF consists of EGF as the main antigen, and Vaxira is an anti-idiotypic vaccine consisting of the humanized monoclonal antibody racotumomab (65). Another of its products is nimotuzumab, a monoclonal antibody to treat tumours of the central nervous system (65,78). CIM also produces other recombinant products, including erythropoietin and granulocyte colony stimulating factor (65). The centre is remarkable for the number of patents it holds and its high degree of collaboration with foreign firms for joint production and technology transfer.

17 Source: interview with Dr Mario Alvarez, September 2013.

4.8 Cuban Neurosciences Center (CNEURO)

This centre opened in 1966 as the CNIC Department of Neurophysiology. In 1982 it became the Division of Neurosciences. In 1990, it was elevated to CNEURO as a scientific production unit of CNIC. In 2005, it attained recognition as a centre independent of CNIC (66).

CNEURO's origins lie in the importance of neurological diseases, their early diagnosis, and the refinement of methods for their diagnosis, which require expensive equipment and complex technology.

CNEURO researchers became one of the first groups in the world to use informatics to analyse electrical activity in the brain. The centre is currently devoted to basic and applied research and the development of advanced technology for diagnosis and intervention in mental health problems.

The development of neuroimaging and neuroinformatics has permitted the identification of brain function, providing useful information for the early detection and accurate diagnosis of neurological diseases and for the selection of appropriate treatment and patient monitoring. The working strategy of this centre has been to develop affordable screening technologies under Cuban conditions in order to select patients with neurological conditions requiring more sophisticated diagnostic methods so they can be treated properly.

Table 8 provides a brief chronology of the development of diagnostic systems, consisting of equipment and computer programs for analysing and diagnosing neurological conditions (67,79).

Table 8. Cuban neurotechnology timeline^a

1969	First use of a CAT-400C computer, donated by United States scientists, for computed evaluation of brain disorders
1970	First Cuban microcomputer used for electroencephalogram (EEG) analysis
1972	First prototype of the MEDICID-01 computerized EEG system
1977	Neurometrics paper on computed brain diagnosis published in <i>Science</i> by joint United States–Cuban group ^b
1982	Industrial production begun of MEDICID-03 computed EEG system; foundation of the national neuroscience diagnostic network
1983	Electric response audiometry screening initiated in Havana for infants aged 3 months at risk for hearing loss
1983	First Cuban video game released for learning assessment in school-age children
1990	MEDICID-3E: first Cuban computed EEG equipment registered in France and Switzerland
1991	Early hearing screening programme scaled up to national coverage
1992	First generalized use of quantitative electroencephalogram (qEEG) in a public health system ^c
1996	AUDIX system developed for detection of early hearing loss
1997	Battery of tests designed for assessing learning disorders in children

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1999	Video games introduced for learning disorder rehabilitation
2001–2003	National disability study conducted ^d
2004	National human brain mapping project initiated
2005	National cochlear implants programme launched; neurodevelopmental disorder study conducted in Cotorro Municipality, Havana City Province
2006	National learning disability prevalence study carried out
2008	Software introduced for diagnosis and treatment of neurodevelopmental disorders

^a Source: Valdés Sosa P, Obrador-Fragoso A. Stratified active screening: where neurotechnology meets public health. MEDICC Rev. 2009;11(1):7–10.

^b John ER, Karmel BZ, Corning WC, Easton P, Brown D, Ahn H et al. Neurometrics. Science. 1977;196:1393–410.

^c Valdés P, Valdés M, Carballo JA, Alvarez A, Díaz GF, Biscay R et al. qEEG in a public health system. Brain Topogr. 1992;4:259–66.

^d Camacho H, Cobas M, Icart E, editors. Lives to live: psycho-social study of people with disabilities and psycho-pedagogic, sociological and clinical genetic study of people with intellectual disabilities in Cuba. Havana: Editorial Abril; 2003.

CNEURO's research lines address issues associated with the neurosciences: cognitive, social and experimental, clinical neurophysiology, neurodiagnostics, molecular biology, bioimplants and neuroinformatics (66,67).

4.9 National Center for Production of Laboratory Animals (CENPALAB)¹⁸

This was created because many centres needed good-quality laboratory animals to ensure research and production in all centres of the Scientific Pole and in other centres and universities that require different species of laboratory animals.

The centre's origins can be traced back to a small production farm belonging to the Carlos J. Finlay Biological Production Enterprise, which was the main consumer of its output. With time and the creation of new drug regulatory policies in Cuba, it became necessary to improve the quality and diversity of the animals, which were not available in the numbers required to meet the needs of production and research centres. In 1992, CENPALAB was moved to a new facility with suitable conditions for producing good-quality animals. Its production is limited primarily to Cuban consumers. CENPALAB also produces the feed required for each species (26,57).

¹⁸ Source: Dr Mario Alvarez, September 2013.

5. Industrial policy

Cuba's biotechnology industry is a product of the circumstances surrounding its origins: it developed in a poor country under a blockade, without prior industrial development but with the political will to develop education and health. This provided it with significant intellectual capital in the early 1980s in the form of human resources and scientific results. To this was added State investment that made possible the infrastructure necessary for the emergence of the Scientific Pole of Biotechnology.

... in any approach to the study of Cuban biotechnology three phenomena stand out: early development, extensiveness and results (33).

The essential features of the Cuban biotechnology experience have been (33):

- research–production centres or full-cycle institutions;
- export orientation;
- treatment of scientific research as an investment.

Parallel to the development of the biotechnology industry, efforts were launched to strengthen the national pharmaceutical industry, which has improved the population's access to medicines and fostered drug exports, mainly to developing countries.

5.1 Creation of BioCubaFarma

On 3 December 2012, by Decree 307, BioCubaFarma was created, comprising biotechnology research institutions and other centres devoted to state-of-the-art, high-technology industrial production of medicines and other pharmaceuticals in Cuba, and their marketing (35). The group consists of institutions that at the time of its creation were part of the Scientific Pole, the Chemical Pharmaceutical Corporate Group, and other organizations devoted to scientific research, production, services, marketing and other activities (35).

For the first time in an official document, the Decree Law includes the concept of high-technology enterprise as an entity in the Cuban socialist economy (33).

The functions of BioCubaFarma are to oversee implementation of the research and development policy for drugs and other products and services with high value added for the entities of the group. Its main priorities are health programmes and medical services in Cuba (80).

BioCubaFarma was created to achieve higher levels of integration between the country's biotechnology and pharmaceutical sectors, as part of the corporate reorganization process being carried out in alignment with the updating of Cuba's economic model. By this means, Guidelines 131, 132 and especially 221, which expresses the need to consolidate the two industries in the country, are implemented (34). It is believed that reorganization of the industry (81), which is regulated by Resolution No. 590 (2012) of the Ministry of Economy and Planning (82), will raise quality standards and export levels in Cuba and facilitate more efficient use of facilities, equipment and human capital, leading to higher levels of scientific and technical development in this field.

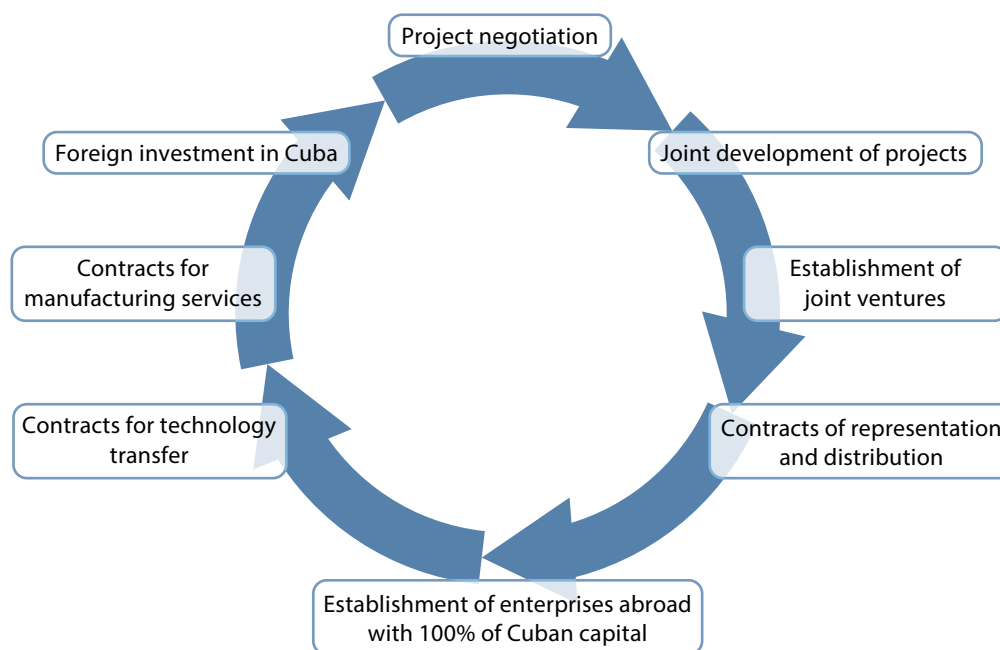
5.2 Funding of the Cuban biopharmaceutical industry¹⁹

The biotechnology and pharmaceutical industries have been funded by the State through different plans that have changed over the years. In the case of biotechnology, in its infancy funding was provided directly by the State. In 2001, changes were introduced and a self-financing plan was adopted, specifically for current expenditures; investments were the exception and had to be approved centrally. In late 2008, another form of financing was introduced, which had to be approved by the Ministry of Economy and Planning.

5.3 Business modalities of the biopharmaceutical industry

BioCubaFarma employs different negotiating modalities (Figure 2). The experience of the Cuban biotechnology industry has been to implement a suitable combination of the full product-development strategy (for negotiating only trade representation) and pre-marketing early negotiation strategies for joint product development (33).

