

**Incorporating Biotechnology Research into Health Policy:
The Case of Vaccine Development and Production in Brazil**

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**Study Carried Out For
The Council on Health Research for Development (COHRED)**

February 2000

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Introduction

This study aims to contribute conceptually to thinking about the links between research and health policy in the light of Brazil's experience in vaccine research, development, production and utilization by the Brazilian health system.

Studying the vaccine field in a peripheral country is particularly illustrative of the factors that condition the utilization of health research results in backward, underdeveloped contexts. In the first place, the vaccines field comprises a strong research component, at the same time constituting one of the most important modalities of government action in the health field. The vaccine field thus figures as one of the most relevant to studying the relationship between research and policy. In the second place, Brazil's experience over recent decades appears a relatively successful case of a backward country managing to engage in vaccine production and progressively making headway in incorporating the research results into its health policies.

As regards basic methodology, this study involved a survey and systematization of the literature, firstly, dealing theoretically with the introduction of innovations into the economic system and, secondly, characterizing the environment that conditions interaction between research, production and health policy in the vaccine field in Brazil. In addition, a field survey (following a qualitative, semi-structured interview format) was made among some of the leading agents in the fields of health science and technology and health policy.

The study is organized into 4 separate topics. Topic 1 offers a concise overview of the economic theory that seeks conceptually to indicate the most generic determinants of the introduction of innovations into the economic system. Topic 2 describes the scientific and technological evolution in the fields of biotechnology (Item 2.1) and recent health policy (Item 2.2) that characterizes the context for vaccine innovations. It also indicates elements on the basis of which to consider the interrelationship among research, production and policy in this field in Brazil's experience (Item 2.3). Topic 3 takes the analysis further to present

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notable cases that illustrate the link between research and policy in the vaccine field. Finally, the last topic submits the main conclusions and indicates the most general factors that condition the establishment of interactions between the science and health policy universes in the context of backward countries.

1. Determinants on the Introduction of Innovations into the Economic System

Recent work on the relationship between health research and health policy (WHO, 1996; Gerhardus, 1999; Trostle et alii, 1999; Bronfman, 1999) has emphasized how the logic of the generation of scientific knowledge relates to the logic of policy. Generally speaking, science figures as an activity that furnishes knowledge that may, or may not, be applied in new practices in public policy implementation, depending on the interest of the actors, the relevance of the research to strategic areas of national policy, the actions of the stakeholders, the exchange of information and the interaction between researchers and policy makers.

Actually, the impact of research on health policy may be evaluated, in part, from the way national governments incorporate scientific outcomes – in the fields of biomedical research, population, social research and so on – into their orientations and practices regarding the way the health system is to be organized and operationalized. In this case, the universe of actors to be considered involves two main groups: the agents responsible for formulating and implementing health policy and the scientists that work in health-related areas. Certainly, when the research-policy relationship is analyzed, a series of other groups also exert considerable influence; for instance, non-governmental and international organizations, interest groups and political parties. Nonetheless, these agents intervene in the research-policy relationship to the extent that they shape the behaviour of the policy makers and the scientists.

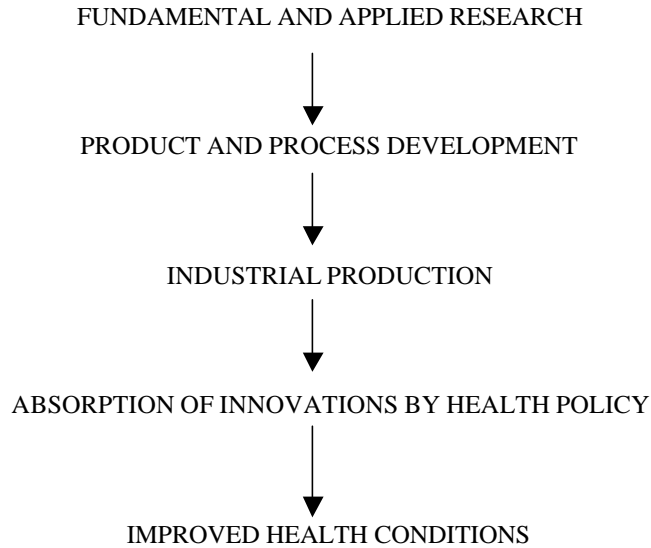
This is only part of the story, however. A substantive and fundamentally important portion of health research can only be applied by way of an intervening activity: the production of goods and services. This is the case with new drugs, vaccines, diagnostic reagents and even the incorporation of new technologies into healthcare services (especially new equipment and materials). As private enterprise occupies a central place in capitalist production, the relationship between research activities and health policies comes to depend, in these cases, on the way the research activity is incorporated into business strategies and how able government is to induce businesses and the scientific community to undertake strategic health research.