Figure 2. Business modalities used by BioCubaFarma (83)



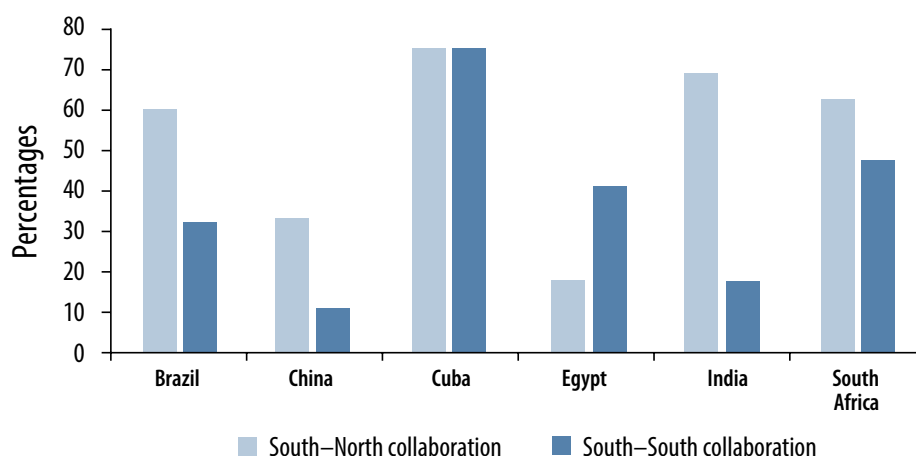
5.3.1 Technology transfer and direct foreign investment

According to a 2010 WHO report, the contribution of south–south technology transfers for vaccine production is modest compared with north–south technology transfers (10% versus 90%), with the possibility of an increase due to the role that Brazil, the Russian Federation, India, China and South Africa (BRICS) intend to play in global health; this will lead to an increase in vaccine production capacity (84,85).

¹⁹ Source: information provided by Dr José I. Goicoechea, November 2013.

Figure 3 shows the results of the expansion of south–north²⁰ and south–south cooperation in a survey conducted in six developing countries. Despite the limitations of this type of survey, Cuba is notable for its number of south–south cooperation projects compared with the rest of the group (86).

Figure 3. Comparison of south–north and south–south cooperation in biotechnology for health in six countries studied (86)



This cooperation policy with countries of the south has been extended to the field of biopharmaceutical production, with positive results (87). Table 9 shows some of Cuba's technology transfers to countries of the south.

Table 9. Technology transfer from Cuba to other countries^a

Marketing company	Recipient institution	Country	Product
Heber Biotec SA	Saidal Groupe	Algeria	Heberbiovac HB Vaccine ^b
	Saidal Groupe	Algeria	Granulocyte colony stimulating factor
	Oswaldo Cruz Foundation	Brazil	Pegylated interferon
	Oswaldo Cruz Foundation	Brazil	Recombinant human interferon alfa 2b
	Changchun Heber Biological Technology Co. Ltd	China	Pegylated interferon
	Panacea Biotec Limited	India	Heberbiovac HB Vaccine
	FGUP Microgen	Russia	<i>Haemophilus influenzae</i> type b (Hib) Vaccine
	Biologicals and Vaccine Institute of Southern Africa (PTY) Limited	South Africa	Heberbiovac HB Vaccine

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²⁰ In the case of south–north cooperation, Cuba has transferred technology to European countries.

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Marketing company	Recipient institution	Country	Product
CIMAB SA	Fiocruz	Brazil	Anti-CD3, anti-CD4, anti-CD8, anti-CD45
	Fiocruz	Brazil	Humanized monoclonal antibody techniques
	Fiocruz	Brazil	Erythropoietin
	CIMAB/CAIF/RECOMBIO	Argentina	Racotumomab (formulation, filling, packing)
	BPL/BJTD/CIMAB	China	Epidermal growth factor
	GEPROC SA	Argentina	Anti-CD3, anti-CD4, anti-CD8
Tecnosuma Internacional SA	Ensayos y Tamizajes SA de CV	Mexico	SUMA technology
Vacunas Finlay SA	University Saints Malaysia	Malaysia	ACYW135 meningococcal polysaccharide vaccine
	Vabiotech	Vietnam	ACYW135 meningococcal polysaccharide vaccine

^a Compiled from information supplied by Business Division, BioCubaFarma, 2013.

^b Hepatitis B vaccine (recombinant).

A new model that has emerged from the cooperation between Cuba and Brazil is worth noting. Since 2004, institutes from the two countries have been involved in joint biotechnology projects, the most important of which are the production of recombinant erythropoietin and pegylated interferon and the development and distribution of the meningitis AC vaccine for Africa (at the request of WHO). The participation of three key players in both countries has been decisive in this new type of cooperation: research and production institutes, regulatory agencies and public health institutions. The model shows three characteristics necessary for success in terms of public access to medicines (87):

- development of scientific and technological capabilities;
- implementation of a regional strategy that goes beyond national borders to reach a scale capable of absorbing the costs of technology development and high standards;
- extensive coverage to maximize the impact on population health indicators.

Table 10 summarizes the characteristics of the technology transfers made by Cuba's biotechnology industry. Unlike other countries, for Cuba there are no technology transfers from the private sector, because in Cuba this industry is owned by the State (87). Another difference to note in this study is that Cuba has transferred technology to developed countries (although to a lesser extent). Finally, unlike the other countries, Cuba has transferred technology involving complex molecules obtained from biotechnology for products other than vaccines.

Table 10. Summary of characteristics of technology transfers made by Cuba^a

Characteristic	Type	Cuba
Commercial partnership development	South–north	Yes
	South–south	Yes
Stage of production process	Packing	Yes
	Formulation	Yes
	Active pharmaceutical ingredient	Yes
Sectors involved in technology transfer	Public–public	Yes
	Public–private	Yes
	Private–public	No
	Private–private	No

^a Compiled from information supplied by Business Division, BioCubaFarma, 2013.

5.3.2 BioCubaFarma companies and representative offices abroad

BioCubaFarma has 14 companies abroad: 5 are joint ventures and 9 are subsidiaries of commercial companies (Table 11).

Table 11. BioCubaFarma companies and representative offices abroad^a

Company	Joint venture or subsidiary	Characteristics
CIMAB SA	Joint venture BPL	–
	Joint venture CIMYM (Canada)	–
	Joint venture Recombio	–
Heber Biotec SA	Joint venture Chang Heber	–
	Norville Venezuela	–
Neuronic SA	IC Neuronic SL	Company that produces medical equipment marketed by Neuronic SA
	Neuronic Mexicana SA de CV	Equipment marketing enterprise for neurodiagnosis and software, Diramic laboratory equipment and coral implant materials, providing technical service for these and Combiomed equipment
	Norville Ecuador	Enterprise that manages government contracts, sales to private individuals, organization, execution and control of technical assistance, equipment installation, training, etc.

Continues...

Continued from previous page

Company	Joint venture or subsidiary	Characteristics
COMBIOMED SA	Combiomed Venezuela	Enterprise that provides installation, training, warranty and post-warranty servicing of equipment marketed by COMBIOMED under the Comprehensive Cooperation Agreement between Cuba and Venezuela
Tecnosuma SA	Tecnosuma Venezuela CA	Enterprise that provides technical assistance, training, post-sale services and installation of new laboratories in Venezuela, including operations of the Comprehensive Agreement and the Barrio Adentro mission
	Tecnosuma Mexico SA de CV	Enterprise that provides technical assistance, training, post-sale service and installation of new laboratories in Mexico
	Tecnosuma Colombia	Enterprise that provides technical assistance, training, post-sale service and installation of new laboratories in Colombia
	Tecnosuma Commerce and Industry Ltd (Belo Horizonte, Brazil)	Enterprise that provides technical assistance, training, post-sale service and installation of new laboratories in Brazil
Biocen	Biocen do Brasil Ltd	–

^a Compiled from information supplied by Business Division, BioCubaFarma, 2013.

5.3.3 Export promotion policy

Biotechnology is one of Cuba's largest sources of foreign exchange, and its export promotion policy follows the general Cuban laws established for this purpose.

Cuba's Ministry of Foreign Trade and Foreign Investment (MINCEX) is responsible for directing, carrying out and monitoring implementation of the Cuban Government policy on trade, investment and collaboration abroad (88).

Approved by Decree Law 264/2009, the purpose and essential mission of MINCEX are to prepare and propose to the Cuban Government a comprehensive policy on foreign trade activity, the creation of joint ventures, and economic cooperation with other countries, foreign organizations and associations. Its main objectives are to diversify its business partners and work towards reorganizing trade policy in pursuit of favourable markets for its exports and the diversity and competitiveness of its export items (89).

Cuba has trade relations with over 170 countries. Since the 1990s, exports of services have played a growing role in the Cuban economy. The country's main trading partners include the Bolivarian Republic of Venezuela, China, the Russian Federation, Spain and Brazil. The sale of professional services, especially in health, engineering, information technology and biotechnology, is Cuba's largest source of foreign exchange. The safe and healthy environment provided by Cuba for business in general is a real plus for promoting goods and services exports, collaboration, foreign investment and progress in import substitution, thus contributing to production and science and technology development in the country.

The Chamber of Commerce was created by Act No. 1091 (1963) as a tool for reintegrating the Cuban economy into the world of international economic relations, since it enhances and exchanges valuable information on business possibilities on a global scale (90). Its mission is to enhance the development of Cuban joint ventures, promoting exports of products and services and business and investment opportunities in Cuban companies and import substitutions to benefit the national economy (91).

Cuban entities authorized to engage in export or import operations must be registered with the Cuban National Registry of Exporters and Importers of the Chamber of Commerce.

In order to export goods, Cuban companies must include this activity in their corporate objective, approved by the Ministry of Economy and Planning, and be authorized to do so by a MINCEX resolution in which the list of products authorized for export is specified. The procedure for granting, amending and cancelling foreign trade authorizations, and the list of authorized products for state enterprises and corporations funded with 100% Cuban capital, is established in Resolution No. 68 (2008).

The Center for the Promotion of Foreign Trade and Foreign Investment in Cuba (CEPEC)²¹ indicates that the most significant actions in regard to export promotion are (92):

- authorization of closed financing plans to exporting companies, which allow entities to retain part of the Cuban convertible pesos (CUC)²² obtained from the foreign sale of goods and services, in amounts large enough to replace all supplies in that currency;
- establishment of production chains or process integration in which all those involved in the value chain of a product or service (from the supplier to the customer) are directly linked;
- promotion of exports of professional services.

5.3.4 Regional integration policies: preferential systems

Cuba has signed a number of trade agreements with various countries and economic blocs (93). Eleven of the existing preferential agreements have been signed with the Latin American Integration Association, a regional bloc made up of several Latin American countries, including Cuba.

Other agreements have been signed with MERCOSUR (Common Market of the South) and CARICOM (Caribbean Community).

5.3.5 Other trade agreements

Cuba also has trade agreements with:

- Guatemala;
- the Association of Caribbean States (CARICOM member countries plus Cuba, Colombia, Costa Rica, the Dominican Republic, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, and Bolivarian Republic of Venezuela);

21 The centre is a MINCEX entity and is one of the key players in promoting these activities under the country's strategies.

22 In Cuba, both the Cuban peso (CUP) and the Cuban convertible peso (CUC) circulate to pay for services charged in each currency in the country. A series of measures have been adopted to unify the two currencies in the business sector as part of the updating of Cuba's economic model.

- the following African countries: Algeria, Angola, Botswana, Burkina Faso, Cape Verde, the Congo, Egypt, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Mali, Mozambique, Namibia, Niger, Nigeria, Seychelles, South Africa, Tunisia, Uganda, United Republic of Tanzania, Zambia and Zimbabwe;
- the following Middle Eastern countries: Iraq, the Islamic Republic of Iran, Lebanon, Qatar, Saudi Arabia, the Syrian Arab Republic and Yemen.

Some of the countries that grant a generalized system of preferences (GSP)²³ are Canada (generalized preferential tariff), Japan and the European Union countries. Cuba benefits from this system, which usually provides most favoured nation (MFN) rates of 3.5% ad valorem. The main difference in the various GSPs lies in the numbers and types of product involved, depending on the country awarding the preference. The tariff on trade is regulated by Decree Law No. 124 (1990), which enacted the customs tariff.

On 1 January 2014, a new customs tariff on commercial operations came into force.²⁴ Domestic production is protected by an increase or decrease in the customs tariff, as appropriate, or by applying tariff regimes established in Decree Law No. 162 (1996) to entities to stimulate exports (94).

5.4 Infrastructure development²⁵

The BioCubaFarma business group has a comprehensive geopolitical structure,²⁶ whereby virtually all research–production centres possess the necessary technological and non-technological equipment. Facilities include direct water supply, dual power supply lines from two independent substations and power-generating equipment in each unit.

5.5 Other policies that apply to the biopharmaceutical industry

The implementation of regulatory policies for the biopharmaceutical industry has promoted technologies and products developed in Cuba, allowing their marketing both in Cuba and abroad.

Use of the legislation enacted by the various entities of Cuba's central administration has allowed processes to be carried out in a way that minimizes negative economic, social or environmental consequences. The main legal documents are:

- Resolution 13 (1998, CITMA): establishes the basic requirements for the bases, evaluation and decisions on technology transfers associated with nominal investment projects proposed in feasibility studies;
- Resolution 157 (1998, Ministry of Economy and Planning): supplementary regulations for the investment process;
- Resolution 77 (1999, CITMA): regulation of the environmental impact assessment process;

23 The GSP is the mechanism whereby a developed country allows products from developing countries to enter its market on preferential terms.

24 Pursuant to the provisions of MFP/MINCEX Joint Resolution No. 1, 21 August 2013, published in Ordinary Official Gazette No. 58, 20 November 2013.

25 Source: interview with Dr José I. Goicoechea, November 2013.

26 The former Scientific Pole of the West was created from the outset with a comprehensive geopolitical concept.

- Resolution 126 (2007, CITMA): process for the evaluation of investment feasibility studies in the fields of science, technology and environment submitted by central administration bodies to the Ministry of Economy and Planning; this assessment is handled by the Single Window system, located in the Ministry's Directorate of Technology and Innovation.

5.6 Results of the industrial policy

No reports were found on the contribution of the pharmaceutical sector to gross domestic product (GDP).

A report from Business Monitor International using data from the United Nations Comtrade Database states that the trade balance in the Cuban pharmaceutical sector during the period 2003–06 was improving, despite inaccuracies in the 2006 figures (95).

A 2011 report from Espicom Business Intelligence shows that in the period 1995–2010, the trade balance was positive except for during four years; in the case of vaccines it was positive for all years (Table 12). It should be noted that the data in the Espicom report are based on what other countries imported from Cuba, which may underestimate exports (95).

Table 12. Pharmaceutical trade balance 1995–2010 (US\$ thousands) (95)

Year	Raw materials	Antisera and vaccines	Semi-elaborated medicines	Retail medicines	Total
1995	–765	29 734	–655	–11 135	17 179
1996	–5695	34 382	–1418	–7628	19 640
1997	–5071	41 200	–125	–3725	32 278
1998	–8251	18 965	143	–15 552	–4695
1999	–4510	12 376	4690	–4827	7728
2000	–6648	15 975	4900	–6527	7700
2001	–6820	16 109	626	–9029	887
2002	–7405	23 654	1070	–5820	11 499
2003	–7979	25 475	841	–306	18 031
2004	–10 782	15 333	1392	–8012	–2069
2005	–6926	16 336	482	–22 761	–12 869
2006	6761	21 524	–654	–25 636	1995
2007	36 127	19 384	–420	–21 880	33 212
2008	–21 723	2960	–1508	–25 978	–46 249
2009	18 894	10 263	–1276	176 013	203 895
2010	30 606	21 505	–824	150 512	201 878

Table 13 shows the export revenues of Cuba's biopharmaceutical industry.

Table 13. *Export revenues of the Cuban biopharmaceutical industry*

Year	US\$ millions
1985	11 ^a
1987	70 ^b
1990	100 ^{a,c}
1992	70 ^a
Mid-1990s	100 ^a
2005	300 ^d
2011	711 ^e
2013	686 ^f

^a Source: reference (96).

^b Source: reference (97).

^c Peak reached thanks to substantial exports to Brazil.

^d Source: reference (26).

^e Source: reference (74).

^f Source: <http://www.granma.cu/ingles/cuba-i/26febre-Cuban%20pharmaceuticals.html>.

6. Intellectual property policy

6.1 General legal framework for intellectual property, copyright and industrial property

Intellectual property in Cuba is governed by two entities, the National Copyright Center under the Ministry of Culture, and the Cuban Office of Industrial Property (OCPI) under CITMA (98).

In this study, special reference is made to the Industrial Property Legal Framework, due to its impact on health-related issues and health technologies.

Cuba is a signatory to a number of conventions, treaties and international arrangements concerning intellectual property, significant among those related to patents including:

- the Paris Convention for the Protection of Industrial Property (99);
- the Patent Cooperation Treaty (100).

Cuba has been a member of the World Trade Organization since 1995 and must therefore enforce the provisions of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) (101), which contains a framework of basic standards for patents and industrial designs and models. This framework led to instrumentation in the national legislation and the promulgation of new decree laws.

In recent decades, the legislation has changed; one example has been the promulgation of Decree Law No. 290 (002/12) (102), which repealed some of the articles of Decree Law No. 68 and Decree Law No. 160.

6.2 Industrial property rights in Cuba

6.2.1 National industrial property system and internal intellectual property systems

Cuba's national industrial property system (NSIP) entered into force through Resolution 21 (2002) of CITMA (103). In this resolution, the NSIP, consisting of the general principles of the national industrial property system, the methodological guidelines for the design and organization of internal industrial property systems (104), and the guide to diagnosis and controls, is annexed.

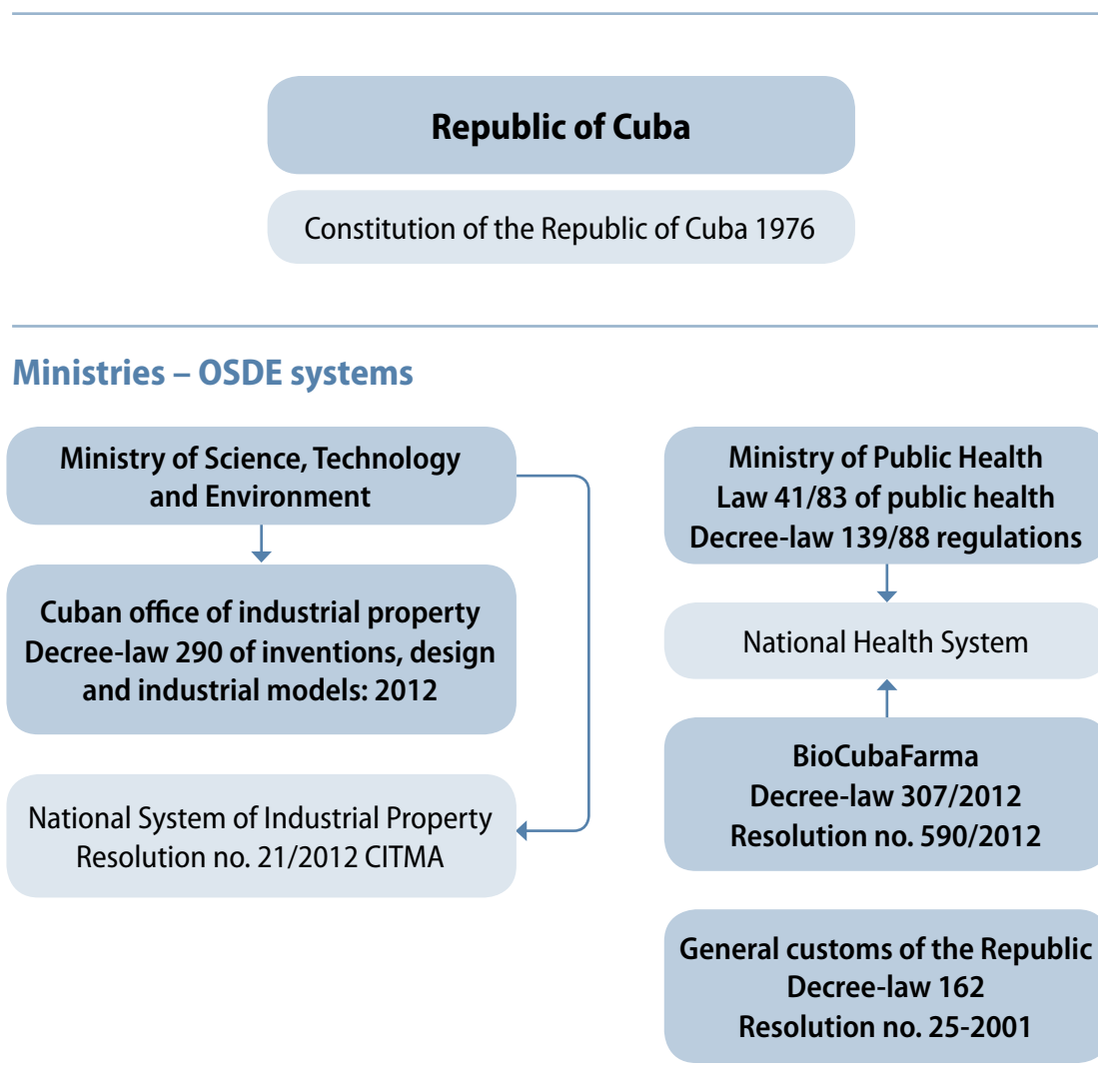
Notable among the actions cited in this resolution are the structuring and implementation of internal industrial property systems in agencies, institutes, companies and other entities to ensure proper and successful execution of the activities subject to the general principles of NSIP.