That is, two mediations have to be taken into consideration. From the material standpoint, standing between research activities for the introduction product and process innovations and absorption of the latter by health policies, one has to consider the activities of technological development (which involves considerable focalized research efforts) and industrial production. Ignoring this dimension entails conducting laboratory research the results of which will be left on the “scientific shelf”, with no industrial use or impact on national health policies.

The figure below offers a simplified linear diagram summarizing this mediation by development and industrial activities in establishing the link between research, policy and impact on public health conditions¹:

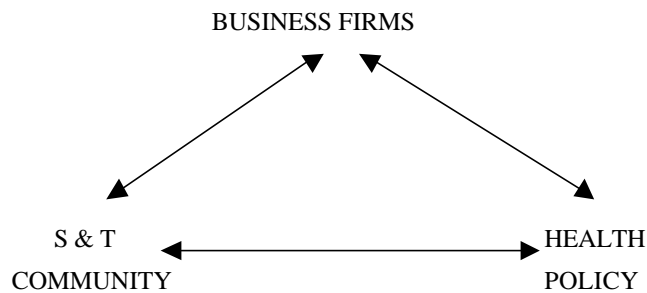
¹ Observe that this chain determining the material stages in the process by which innovations are introduced into the economic system is intended merely to identify the various activities involved which have to be orchestrated. In fact, the interactions among the various stages are multiple and systemic. For example, production activity may generate demands for technological development that, in turn, raise new issues that prompt academic activity, thus inverting this stylized causal arrangement.

Figure 1
Material Stages in the Introduction of Health Innovations
 (linear model)



From the economic standpoint, between the scientific community and the policy makers stand business firms (private enterprise being the most usual form in capitalist society), a new central agent whose strategies condition application of the results of research activities. The figure below illustrates how this new agent intermediates in the process:

Figure 2
Central Agents in the Introduction of Health Product and Process Innovations



This said, it is felt that the frame of reference usually employed in dealing with the relationship between research and policy can be enhanced by introducing, as mediation, the economic logic of capital, particularly when the application of scientific knowledge depends on innovations – expressed in new, publicly available products and processes – being

generated within the economic system. In capitalism, innovations constitute privately appropriated assets and are the main weapon in business competition, as well as being an essential element for national development processes, as shown a long time ago by Marx² (1983) and Schumpeter (1985).

On this view, science figures as a productive force of capital. In the words of Marx (1983), science features “as an autonomous power at the service of capital” (Volume 1, Part 1, p. 284³), and this incorporation results from a historical process that led to a replacement of the “natural forces and empirical routine by the conscious application of the sciences of Nature” (Volume 1, Part 2, p. 17). In this way, as a property inherent to the very foundations of capitalism, it systematically encourages the introduction of innovations into the economic system, constantly revolutionizing the production base and social relations.

The following, well-known quote from the same author shows how in capitalism the endeavour to transform the production base becomes systematic and constitutive of the economic system itself, and tends to generalize world-wide:

“The bourgeoisie cannot exist without constantly revolutionizing the instruments of production, and thereby the relations of production (...). All fixed, rusted relations with their traditional representations and conceptions are dissolved, and the more recent ones become antiquated before they consolidate. All that was solid melts into air, all that was sacred is profaned (...). The need for ever-growing markets drives the bourgeoisie to conquer the whole globe (...).” (Marx, 1997, p. 11)

Along the same lines, Schumpeter characterizes capitalism as a system that develops by a permanent process of innovation and the destruction of the previous production base, as shown clearly by the following passage:

“the fundamental impulse that sets and keeps the capitalist engine in motion results from the new consumer goods, from new methods of production or transport, from new market, from new forms of industrial organization that the capitalist firm creates (...). There is a process of industrial mutation (...) that incessantly revolutionizes the economic structure from within, incessantly destroying the old

² Despite the failure of the socialist experiences and of the historical determinism present in Marx’s analysis, this author’s work in economics continues unsurpassed in its grasp of the foundations of capitalist society.

³ All quotations are free re-translations from Portuguese editions.

one, incessantly creating a new one. This process of Creative Destruction is the essential fact about capitalism. It is what capitalism consists in and what every capitalist concern has got to live in. (...) Normally the problem considered is how capitalism administers the existing structures, when the important thing is to know how it creates and destroys them.” (Schumpeter, 1984 – pp. 112, 113 e 114).

The driving force behind this process of innovation and creative destruction is capitalist competition, given that innovation is the essential competitive force that determines both certain companies' advantage over others and the magnitude of private profits.