OCPI is charged with training human resources for Cuba's various entities and agencies through graduate-level courses aimed at educating the different NSIP actors, such as official agents, representatives, attorneys, judges, customs officers, journalists, researchers and negotiators.

6.2.2 Conceptual framework for intellectual property and public health

Figure 4 shows the relationship between intellectual property aspects of Cuba's national health system and biopharmaceutical industry and the current legal framework. It should be noted that there is a close relationship between OCPI and various entities of the central administration, which interact with MINSAP and BioCubaFarma. Reference to the Law of Laws (Constitution of the Republic of Cuba) (38) and customs legislation related to intellectual property is observed.

Figure 4. Concept map and legal framework for public health and intellectual property



The will of the country regarding the protection of research results, both in Cuba and abroad, can be found in Guideline No. 228, which states: “strengthen capabilities for technological exploration and surveillance and the policy for the protection of industrial property in Cuba and the principal foreign markets” (34).

Of particular importance for the population’s access to medicines and health technologies is the promulgation of Decree Law No. 290 (2012):

The new legislation should make it possible to counter the abusive exercise of acquired rights or the use of practices that unjustifiably restrain trade, as well as to safeguard the rights that aid the Republic of Cuba in adopting the necessary measures to protect public health and, in particular, the right to promote access to medicines, as recognized by the Doha Declaration on the TRIPS Agreement and Public Health of November 2001; likewise to protect the population’s nutrition and other fundamental general public policy objectives, supreme interests of the Cuban State. Articles of this Decree-Law contain different clauses related to health (102).

6.2.3 Intellectual property and the Cuban biopharmaceutical industry

The development of new technologies and products and a sound strategy to protect them in Cuba and abroad has enabled BioCubaFarma to build a significant portfolio of patents and trademarks around the world (Table 14), with access via its products or processes to markets they would not have otherwise and transfer of technologies that enjoy intellectual property rights.

Table 14. Rights granted and requested by BioCubaFarma, December 2013^a

Inventions				Other protection modalities ^b		BioCubaFarma trademarks			
Patents requested		Patents issued				Trademarks requested		Trademarks issued	
Ntl.	Intl.	Ntl.	Intl.	Ntl.	Intl.	Ntl.	Intl.	Ntl.	Intl.
43	957	172	1333	22	3	76	198	219	332

^a Compiled from information supplied by BioCubaFarma, 29 December 2013.

^b For example, utility models and industrial models.

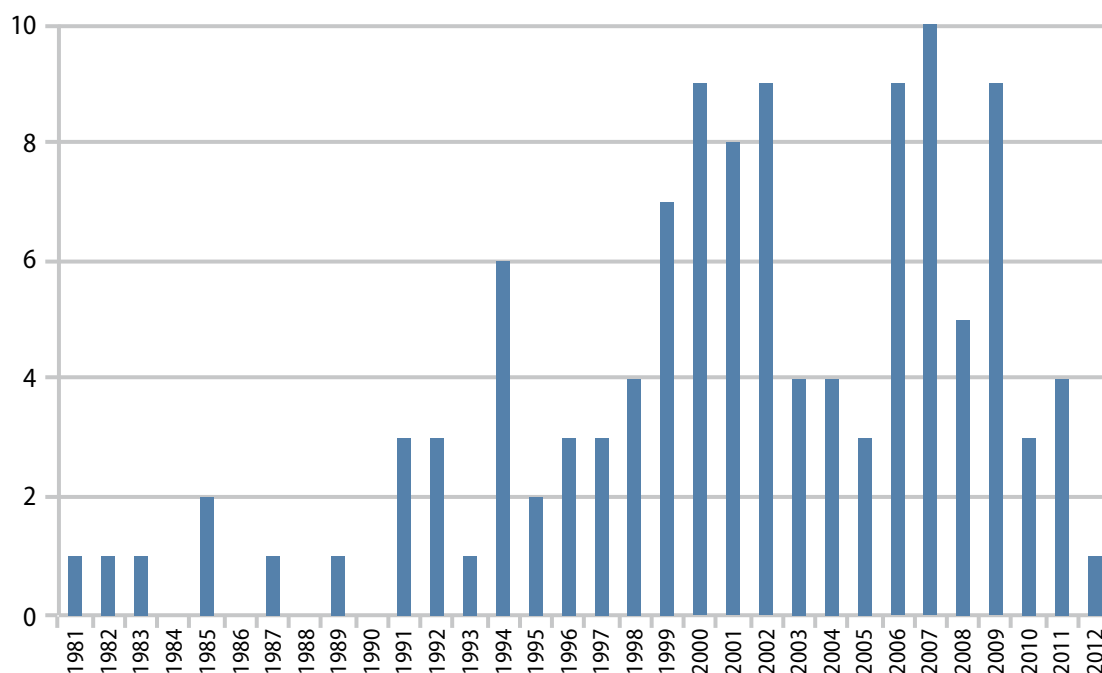
This portfolio is an expression of the outcomes and technological impact of the results obtained by the institutions belonging to this industry, which possesses intellectual property rights in all five continents (105). One example of the impact of the portfolio is the commercial use of 60% of the patents (106).

A study of the 117 patents issued to Cuban interests (1984–31 December 2014) by the United States Patent and Trademark Office shows that 110 involve health technologies (drugs, biotechnology products, diagnostic and treatment devices and equipment).²⁷ The

27 Garcia B, Di Fabio JL. Una mirada al desarrollo de las tecnologías sanitarias en Cuba a partir del estudio de sus patentes (unpublished).

entities that hold the highest number of patents are CIGB (64), CIM (23) and CNIC (15).²⁸ Figure 5 shows an increase in inventive activity in the past 20 years, corresponding to the development of biotechnology in Cuba and the work of its institutions.

Figure 5. Number of patents issued by the United States Patent and Trademark Office to Cuban entities, by priority year



The patented products and processes include:

- Heberprot-P, which can reduce the need for amputations in people with diabetic foot ulcers; this is a unique and exclusive product with a Cuban patent (107);
- Vaxira (racotumomab), used in stage 2 advanced lung cancer;
- Quimi-Hib vaccine, obtained by the Synthetic Antigen Laboratory at the University of Havana; this is an example of the importance of integration and collaboration at the national and international level – the holders of this patent are the University of Havana School of Chemistry and the University of Ottawa, Canada.

Since 1989, nine Cuban inventions have received the WIPO Gold Medal (Table 15), and four WIPO trophies have been awarded to innovative Cuban companies – two of them to CIGB and CIM in 2012 for their successful management of intellectual property.

²⁸ Patents issued to Laboratorios Dalmer SA and CNEURO (belonging to the CNIC multicentre at that stage) are included.

Table 15. Cuban inventions awarded the WIPO Gold^a

Year	Invention	Centre
1989	Method for obtaining broad-spectrum vaccine against group B <i>N. meningitidis</i> and the resulting vaccine	Finlay Institute
1996	Pharmaceutical compounds containing mixture of primary higher aliphatic alcohols for treatment of hypercholesterolaemia and type II hyperlipoproteinaemia, and stimulant of sexual behaviour in animals and humans	CNIC
2000	Procedure for obtaining 1-(5-bromofur-2-IL)-2-bromo-2-nitroeteno and its microbicidal action	Chemical Bioactive Center, Villa Clara Central University
2002	Obtainment of chimeric and humanized monoclonal antibody against epidermal growth factor receptor for diagnostic and therapeutic use	CIM
2002	Practical method for raw milk preservation	National Agricultural Health Centre
2005	Oligosaccharides derived from ribosyl-ribitol-phosphate, methods to prepare them, immunogens that include them, and vaccines that include these immunogens	University of Havana and University of Ottawa, Canada
2007	Equipment and method for rapid microbiological diagnosis	CNIC
2007	Swine lung surfactant	National Agricultural Health Centre
2011	Use of pharmaceutical compound containing epidermal growth factor for prevention of diabetic foot amputation	CIGB

^a Source: <http://www.ocpi.cu>.

7. Public health policy

This section discusses elements of the law and public health policy in Cuba as they relate to public access to medicines and other health technologies and also reviews selected aspects of pharmaceutical regulation.

In Cuba, MINSAP is responsible for implementing the country's public health policy.²⁹ According to the 1976 Constitution (38), the State is responsible for ensuring there is no sick person who does not receive medical attention and that medical and hospital care is free for the entire population, regardless of race, sex, religious belief or social origin.³⁰ Public Health Law No. 41, enacted in 1983, establishes the premise that health protection and care for the population is a permanent, fundamental obligation of the State (108,109).

The Cuban health system guarantees universal access to its services and is funded entirely by the State (Box 1). It is structured around three levels of care: the primary level handles around 80% of the population's health problems and provides health services through polyclinics and family doctors' offices under municipal management; the secondary level handles around 15% of health problems and provides services in provincial hospitals; and the tertiary level handles 5% of health problems in specialized hospitals and health institutes (110). Access to medicines and other health technologies as part of the right to health has been a State priority since 1959.

Box 1. Principles of the Cuban public health system

- Provided by the State
- Universal
- Free
- Full coverage and access
- Focused on prevention
- Regionalized
- Based on primary health care
- Based on social and community practice
- Intersectoral approach

The BDL includes all drugs available in the Cuban national health system. MINSAP reviews and updates the medicines for inclusion in the BDL every year, based on morbidity and mortality studies. The BDL classifies drugs as essential, nonessential and special. Medicines whose distribution is controlled centrally, such as those for certain services and programmes, in vitro fertilization and organ transplants, are placed in the special category (111).

The way a country's pharmaceutical sector is organized can affect the availability of, price of and access to medicines (112). Cuba has no private pharmaceutical sector, and drug production and distribution is the purview of the State (113), which has monopsonistic³¹ control over drugs. MEDICUBA is the country's largest importer of drugs, reagents and disposable materials, servicing the national health system and the tourism and health organization (114). In Cuba, it is unusual to find domestic and imported supplies of the

29 Decree Law no. 67 (1983) of the Organization of the Central State Administration.

30 Articles 9, 43 and 50 of the Constitution of the Republic of Cuba. The Constitution was enacted in 1976 and amended by the Constitutional Reform Act in 1992 and 2002.

31 That is, there is only one buyer.

same drug in the pharmacy network, because generally only medicines that cannot be produced domestically by the local industry are imported.

MINSAP is responsible for ensuring the stability of drug prices for the population and has approved prices since 1988, using a methodology endorsed by the Ministry of Finance and Prices, in which the Cuban Government subsidizes part of the price, as necessary (113). MP Resolution 21 (1999) and Instruction 16 (2000) establish the general methodology for drug pricing. Resolution No. 556 (2013) entered into force on 1 January 2014 for new products from the biotechnology and pharmaceutical industries. The Drug Marketing and Distribution Company (EMCOMED) is responsible for setting the retail price and the subsidy, when applicable (115).

The methodology and provisions related to the drug-supply chain in Cuba are established in the National Drug Programme (Box 2). One of the specific objectives of this programme is to ensure adequate availability of medicines in pharmacies and health institutions.

Box 2. *National Drug Programme*

- Implemented in 1991; revised in 1994, 1998, 2001, 2007 and 2012 (115).
- Includes the methodology for the procurement, prescription, dispensing and rational use of drugs; contributes to access to medicines (115).
- Modified to keep pace with the changes taking place in Cuba, but while its essential concepts remain unaltered (116,117).

In this analysis, it is important to point out that the drug policy implemented by MINSAP is determined by two factors (115):

- the political will of the State to guarantee the health of the population (22,23,118);
- the United States economic blockade of Cuba (9,10,119–121).

These two factors have had a decisive influence on the development of the Cuban national biopharmaceutical industry, and as a result of the policy the national health system has drugs and other health technologies manufactured in Cuba (69,111,122,123).

It should be noted that one of the basic principles of the National Pharmaceutical Policy in terms of state control of the quality of medicines and diagnostic tools has been to ensure that the quality, safety and effectiveness of drugs meet the required standards and that diagnostic tools guarantee good performance and reliable results. Similarly, since its adoption, this policy has included ongoing improvement of the programme for state control of drug quality to contribute to the development of the national biopharmaceutical industry (124).

7.1 *Setting priorities for local production of medicines and other health technologies in Cuba*

MINSAP and BioCubaFarma are responsible for setting priorities in local drug manufacturing. Both entities prepare an annual plan for domestically manufactured and imported drugs,

using the approved BDL and analysis at the provincial level that considers demand, based on different demographic and health service parameters (115).

The programme for import substitution and the development of generic products for the BDL is used for introducing new products. Implementation and monitoring of this programme follow an established procedure, which takes into account industry responsibilities in this process (115).

7.2 Pharmaceutical regulation of medicines and other health technologies in Cuba

7.2.1 National regulatory authority

Cuba's drug regulatory authority CECMED was created in 1989 for the purpose of centralizing action for the regulation and control of drugs and diagnostic tools, previously scattered across various MINSAP agencies.³² The functions and powers of CECMED were established in 1994.³³

Under the programme for strengthening national regulatory authorities, CECMED has been evaluated by WHO as a functional national regulatory authority since 2000 (125), a status it has maintained after several follow-up evaluations (2002, 2003, 2004, 2005, 2008) (126). CECMED has been a PAHO reference national regulatory authority since 2010 (127).

CECMED participates in international cooperation agreements with counterparts in other countries, with the aim of achieving greater efficiency and effectiveness in the regulation and control of drugs and other health technologies. It has signed many bilateral agreements and memorandums of understanding with countries inside and outside the region and participates in the activities of the Pan American Network for Drug Regulatory Harmonization.

CECMED is the focal point of ALBAMED, a subregional project launched in 2009 and consolidated in 2013, aimed at facilitating access to good-quality, safe, efficacious medicines with better prices through the common registry recognized by the member countries. It is geared to the basic drug lists of the countries of the Bolivarian Alliance for the Americas (128).

Over the past two decades, CECMED has faced the challenge of regulating a national industry with great scientific and innovative potential (122), which has contributed to the development of comprehensive drug regulations (129) consistent with the WHO recommendations and other applicable regulations and guidelines for national regulatory authorities with internationally recognized performance.

7.2.2 Sanitary registration of medicines and other health technologies

The legal foundation for the production, distribution and marketing of drugs and medical equipment and devices in Cuba is established in Public Health Law 41.³⁴ Domestically manufactured and imported medicines for human use are circulated after their entry in

32 Ministerial Resolution No. 73 (1989).

33 Ministerial Resolution No. 120 (1994).

34 Chapter VII, Section 2, Article 98, Section 6, Article 102 and Section 8, Article 104.

the sanitary register, as established by that law³⁵ and Decree Law 139,³⁶ although the first regulation on the registration of medicines for human use was enacted in 1979³⁷ before Law 41.

This regulation establishes differentiated evaluation procedures based on the classification of the drugs and type of registry.

Initially, in the regulations for sanitary registration, drugs were classified according to their degree of novelty, such that new and known products and biological and biotechnology products were included in category A (highest degree of novelty). In 2009, faced with the challenge of regulating the approval of biosimilar products developed by Cuba's domestic industry, CECMED updated those rules and created new classes and categories (122).

In Cuba, bioequivalence studies to demonstrate the therapeutic interchangeability of generic drugs in the registry were mandated in 1999, and the regulation was updated and superseded by Regulation No. 18 (2007).³⁸ These studies are indispensable for only a limited group of products (113,130).³⁹

At the end of 2012, a total of 1953 products were registered; in December 2013, the total was 2009 products (131).

In Cuba, diagnostic tools are classified into three categories, depending on the risk posed to the health of the population by a defect in their performance. The year 2012 marked a breakthrough in the control of diagnostic tools through the increase in their sanitary registration (131).

In the registration of medical equipment, two regulations are applied that complement the Regulations for the State Evaluation and the Registry of Medical Equipment.⁴⁰ Imported equipment is evaluated and registered in accordance with its risk classification. In 2012, 186 registries and 32 extensions for medical equipment were completed (131).

7.2.3 Clinical trials

Ministerial Resolution No. 178 (1991) empowered CECMED to approve the start of investigations or clinical trials in humans. Regulation 21 (2000) spelled out the requirements for the approval and modification of clinical trials.⁴¹ In the period 1996–2000, 82 clinical trials were authorized (132); this increased to 280 in the period 2008–12 (133,134). The majority of clinical trials conducted in the latter period were phase II trials (43.2%), followed by phase I trials (27.5%) and phase III trials (13.2%). It should be noted that 91% of the clinical trials authorized in 2008–12 were studies promoted by the manufacturers of biological and biotechnology products, while 6.4% were sponsored by the medical/pharmaceutical industry (131).

35 Chapter VII, Article 102.

36 Chapter XVI, Article 197.

37 The regulations and requirements for the registration of medicinal products for human use have been amended many times. Resolution No. 321 (2009) and Regulation No. 61 (2012) are the documents in force.

38 CECMED Resolution No. 17 (2007).

39 CECMED Resolution No. 94 (2008).

40 Regulation ER-1A (1992) and Regulation ER-3 (1993).

41 Ministerial Resolution No. 166 (2000).

The National Programme for Clinical Trial Inspection was established in 2001, and certification for good clinical practice for sites and clinical services was established in 2008. From 2005 to 2009, 56 inspections of clinical trials were conducted and 2 sites were certified for good clinical practice (133). In 2013, 16 inspections of clinical trials were conducted and 4 sites certified for good clinical practice.⁴²

Since 1991, Cuba has had the National Coordinating Center for Clinical Trials (CENCEC), a MINSAP contract research organization whose purpose is to ensure the clinical evaluation required for the registration and marketing of medical, pharmaceutical and biotechnology products and medical equipment in Cuba and other interested countries. From its inception until 2013, CENCEC completed 124 clinical trials in collaboration with 24 manufacturing centres (134).