As the modern pharmaceuticals industry developed, for instance, it swept away the former industry that had existed until the first half of the 20th century by systematically applying science, which generated the knowledge behind the wave of innovations pervading the introduction of chemotherapy and antibiotics. The large corporations that took the lead on the world market set up their own research and development (R&D) structures and were able to forge solid links with scientific institutions and to transform the results of their research into products and processes that were both highly lucrative and widely utilized by national health policies (Gadelha, 1990).

On the basis of this general frame of reference demarcating the role of private enterprise and the subordinate incorporation of science, it is possible to identify, in the field of economic and administrative theory on processes of innovation, intense debate over what determines the introduction of new products and processes into the production system.⁴ On the one hand are those who hold that the results of research and development (R&D) activities reflect demand conditions and are a natural outcome of the needs of the economic or social system. The more favourable these needs in terms of profitability, the more companies will invest in R&D activities, absorbing the knowledge generated in academic circles. This view of the introduction of innovations into the economic system has become known as “demand pull”.

On the other hand, there is a substantial body of authors (adherents to an interpretation known as “technology push”) who take a linear view of the generation and spread of innovations. The accumulation of scientific knowledge is seen to open up new technology possibilities which can be absorbed by economic agents, thus setting up a linear flow that begins with science and follows through to the market and social needs.

⁴ Dosi (1984) provides a good summary of the different approaches.

More recently, these simplified models have been surpassed in favour of a systemic view of the process of innovation (Freeman, 1995; Nelson, 1993; Edquist, 1997; and Lundvall, 1992). Depending on conditions in the different national systems of innovation (science and technology infrastructure, economic base, conditions of financing, role of the State, etc.) an interactive process is seen to be set up among the agents and institutions favouring, more or less intensely, the emergence of new products and processes with most direct impact on the goods and services available to the society. The emergence of innovations is determined simultaneously by the scientific environment and by the economic and social environment by the incorporation of science into companies' R&D strategies. This being the case, both the conditions of economic demand (which very often differs from social demand) and the conditions of technological supply and, thus, of research, are determinant for the introduction of new health products and processes, and both must pass through the trade filter of private strategies on the various markets.

In this regard, the health products field is particularly illustrative of the systemic, entrepreneurial dimension of innovations in capitalism. The emergence of a new vaccine or drug normally depends strongly on the convergence of appropriate systemic conditions. As a general rule, for a new prophylactic or therapeutic product to be discovered and launched, there must first exist a scientific and technological base at a reasonable level of complexity, an advanced regulatory structure (a network of quality control laboratories, rules for the approval of new products, a system of patents, etc.), the State playing a direct role in funding certain activities, and a business system qualified in terms of economic and technological capability. When these systemic conditions are favourable – in that they signal prospects of profitable business – investments in innovation tend to increase and research results to overflow into the market and society. It is the confluence of these systemic factors that explains the wave of innovations in antibiotics, anti-depressives, cardiovascular products and many others and, at present, in biotechnology and vaccines in particular.

This study's point of departure was thus the theoretical challenge of examining the systemic relationship between research and policy, in an effort to introduce the technological, production and entrepreneurial dimensions, which are essential to dealing with this subject in the field of vaccines and, in more general terms, of other health product and process innovations.

On the basis of this overall theoretical framework, one may extrapolate the following implications for the issue of the relationship between research and policy in the capitalist system in general:

- 1- Business market interests tend to prevail in orienting activities directed to securing product and process innovations, and thus decisively condition the concrete utilization of research results by health policy and by society. There is consequently an ever-present possibility that research and innovation efforts may become divorced from public needs.⁵
- 2- Given this typical situation of market failure, the State has an essential role to play in steering private activity, both by indirect means (providing funding for under-explored areas of research, for instance) and, in more extreme cases, by intervening more directly in efforts to apply research results in industry.

In the specific case of the less developed regions and countries, the situation of the link between research and health policy needs is still more problematical as a result of the following factors:

- 1- Normally, there is no core business capability able to manage, absorb and spread health innovations into production. Those companies that do introduce new products and processes are generally indifferent to the (less profitable) needs of the backward countries, which aggravates still further the risk of a divorce between research investment and health needs.
- 2- Systemic conditions (S&T infrastructure, regulatory base, State capability, consumer representation, etc.) are more precarious and do not produce entrepreneurial investment in R&D in areas of strategic importance to health policy.
- 3- As a result of the two foregoing factors, less developed regions are generally excluded from innovation efforts at the world technology frontier, which invariably results in research activity whose results are destined for the “shelf” and for scientific papers, or are absorbed by multinational corporations whose R&D activities are located in the developed countries.
- 4- It becomes even more pressing that the State play a role in correcting market distortions, and there tends to be a far greater need for a more direct pattern of

⁵ These economic factors, together with a certain tendency to autonomy in research activity (Rovere, 1996), certainly explain the fact that the illnesses caused by pneumonia and diarrhoea cause 15.4% of the disease burden and only 0.2% of world research efforts (WHO, 1996).

intervention in research, absorption and production efforts. In these regions, the endeavour is to discover what particular systemic conditions will permit them both to absorb and to develop new technologies that are suited to specific local conditions and will also function as sources of impetus for economic development.