The Cuban Public Registry of Clinical Trials was set up in 2007. This is a database developed by CENCEC with the collaboration of Infomed for the registration of clinical trials. As it meets the requirements of the WHO International Clinical Trial Registry, in 2011 it was granted the status of primary record. It is the first Latin American record with this category (135).

7.2.4 Regulation of manufacturing of drugs and active pharmaceutical ingredients

Obtaining a sanitary licence for pharmaceutical operations is a mandatory requirement in pharmaceutical regulation, established for the manufacture, importation, distribution and export of drugs and active pharmaceutical ingredients (APIs). Inspection to verify compliance with applicable good practice is also essential for obtaining a licence. In 2012, 33 licence applications were reviewed and 30 licences were issued. Of the 30 licences issued, 16 were to manufacturers of biological products (136).

Like other drug regulatory authorities, CECMED verifies that during the production, control, storage, distribution and marketing of APIs and medicines for human use, applicable current good practices are assured through state inspection of good practices. In 2012, CECMED conducted 80 inspections, most of which corresponded to manufacturers of biological products (136).

Since 1997, Cuba has had a programme for the development of natural and traditional medicine, which was recently updated pursuant to Guideline 158 (34) and incorporated into the National Drug Programme (117). The role of CECMED under the National Programme for Natural and Traditional Medicine was established in Decree 4282 of the Council of Ministers in 2002; since then, specific provisions have been added for the registration of drugs of natural origin. In 2011 good manufacturing practices for homeopathic medicine⁴³ were approved, and in 2012 good manufacturing practices for natural and locally produced products were approved.

CECMED conducts inspections to assess compliance with good manufacturing practices in the production of diagnostic tools and audits the quality management system in the production of medical equipment.

⁴² Source: Department of Clinical Trials, CECMED.

⁴³ Regulation No. 58 (2011) adopted and enforced by CECMED Resolution No. 97 (2011).

7.2.5 Control of imports

Cuba imports almost all APIs and excipients used in drug production. Since it has no plants for chemical synthesis, its strategy has been to develop formulation capacity and produce finished forms of pharmaceutical products. APIs are produced in the case of vaccines and other biotechnology products. Regulation of good manufacturing practices for the production of APIs⁴⁴ is one of the annexes that supplements the current guidelines on good manufacturing practices for pharmaceutical products and applies to APIs produced and used in Cuba.

Cuba has a sanitary control system for drug imports, which requires a certificate issued by CECMED for the commercial importation of medicines for human use.⁴⁵ In 2012, 861 import authorization certificates were issued, covering 1509 products (131).

7.2.6 Regulation of the distribution of pharmaceutical products and materials

Distribution of drugs, reagents and raw materials for medical care is the responsibility of EMCOMED and the BioCubaFarma production facilities (115).

In 2012 during drug monitoring, 233 pharmaceutical products in the distribution chain were inspected (136). CECMED regularly publishes information on counterfeit products and potential risks to the health of the population (137).

As part of supply chain control, CECMED monitors compliance with good operating practice with diagnostic tools⁴⁶ by diagnostic tool importers, exporters and distributors, which is a requirement for obtaining and maintaining a licence.

7.2.7 Compliance with established conformity requirements

In addition to inspections at local and foreign pharmaceutical facilities, CECMED conducts research on medicines and other health technologies to monitor compliance with current conformity requirements.

CECMED coordinates the post-marketing surveillance system, which benefits from the centralization of drug manufacturing, import and distribution activities, and the characteristics of the national health system (139). The programme for surveillance and quality control of medicines is intended to prevent the marketing of defective, counterfeit or adulterated products, whether imported or domestically produced, through active surveillance and periodic batch sampling (136). In the period 2008–12, 546 product investigations were conducted as part of post-marketing surveillance, 346 of them relating to quality defects and 9 to suspected counterfeit medicines. During this period, 51% of the quality control tests performed by CECMED corresponded to post-marketing surveillance (131).⁴⁷

CECMED has the authority to institute health safety measures or impose sanctions. From 2008 to 2012, it issued 238 health safety measures involving batch recalls for a total of 749

44 Annex 09 of Regulation 16 (2006).

45 Regulation No. 43 (2005) approved and enacted by CECMED Resolution No. 73 (2005).

46 Resolution No. 83 (2005) approved and enacted by Regulation No. 42 (2005).

47 47% of the quality control tests performed by CECMED from 2008 to 2012 were for batch releases and 2% for registration procedures.

batches of products recalled, and 58 warning letters (131). Resolutions corresponding to the temporary or permanent suspension of drug manufacturing before 2008 are published on the CECMED website (140). Health safety measures can be found in *Ambito Regulador*, the official CECMED publication.

Similarly, other regulations indicate the health measures or sanctions to be adopted by CECMED in case of noncompliance with the requirements. These administrative actions are taken by CECMED but may be appealed to MINSAP. A new regulation on specific complaints, claims and reconsideration of regulatory decisions (Annex 3 of Good Regulatory Practices) entered into force in 2014 (141).

Publication of the report on its activities during the period 2008–12 is an example of CECMED transparency in the exercise of its functions. The information gathered in the form of lists, figures, tables and graphs to characterize and illustrate basic CECMED performance results in its core functions of regulation and control is available on its website (131).

7.3 Results of the public health policy

This section reviews some results of Cuba's public health policy with respect to the population's access to medicines and other health technologies and its impact on health indicators.

Cuba is an example in which a well-developed public health strategy has generated indicators comparable to those of industrialized countries (10,19,142). Despite limited resources, the Cuban health system has solved problems that other national health systems have not been able to (30,121,143–145).

Cuba's public health outcomes are based first on the principle that health is a right of its population, and second on the development of the following areas: a national health system, training of human resources, development of research and biopharmaceutical production, and establishment of an international health cooperation and assistance programme (146). In 2013, total health expenditure per capita was 439.06 Cuban pesos (3), a figure that belies the health indicators.

7.3.1 Contribution to local production of medicines

Scarce resources, coupled with the need to develop a sustainable independent health model, despite global financial and economic constraints, has led to the creation of the national biopharmaceutical industry as a basic component of the health system (83).

Before 1959, Cuba imported most of the drugs it used, mainly from the United States (96,97,147). Today, it has a biopharmaceutical industry that has been able to maintain about 65% stability in domestic drug production. In 2013, 87% of the products to be sold in pharmacies were assigned to the domestic industry. According to the 2014 BDL, 408 of 888 drugs (46%) were intended for sale in pharmacies and the rest for use in health institutions (111,148).

Table 16 shows the contribution of domestically produced drugs in selected therapeutic categories. In addition, 8 of the 11 vaccines used in the national immunization programme (28) and 6 antiretrovirals are produced domestically.⁴⁸

Table 16. Contribution of national drug production by therapeutic category, Cuba 2013

Group	Pharmacological group (according to BDL, 2013) (111)	National production/total (%)
3	Anti-allergics	9/9 (100)
4	Antidotes and other substances used for poisonings	5/20 (25)
5	Anticonvulsives/antiepileptics	16/26 (61.5)

In 2010, of the 133 biological products registered, 67 were produced by Cuba's domestic industry. Vaccines were the largest group of registered products, followed by interferon alfa and blood products. Of the imported products, insulins and pegylated compounds were the largest group, followed by vaccines. It is noteworthy that the products manufactured domestically are largely produced by a single manufacturer (122).

In Cuba, the population's access to medicines is generally guaranteed (110, 113). However, in late 2013, 41 drugs of the 880 on that year's BDL (4.6%) were reported "missing".⁴⁹ Of these shortages, 8 corresponded to imported drugs and 33 to domestically produced drugs (148). The national health system has established a methodology for analysing and monitoring drug shortages (115).

7.3.2 Prices of imported and locally produced medicines

Drug prices are low relative to the income level of the Cuban population (74,110,114). They are free for hospital services, specialized health programmes such as the tuberculosis programme, people undergoing transplants, people with AIDS (113), and people in the social security system (110,113). Prices for the purchase of some prostheses and devices are subsidized by the State (110).

A national survey conducted between 2003 and 2012 on the consumption, safety and cost of medicines used to treat hypertension, covering about 250 000 patients, found that although the prices of drugs for sale to the public in Cuba have not changed, treatment costs for patients have risen, since there has been a shift to safer, more effective but more expensive drugs.⁵⁰

7.3.3 Quality, safety and efficacy of locally produced drugs

The Cuban government, through MINSAP, has ensured the financial sustainability of CECMED as an essential component of the national health system with a view to developing local production of drugs and other health technologies that meet international standards. CECMED has been evaluated on many occasions with respect to the health regulatory

48 Source: Novatec Laboratories, 17 March 2014.

49 The "missing" drug indicator is defined by a shortage in three or more provinces.

50 Source: Department of Planning and Drug Analysis, MINSAP.

functions recommended by WHO and PAHO to ensure the quality, safety and efficacy of drugs that it regulates and controls. As a result, it has enjoyed the status of functional national regulatory authority since 2000 and of reference national regulatory authority for drugs since 2010.

7.3.4 Differentiation between innovative and generic products

In Cuba, drugs that are not innovative⁵¹ are known as “generic”. The terms “similar” and “competitor” are not used, due to the nature of the Cuban market. In national drug regulation, the term “multi-source drug”⁵² is used, following the WHO recommendations (113).

Studies conducted from 2007 to 2012 in low- and middle-income countries showed that, on average, only 57% of selected drugs were available as generics in the public sector (149). In Cuba, the pharmaceutical sector is State-owned, and generics are widely employed in the various stages of drug supply, since they are used as a suitable alternative to ensure the population’s access to medicines and the sustainability of national health system programmes.

In a study conducted in Cuba, of the 492 medicines registered in the period 1996–2000, 417 (85%) were generic products (132).

7.3.5 Impact of local drug production on public health outcomes

The biotechnology industry in Cuba has been notable for its highly innovative nature, with the generation of products unique in their class. A 2009 *Nature* editorial described it as the most established biotechnological industry in developing countries, with growth in the absence of a venture capital model, considered a prerequisite in industrialized countries (150).