2. Context of Innovation in Vaccines: Emergence of Modern Biotechnology and Incorporation of Vaccines as a Priority for Health Policy

Brazil embarked on efforts to research, develop and produce vaccines in a context characterized by two major conditioning social factors. On the one hand, in the 70s and 80s, modern biotechnology was coming into being among the international scientific and technological community, and consolidating into a new technological paradigm that was accompanied by an extensive program of research.⁶ As a result, innumerable opportunities opened up for innovating in health and for utilizing the research results that had accumulated ever since Crick and Watson discovered the double helix structure of DNA in 1953. Here vaccines were one of the most promising areas. This movement overflowed into the Brazilian scientific community, which went on to organize and to articulate its research interests among funding agencies and the State in general. On the health policy side, and also reflecting an international movement, the 70s saw the beginning of a whole move to extend national vaccination programs in association with initiatives to promote research and develop vaccines, which also affected the less-developed countries in general and Brazil in particular.

Thus a confluence of factors, connected with the technical and scientific base and with health policy, lay behind the process of research and development of vaccines in Brazil, which intensified from the 70s onwards. The topics below seek to explore further these macro conditioning factors that characterize the basic context in which research into new vaccines and their utilization by public policy occurred in Brazil.

⁶ On the concept of technological paradigm – inspired by Thomas Kuhn’s idea of scientific paradigm – see Dosi (1984). The central notion is that technology, like science, evolved within certain cognitive realms apprehended by the notion of technological paradigm. Inside each paradigm there is always a positive heuristic which defines the possible and probable R&D activities, as well as a negative heuristic that excludes problems and lines of research that lie outside its cognitive horizon.

2.1. The Emergence of the New Biotechnology

International Context

The birth of modern biotechnology is bound up with the advance of knowledge in the biological sciences in terms of their understanding of the metabolism of living things at the level of molecular interaction.⁷ In particular, on the basis of the scientific discoveries of the early 50s (especially Crick and Watson's contribution mentioned above), they came to understand the relationship between the structure of a given group of molecules containing the genetic code and how living organisms function and are structured. The biotechnology revolution proper ensued two decades later – on the basis of Cohen and Boyer's work at Stanford University in the early 70s – when the scope for industrial application of the scientific knowledge that had accumulated in molecular biology, biochemistry, immunology, microbiology and related fields became evident. Now, building on the new understanding of how living things function at the molecular level, the thrust was to develop products using micro-organisms – or biological material from them – genetically manipulated to fulfil a pre-determined purpose.

In fact, this went far beyond the specific field of genetic engineering. Rather it resulted in a process that transformed the whole understanding of the industrial utilization of biological knowledge. In this movement, the empirical knowledge used to obtain products gave way to rational knowledge at the molecular level, comprising, in addition to genetic engineering, the production of monoclonal antibodies using hybridomas (based on Milstein and Köler's work in 1975 at Cambridge/UK), new bio-processing technologies, techniques for the purification and chemical conjugation of biological material, and other contributions to technology offered by research activity.

Together with agriculture, the health field offered the greatest scope for applying the new biotechnology know-how. Among the various groups of products of major social interest that offered the best development opportunities, the following are outstanding (OTA, 1984): biopharmaceuticals (antibiotics, vitamins, hormones, etc.), diagnostic reagents, blood products and vaccines.

⁷ For details about the biotechnology trajectory see Gadelha (1990) and OTA (1984).

In the vaccine field particularly, the first product obtained using the new biotechnologies was the **hepatitis B vaccine**. From the early 80s onwards, it was produced by genetic engineering, which surpassed the former method of production from human plasma taken from infected patients. Although genetic engineering know-how still found only limited use in the vaccines field, a series of other purification, conjugation and bio-processing technologies introduced in the last two decades offered the following salient contributions in terms of health policy:

- new products to combat diseases that were not preventable by immunization (vaccines against meningitis and pneumonia, various types of influenza vaccines, new prospects of vaccines against AIDs, are a few examples);
- production without the need to manipulate and process infected biological material (as with production of the hepatitis B vaccine by genetic engineering);
- protection for population groups (particularly children) whose immune response is not effective in preventing contagion by transmissible diseases, by application of chemical conjugation technologies (as with the conjugate vaccine against *Haemophilus influenzae* type b (Hib), particularly to combat meningitis in childhood);
- greater effectiveness in obtaining immune response and lower toxicity than traditional products (as with advances in the triple acellular bacterial vaccine - DTP);
- increased opportunities for combining several vaccines in a single presentation (as with the possibility of combining the triple bacterial vaccine with hepatitis B and Hib in national vaccination programs); and
- overall gains in process yields and product quality (greater stability and heat resistance, fewer side effects, etc.).

Thus, the new scientific knowledge in the various fields of biotechnology came to offer greater concrete opportunities for contributing to public health. It now has to be asked how this knowledge was absorbed by production activities in such a way as to make new products available for public health measures.

Initially, in a process analogous to that of informatics, advances in biotechnology were obtained in academic circles as a natural spin-off from research activities (the cases of know-how in genetic engineering and monoclonal antibodies cited above are illustrative). The link-up with production started in the United States when technology-based companies (known as “new biotechnology firms”) were set up with venture capital funding. These companies

generally formed at the initiative of researchers themselves motivated by the possibility of applying the results of their research industrially and commercially. This can be considered the “romantic” phase of the link between research and policy, where the linear model connecting science and social use can be applied.

Progressively, with the opportunities for profit that presented themselves, the major private producers came to master the new technologies and incorporated the existing results by buying out the small “new biotechnology firms” and by exercising industrial property rights ever more restrictively (Gadelha, 1990; Leveque et alii, 1996; Quental, 1996). At present, biotechnology is the business of major multinational groups that have come to mesh their activities with technology research and development institutions. The link between research and production in biotechnology has come to obey the logic of business competition among major economic groups.⁸

In the vaccines field, this process proves to be paradigmatic. What used to be a marginal market supplied by independent producers (including the public sector) and which incorporated scientific advances slowly and gradually, became a market dominated by the interests of the major pharmaceuticals groups. At present, the world’s largest chemicals or pharmaceuticals groups account for around 80% of the value of world sales (Gadelha & Temporão, 1999). They have set up strategic channels for interaction with the scientific institutions with greatest capability to generate the knowledge most likely to find industrial application and, thus, utilization by national health policies.

Simultaneously with this process, practically all the nation-states of the developed countries have come to pursue biotechnology programs and to prioritize biotechnology in their science and technology agenda, with the vaccines field always to the fore. The activities of the National Health Institute in the United States, the biotechnology programs of the European Community, Japan and other Asian countries (such as South Korea) constitute striking examples of the initiatives and mobilization of resources to encourage biotechnology research as a source of competition among national industries and a leading edge of research that provides essential knowledge for attacking health problems.

There thus occurred a systemic confluence of the interests of business, the scientific community and the nation-states that lies at the root of the increasing links between vaccine research and development, private production and national health policies.

⁸ Development of the recombinant vaccine against Hepatitis B, for instance, as evident from the related patent documents, was the result of efforts involving more than a dozen companies and scientific institutions led by

National Context

The 70s and 80s were also the period when this know-how associated with the new biotechnologies reached Brazil.⁹ The highest authority for science and technology in Brazil, the National Research Council (*Conselho Nacional de Pesquisa*, CNPq), drew up programs and guidelines for the new disciplines connected with biotechnology (genetics, molecular biology, and so on). An Integrated Program in Genetics was set up in 1975, as, in the late 70s, was the Integrated Program in Genetic Engineering, the latter also receiving financial support from the federal Study and Projects Funding Agency (*Financiadora de Estudos e Projetos*, FINEP), then the main national funding agency for research and technological development activities.

In 1981, the National Biotechnology Program (*Programa Nacional de Biotecnologia*, PRONAB) was set up in the ambit of these organizations. This, the first overall, national biotechnology development program, focussed especially on the areas of energy, agriculture and livestock, and health – and, as part of the latter, vaccines. From then on, as a result of the crisis in the State and the planning process in Brazil, no other national program of comparable scope was set up, but the health biotechnology field in general – and vaccines in particular – came to gain explicit priority in practically all the research institutions working in the biomedical field, as well as in the policies of federal and state funding agencies.

One national initiative continued to retain significant scope and, to a point, has occupied the role of defining priorities for the S&T area to this day. The Scientific and Technological Development Support Program (*Programa de Apoio ao Desenvolvimento Científico e Tecnológico*, PADCT), funded by the World Bank and the Brazilian government (each contributing 50% of the funds involved), was formulated jointly by the funding agencies in the area: in addition to the CNPq and FINEP, it involved the Further Education Personnel Improvement Co-ordination Bureau (*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*, CAPES) and the, now extinct, Industrial Technology Secretariat (*Secretaria de Tecnologia Industrial*, STI).