Although a comprehensive and deep analysis of Cuban biotechnology has yet to be made by any of the major players (33), there are reports showing its development and impact on public health (24,26,54,151–154) and its particular characteristics (25,33,52,53) focused on improving the health of the population and developing life-saving drugs.

Below are some examples to illustrate product generation in the biopharmaceutical industry and its impact on health indicators, which is the main objective of Cuba’s policy on access to medicines.

7.3.5.1 Prophylactic vaccines

Antigen production for 8 of the 11 vaccines used in the national immunization programme, which protects against 13 diseases, is one of the achievements of Cuban biotechnology. However, the coverage attained in children to protect against these diseases is an even greater accomplishment (22).

51 Used as a reference product, an innovative pharmaceutical product is generally the product registered for the first time; thus, it usually corresponds to a patented active ingredient for which complete studies of quality, safety and efficacy have been performed.

52 A multi-source drug or drug of multiple origins may be obtained from multiple manufacturers, which may have the same or a different pharmaceutical form and strength as the innovative product, may be a pharmaceutical equivalent or an alternative one, and may or may not be a therapeutic equivalent.

More than 55 million doses of meningococcal vaccine VA-MENGOC-BC have been administered in Cuba and 15 other countries, primarily in Latin America and the Caribbean (27).

The Cuban recombinant hepatitis B vaccine has reduced the incidence of hepatitis B from 376 cases in 1991 to 16 cases in 2012 (24), an incidence of 0.1 per 100 000 inhabitants (3), dropping to zero in children aged under 15 years (33).

The conjugate Hib vaccine, the first vaccine containing a capsular polysaccharide antigen obtained by chemical synthesis, has proven to be as safe and immunogenic as marketed vaccines containing the native polysaccharide (73). This vaccine has been used in the Cuban national immunization programme as a component of the pentavalent vaccine since 2006. The introduction of this vaccine has had a dual impact: it reduced annual costs by substituting the similar imported vaccine with savings of US\$ 2–3 million (154), and it reduced the incidence of infection by these bacteria.

7.3.5.2 Therapeutic vaccines

Two therapeutic vaccines for non-small-cell lung cancer (CIMAvox EGF, Vaxira) are worth noting. They have different characteristics: CIMAvox EGF consists of epidermal growth factor as a major antigen, and Vaxira is an anti-idiotypic vaccine consisting of the humanized monoclonal antibody racotumomab (65).

7.3.5.3 Diagnostic tools

In 1981, a pilot programme was launched using SUMA⁵³ equipment to detect congenital malformations. In 1986, Cuba became the second country in the northern hemisphere (after Canada) to guarantee monitoring of all newborns for congenital hypothyroidism. Currently, under the national neonatal screening programme (60), all Cuban children are tested at birth for hypothyroidism, phenylketonuria, congenital adrenal hyperplasia, biotinidase deficiency and galactosaemia (51). Since its implementation, this programme, which performs 33 diagnostic tests introduced in the health system for the detection, monitoring and evaluation of 19 diseases (Table 17),⁵⁴ has contributed to an improvement in the health of the population. Similarly, diagnostic systems and equipment developed and manufactured by the Immunoassay Center have had an impact on global health through 463 laboratories with SUMA technology in countries such as Argentina, Brazil, China and Mexico (74).

53 SUMA is an immunodiagnostic technology developed at the Immunoassay Center in which a very small sample permits active screening of various diseases.

54 A network of 234 laboratories and 168 specialized centres in active comprehensive screening nationwide is included in the implementation of this health technology. Five regional technical assistance centres support the work of the laboratory network.

Table 17. Cuban immunoassay technology in the national public health system^a

Test	Technology	Year introduced	Number of tests performed up to 31 July 2012	Cases detected
Pregnant women				
Birth defects (alpha-fetoprotein)	UMELISA AFP	1982	3 755 511	8011
Ectopic pregnancy and trophoblastic disease (human chorionic gonadotrophin)	UMELISA HCG	1992	Case-by-case basis (available nationwide)	NA
Newborns				
Congenital hypothyroidism (thyroid-stimulating hormone)	UMELISA neonatal TSH	1986	3 350 373	801
Phenylketonuria (Phe)	UMTEST PKU	2000	1 055 575	20
Congenital adrenal hyperplasia (17-OH progesterone)	UMELISA 17-OH neonatal progesterone	2005	780 771	45
Biotinidase deficiency (biotinidase)	UMTEST biotinidase	2005	759 935	5
Galactosaemia (galactose)	UMTEST Gal	2005	723 182	7
Infectious diseases				
HIV/AIDS (anti-HIV 1 and 2 immunoglobulin G antibodies)	UMELISA HIV 1 and 2 recombinant	1988	47 411 375 (includes blood donors, pregnant women and general epidemiological surveillance)	15 284 seropositive tests
Hepatitis B (HBsAg and other serological markers)	UMELISA HBsAg plus, HBsAg confirmatory test UMELISA anti-HBsAg, UMELISA anti-HBc, UMELISA anti-HBcIg M	1986	20 270 560 (includes blood donors, pregnant women and general epidemiological surveillance)	77 508 confirmed cases in blood donors
Hepatitis C (anti-HCV)	UMELISA HCV	1992	10 615 685 (includes blood donors, pregnant women and general epidemiological surveillance)	0.90% reactivity in blood donors

Hepatitis C (anti-HCV)	UMELOSA HCV (PCR)	2005	6531	3282
Dengue (immunoglobulin M antibodies)	UMELISA dengue IgM plus	1995	530 677	NA
Leprosy (immunoglobulin M antibodies)	UMELISA Hansen	1993	25 354	8.1% reactivity
Chagas disease (immunoglobulin G antibodies)	UMELISA Chagas	1994	12 260	4.9% reactivity
Tetanus (immunoglobulin G antibodies)	UMELISA tetanus	1996	47 070	23 208 donors with required titres used for production of human tetanus immunoglobulin
Chronic noncommunicable conditions				
Diabetes mellitus (blood glucose)	SUMAsensor (glucometer and biosensors)	2008	513 405	130 316 glucometers and 26 million dipsticks (85% for people registered and treated in primary care)
Prostate cancer (prostate-specific antigen)	UMELISA PSA	2003	464 683	NA
Microalbuminuria (microalbumin)	UMELISA microalbumina	2010	351	109
Colon cancer (faecal occult blood)	SUMAsohf	2012	7450	14; other diseases – 541
Atopic diseases (total immunoglobulin E)	UMELISA IgE	1987	Children with suspected allergies	n/a

^a Source: reference (74).

NA: no information available.

7.3.5.4 Other biopharmaceutical products

Other products derived from biotechnology are produced in Cuba and used in the national health system (Table 18), including recombinant erythropoietin; the fact that this costly product is available to people with chronic kidney disease and other serious illnesses is a great accomplishment (22). Heberprot-P is an innovative product containing recombinant human epidermal growth factor and used for chronic ulcers to reduce the risk of diabetes-related amputations. Heberprot-P was registered in Cuba in 2006 and is now registered in 15 other countries, making it possible to treat more than 100,000 patients; applications for its registration are under review in other countries, including Brazil, China, the Russian Federation, South Africa and the Arab states of the Persian Gulf. Heberprot-P has been on the Cuban BDL since 2007 (29).

Table 18. Products for human use developed by CIGB and approved for sale^a

Year	Product	Indication
1981–1990	Leuferon (human interferon)	Viral infections, cancer
	Hebertrans (human transfer factor)	Immunodeficiency, herpes, ataxia
	HeberonalfaR (recombinant interferon alfa 2b)	Hepatitis C, cancer
	Hebermin (recombinant epidermal growth factor)	Burns, skin ulcers
	Heberbiovac HB (recombinant hepatitis B vaccine)	Hepatitis B prophylaxis
1991–2000	Heberkinasa (recombinant streptokinase)	Cardiovascular disease
	HeberonalfaR (recombinant interferon alfa)	Juvenile rheumatoid arthritis
2001–2010	Quimi-Hib (Hib vaccine)	Prophylaxis of Hib pneumonia and meningitis
	HB–Hib bivalent vaccine	Prophylaxis of hepatitis B and Hib pneumonia and meningitis
	Trivac HB (tetraivalent vaccine DPT–HB)	Prophylaxis of diphtheria, pertussis, tetanus and hepatitis B
	Heberpenta (pentavalent vaccine DPT–HB +Hib)	Prophylaxis of diphtheria, pertussis, tetanus, hepatitis B and Hib pneumonia and meningitis
	Hebervital (granulocyte colony stimulating factor)	Leukopenia, neutropenia
	Heberitro (recombinant erythropoietin alpha)	Anaemia
	Heberprot-P	Diabetic foot ulcer

^a Compiled from reference (24).

7.3.5.5 Antiretrovirals

Since the introduction of domestically produced antiretroviral therapy in 2001, the number of people who have benefited has increased substantially, reaching 100% coverage with highly active antiretroviral therapy in 2003 (155). The use of domestically produced generics has resulted in lower patient morbidity and mortality and fewer opportunistic infections and hospitalizations, with lower therapy costs (156,157). The economic impact in the period 2001–10 was considered significant, yielding potential savings of US\$ 46 million, thanks to import substitution (157). The decision to produce antiretrovirals to ensure access to free treatment for patients who need it, together with the existence of an HIV/AIDS control programme and the specialized medical care provided in the national health system, has contributed to Cuba's favourable status in terms of the incidence of infection compared with most Latin American and Caribbean countries (Table 19) (157–159).

Table 19. *Indicators associated with antiretroviral therapy*

Indicator	Result
Universal access ($\geq 80\%$) to antiretroviral therapy?	Yes (158)
Test performance rate	300/1000 (median 57/1000 in Latin America and the Caribbean) (158)
Estimation of people with HIV who know their status	80% (158)
HIV 1 and 2 diagnostic tests (since 1988)	47 411 375 (includes blood donors, pregnant women and general epidemiological surveillance) (74)

8. Final considerations

Analysis of the Cuban experience with the domestic production of drugs and their impact on access to health underscores the role of the State in achieving one of its main objectives: an improvement in the health of the population and its quality of life.