This program began to be implemented in 1985, and has since gone through 3 stages (begun in 1985, 1991 and 1998). Organized into components and sub-programs, it has from

major pharmaceutical firms (Merck and SmithKline, especially) that retain effective control of the use of the technology.

⁹ Fiocruz (1987) and Gadelha (1990) describes this historical process until the eighties.

the outset had a Biotechnology Sub-program that has always selected the areas of agriculture and health, in addition to others mentioned at each stage. Within the health area – whose share of the Biotechnology Sub-program as a whole has been declining – vaccine research has repeatedly been defined as a priority for project funding. In the first stage of the program, of the 5 health priorities, two related to the vaccine field; that is: “Development of vaccine production processes using conventional technology” and “Characterization of parasite antigens and molecular cloning of their corresponding genes for the purpose of vaccine research and development”. The present stage of the program continues to cite vaccine development as a health product priority, albeit less emphatically.

These initiatives, allied to interest from outside the scientific community in a new and promising field of knowledge, can be said to have prompted nation-wide mobilization in favour of biotechnology research, involving the scientific community, government and, to a lesser degree, business with a view to strengthening health-related biotechnology research, with vaccines clearly to the fore, among other priorities. The context surrounding this same area must now be analyzed from the health policy standpoint.

2.2. Evolution of Vaccine-related Health Policy

International Context

The gains resulting from national vaccination programs, the opportunities offered by the recent spate of innovations in vaccines, and the permanent threat of new or re-emerging transmissible diseases, have endowed vaccine research, development and production with increasing legitimacy as essential health policy instruments. The following passage from a recent WHO study summarizes the international perception of the impact of vaccines on health and the excellent cost-benefit ratio they embody:

“(...) vaccines for a handful of childhood diseases such as diphtheria and whooping cough have cut the burden of disease in under-fives by almost a quarter and now avert the death of about three million children a year. In the United States alone, the major childhood vaccines save between US\$3 and US\$30 for every US\$ 1 invested in them” (WHO, 1996, p. xxii).

Historically, the eradication of smallpox, the elimination of poliomyelitis and the possibility of eliminating measles and neonatal tetanus were important landmarks that gave legitimacy to international efforts in the vaccine field. As a result of the prospects offered in terms of reducing the disease burden, the international agencies and civil society have come to exert pressure for national health policies to prioritize vaccines, with emphasis on their importance in the less-developed countries. Among the various initiatives taken in recent decades, the following may be singled out (Gadelha & Temporão, 1999):

- In 1974, the Expanded Program of Immunization was set up under the WHO with a view to encouraging vaccination policies in all countries, with special emphasis on a priority group of diseases: measles, tetanus, whooping cough, diphtheria, tuberculosis and poliomyelitis. At present, a further two new vaccines are being encouraged – against hepatitis B and Hib – although these are not yet widespread because of their cost.
- In the purchase and distribution of essential vaccines for less-developed countries, UNICEF (free distribution) and PAHO/WHO (low-cost distribution) are playing an increasingly important role.
- The WHO has restructured its vaccines effort by setting up the Global Vaccine Program designed to secure integrated action for the field, involving production, research and development, and quality.
- In 1990, the Children's Vaccine Initiative (CVI) was set up as a non-governmental organization representing a coalition of (very often antagonistic) interest groups to develop new vaccines. It involves representatives of academia, civil society, private enterprise and the public sector. Conspicuous among the essential aims of this initiative is that of working for communication and integration among the various parties, seeking to define consensus, priorities, co-ordinated strategies and of mobilizing funds for critical areas, with emphasis on research and development in new vaccines to meet the needs of less-developed countries (CVI, 1997).
- On the basis of these stimuli at the international level, national health policies – largely in the less-developed countries – came to reinforce their vaccine strategies by setting up local programs for the basic group of vaccines mentioned above.

This international mobilization has led to a situation where 80% of the world's child population has been immunized by the triple bacterial vaccine (diphtheria, tetanus and

whooping cough), against measles and against poliomyelitis, and increasing use is being made of the vaccines against hepatitis B and *Haemophilus influenzae* type b (WHO, 1996).¹⁰

Despite these striking results that offer a glimpse of the impact of vaccine research and development on health policy, three important qualifications have to be made with regard to the less-developed countries. The first has to do with the lag with which these new vaccines, which incorporate the recent research advances, are introduced into these economies. Particularly for reasons of cost, there has been significant delay in incorporating these new vaccines into national health policies. Even the vaccines against hepatitis B and Hib, which embody high technological content and are of major social importance, have still not entered the vaccination arrangements of a large part of the less-developed countries – despite their having been licensed in the USA, in 1986 and 1990, respectively (CDC, 1997)¹¹. The second qualification is connected with the bias present in vaccine development efforts at the world level which, as a result of the trade logic that has predominated in the field, concentrate primarily on the needs of the more developed countries (CVI, 1993). One conspicuous example is the scant effort made to develop a malaria vaccine, considering its technical and scientific feasibility and the great social benefit compared with the cost (WHO, 1996). Lastly, attention must be drawn to the fragility of the production base and the scientific and technological capability observed in the group of backward countries, which has been a structural constraint not just on directing research and industrial activities to the more modern vaccines, but also on efforts to absorb the results obtained in the more developed countries.