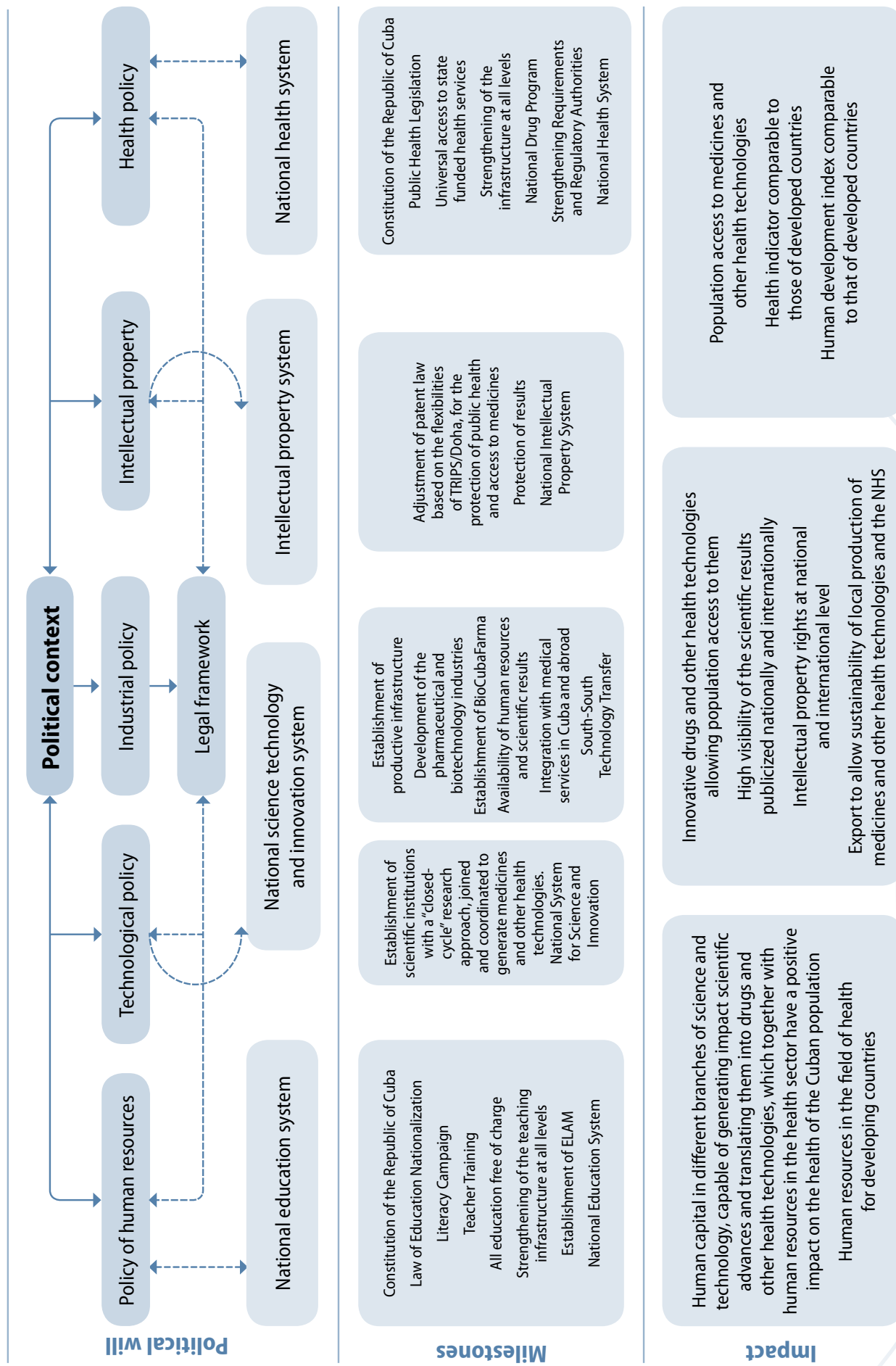
This political will has remained constant for over five decades and has been expressed in a political context that has systemically integrated the different policies described in health, education, industrial technology and intellectual property. These policies have converged and enhanced one another, always maintaining the regulatory and normative support of the different systems and their associated legal framework. This legal framework has been adapted to enable it to respond to the health needs of the population, taking into account regulatory requirements and the requirements for compliance with the international agreements to which Cuba is a signatory.

Figure 6 summarizes the interaction between various policies, legal framework and systems in Cuba, and the major milestones and impacts that have been achieved.

The main milestones are:

- a legal framework that has supported the population's right of access to health and education;
- a literacy campaign;
- creation of the educational and public health infrastructure, and education of human capital in all areas related to the biotechnology and pharmaceutical industries and public health;
- degrees in medical sciences under MINSAP;
- a close relationship between the national health system and biotechnology centres and state supervision and support;
- creation of biotechnology centres based on the will to develop scientific activity and obtain products needed by Cuba's national health system to address the health problems of the population, and implementation of scientific and technical activity under the full-cycle project concept;
- creation of the infrastructure for research, development, production and marketing to obtain the products needed for the national health system;
- having intellectual capital consisting of human capital and scientific results;
- having a national industrial property system that protects the results obtained, and a legal framework that takes into account the flexibilities in TRIPS/Doha to safeguard the country's right to adopt the necessary measures to protect public health and promote access to medicines;
- adoption of the Resolution on the Guidelines of the Economic and Social Policy, which includes aspects with a positive impact on the domestic production of medicines and other health technologies and, hence, the population's access to health;
- integration of the pharmaceutical and biotechnology industries;
- health regulations and strengthening of regulatory authorities;
- national drug programme.

Figure 6. Concept Map: Cuban experience in the local production of medicines, technology transfer, and improvement in access to health care



Implementation of the results obtained in social practice has yielded social and economic impacts, including:

- health indicators and a human development index comparable to those of developed countries (160);
- access by the Cuban population to medicines and other health technologies through the development and manufacture of novel and generic products;
- the national health system and, consequently, the Cuban population being the main beneficiary of biopharmaceutical technology development;
- having significant human capital trained in the various specialties of the biotechnology and pharmaceutical industries, health services and other related specialties, and training of human resources for developing countries;
- novel scientific results with high visibility and intellectual property rights, which have resulted in the generation of products that improve the health of the population;
- sustainability of research and local production through exports of products and technology transfer.

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Annex: Aspects impacting on the access to health technologies included in the Resolution on the Guidelines of the Economic and Social Policy of the Party and the Revolution (34)

I Economic Management Model	State-funded entities	<p>30. State-funded entities fulfil State and Government functions and others, such as the provision of health-care and educational services. These have definite missions, functions, duties and powers.</p>
III External Economic Policy	Foreign Trade	<p>81. Design and implement a strategy to secure new markets for the export of medical services and products from the medical-pharmaceutical industry.</p>
V Science, Technology, Innovation and Environment Policy	Guidelines	<p>131. Sustain and develop the results achieved in the field of biotechnology, medical-pharmaceutical production, software industry, the information society process, basic and natural sciences, the studies and use of renewable energy sources, social and education technologies, industrial technology transfer, manufacture of high technology equipment, nanotechnology, and scientific and technological services of high added-value.</p> <p>132. Improve organizational, legal and institutional conditions to establish types of economic organization that combine scientific research and technological innovation, prompt and effective development of new products and services, their efficient manufacture based on appropriate quality standards, and domestic and foreign marketing that reverts as benefits to society and promotes cycle reproduction. These concepts must be extended to the scientific activity carried out in universities.</p>
VI Social Policy	General Guidelines	<p>143. Continue improving education, health care, culture and sports, for this purpose, it is essential to reduce or eliminate excessive social expenditures, generate new income sources and evaluate all activities that can be transferred from the state-funded sector to the business sector.</p>

VI Social Policy

Health

154. Increase the quality of the service provided to the satisfaction of the population; improve working conditions and health-care employee attention. Ensure that resources are efficiently utilized and economized, and unnecessary expenditures eliminated.
155. Reorganize and concentrate health-care services, including emergency care and transportation, on a regional basis according to the needs of each province and municipality. The Health-care System must ensure that each patient received appropriate and quality assistance.
156. Reinforce the teaching and the use of the clinical and epidemiological method, as well as the study of the social environment in addressing public health care problems, to promote a rational use of technology in the diagnosis and treatment of diseases.
157. Continue to promote educational programs to avoid self-medication by the population and implement other steps that foster rational use of drugs
158. Strongly support the development of traditional and herbal medicine.
159. Reinforce health promotion and disease prevention actions that help improve lifestyles and increase public health standards, by an intersectoral and community approach.
160. Ensure that the training of medical specialists responds to the needs of the country, as well, as Cuba's international commitments

Free Benefits and Subsidies

173. Remove undue free benefits and excessive subsidies under the principle of individual compensation based on need, rather than blanket subsidies on products.
175. Maintain the food services provided in public institutions, with priority given to the health-care and educational facilities that may require them. Improve the mechanisms that provide food support to vulnerable and risk population.

General Guidelines

216. Improve the technical infrastructure for standardization, metrology and quality assurance according to the prioritized objective of export promotion and import substitution.

VIII Industry and Energy Policy

Guidelines for the Main Branches

221. Reinforce the pharmaceutical and biotechnology industry as one of the economic activities with greater export potential and introduce new products in the national market as import substitution.
222. Develop an industry that produces dietary supplements and natural medicines from local resources for domestic consumption and export.
228. Strengthen technical prospection and technological monitoring capacities, as well as the policy on the protection of industrial property rights in Cuba and in the main foreign markets.
232. Develop industries for the production of packaging materials and containers on the basis of a comprehensive approach to this activity. Priority shall be given to the production of the containers required by the Cuban exports and agricultural development.



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