National Context

Brazil's health policy strategy for the vaccine field is certainly one of the more successful in the group of the less-developed countries, and has kept pace quite closely with the international movement outlined above. In recent history, intervention by the State is beginning to occur in a more systematic, planned manner with the successful campaign to eradicate smallpox, which started in the 60s and ended in 1973, and with the setting up of vaccination programs like the National Plan to Control Poliomyelitis, as well as more local experiences. Also in 1973, the State's role in the field took a quantum leap with creation of the National Immunization Program (*Programa Nacional de Imunizações*, PNI) – an integral

¹⁰ Vaccination against certain diseases that are highly incident in specific regions is also quite high, as in the case of immunization against Yellow Fever.

¹¹ In other countries, with less rigid legislation, they have been in use still longer.

part of the WHO's Expanded Program of Immunization – which sets out progressive vaccination strategies for the major immunization-preventable diseases with high national or regional incidence (poliomyelitis, tuberculosis, measles, diphtheria, tetanus, whooping cough, rabies, yellow fever and so on).

This entry of the State into vaccine policy was accompanied by increasing civil society participation in the national programs, involving the state and municipal governments, the armed forces, community representatives and international organizations (primarily WHO/PAHO). Since 1980, national vaccination days have been declared. They are promoted by strong media (television, radio and the press) mobilization and with the participation of public figures and the community in general. A wide-ranging poliomyelitis vaccination campaign is run on these days and twice a year, taking in the population of under-4s and accompanied, since 1990, by a multi-vaccination strategy to complement the basic scheme in place for the early years of life. To give an idea of the evolution and inclusiveness of these campaigns, in 1992 a little over half the municipalities covered 90% of children, while today 87% (or 4,500 municipalities) achieve this rate of coverage (PNI, 1998).

In order to make immunization a feasible policy strategy, a entire support infrastructure has been set up over recent decades, involving the following measures:¹²

- in 1981, the National Health Quality Control Institute (*Instituto Nacional de Controle de Qualidade em Saúde*, INCQS) was set up under the Oswaldo Cruz Foundation, and went on to take responsibility for quality control in immunobiologicals in 1983;
- an Immunobiologicals Self-Sufficiency Program (*Programa de Autosuficiência em Imunobiológicos*, PASNI) was set up to invest in capacity-building at national producer laboratories to ensure supply of essential vaccines and sera;
- a cold chain was set up to make vaccination workable over a territory of continental dimensions;
- human resource capacity-building to operationalize mass vaccination activities;
- reference centres in special immunobiologicals were set up and today cover 89% of the states (PNI, 1998), to ensure vaccination of special groups (the immuno-depressed, and others); and

¹² In order to evaluate the scope and complexity of the structure that was set up, it should be noted that Brazil is a country of continental dimensions with a population of more than 160 million.

- a health information and epidemiological surveillance system was set up to make it possible to evaluate indicators of coverage, immune response, adverse reactions and epidemiological evolution at the level of the various regions.

A noteworthy result of this health policy priority and strong social mobilization is that the last recorded case of poliomyelitis was in 1989, and Brazil was awarded the certificate of eradication of autochthonous wild polio virus in 1994. In more general terms, vaccine coverage was extended from around 20% when the PNI was set up, to around 90% of the target population of the set of vaccines provided. The chart below shows how the coverage rate for the group of basic vaccines in routine use nation-wide has evolved among the infant population, evidence of the success of the national vaccination policy.

Chart 1
Evolution of Vaccination Coverage among the under-1s – BRAZIL: 1980 / 1997
Population Covered (%)

VACCINE	Year																	
	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
DTP	37	47	56	60	68	66	58	58	58	56	65	78	71	75	74	84	75	79
Measles	56	72	66	68	73	67	62	64	62	60	78	85	91	85	78	90	80	100
BCG	59	65	67	69	79	66	68	72	79	74	79	87	90	98	94	100	100	100
Polio	69	38	51	55	55	52	51	53	57	54	58	67	65	66	71	82	72	89

Source : PNI/CENEPI/FNS-MS

DTP = Vaccine against *Diphtheria, Tetanus and Whooping Cough (Pertussis)*.

BCG = Vaccine against *Tuberculosis*.

At present, according to information from the Ministry of Health, the vaccine program has been extended, as can be seen from the fact that vaccine purchases have increased from around US\$ 70 million in 1998 to US\$ 130 million in 1999. In addition to the basic vaccines for the child and adult population (DTP/DT, measles, BCG, poliomyelitis and yellow fever), vaccination campaigns have come to include the vaccines against hepatitis B, Hib, the triple viral vaccine (measles, mumps and rubella), rubella (puerperal) and influenza (for the over-60s).

It now remains to consider how local vaccine production – which is the main way biomedical research is utilized by health policy – evolved in this period and its relation to vaccination policy.¹³

In the more overall context of science and technology policy and health policy, the decisive factor for Brazil's entry into modern industrial production of vaccines and into

¹³ For further details on how vaccine production has evolved in Brazil, see Fiocruz (1987), Gadelha (1990) and Gadelha & Temporão (1997 and 1999).

research activities directed to technological development was the crisis in supply of essential immunobiologicals, which jeopardized its entire immunization strategy. Up until the end of the 70s, Brazil's vaccination needs were met by local and imported private production. In the early 80s, when the demand for vaccines expanded acutely as a result of the success of the PNI, and a national health quality control system began to be set up, it became evident that production capacity was inadequate and locally produced vaccines were of poor quality. In response to the new health policy requisites, the private producing laboratories stopped producing, precipitating a crisis in the supply of sera and vaccines.

In this context, the Immunobiologicals Self-sufficiency Program (*Programa de Autosuficiência em Imunobiológicos*, PASNI) was formulated in 1986 with a view to encouraging national production by a group of public institutions (primarily the Oswaldo Cruz Foundation and the Butantan Institute) that had a rather more developed technology base. For this purpose, between 1986 and 1998, the Federal Government channelled a total of approximately US\$ 150 million for these producers to invest in production capacity and quality. Although the goals of self-sufficiency have not been attained, Brazil has installed the largest vaccine production capability in Latin America and certainly one of the largest among the less-developed countries.

At present, Brazil has the capacity to produce the following more traditional vaccines in routine use:

- DTP (diphtheria, tetanus and whooping cough)
- Human and animal rabies
- Yellow fever
- Measles
- BCG (tuberculosis)
- Poliomyelitis (packaging only).

These vaccines are traditional, the technology involved is widely known and at present they do not incorporate very substantive research results, except for certain process improvements (production in cell culture, new adjuvants, etc.). In the group of the new vaccines, which are manufactured using the new biotechnologies, only the vaccine against hepatitis B by genetic engineering went into production in 1999, while the process of

absorbing the technology for the *Haemophilus influenzae* type b (Hib) conjugate vaccine is scheduled for completion in the near future.¹⁴

To close this topic, Brazil may be said, over the last two and a half decades, to have set up a formidable mass immunization and vaccine production structure that has had considerable impact on its population's health conditions. Nonetheless, there are points to be criticized in this dimension of health policy, particularly the existence of a substantial lag in the introduction of new vaccines (like the hepatitis B and Hib vaccines) into health programs, due to the high cost of imports and local production's specializing in immunobiologicals that incorporate a smaller research and development content. This is evidence of a situation of structural and entrepreneurial dependence where lack of technological capability may threaten the long-term survival of production ventures in Brazil.

2.3. Disconnection among Vaccine Research, Production and Policy

The foregoing topics have characterized the macro-context surrounding Brazil's vaccine policy. From the technical and scientific standpoint, vaccines figure as a privileged field for health-related biotechnology research efforts. From a health policy point of view, they constitute one of the areas where greatest impact has been achieved in recent decades. Now the relationship between these two contexts has to be considered, and the relationship between vaccine research and health policy examined.

The elements that characterize this interaction are apparently quite favourable: biomedical research is a field where Brazilian research holds comparative advantages (Albuquerque, 1996) and which has enjoyed government support for vaccine development; a production base has been set up that is unique in Latin America; there is intense social mobilization and legitimacy in favour of the field; and the supporting factors (quality control network, intense international relationships, for example) are favourable.

Nonetheless, following the field survey carried out at the main scientific institutions engaged in biomedical production and research in Brazil (Oswaldo Cruz Foundation and the Butantan Institute) and the policy agencies for the field (agencies of the Ministries of Health and of Science and Technology), it became clear that the relationship between vaccine

¹⁴ Not by chance, these were the two vaccines chosen for a more thorough study of the use of vaccine research results by health policy (following topic). More recently still, moves have been noted towards absorbing others technologies, such as the influenza vaccine technology.

research and health policy is rather precarious. In fact, the scientific and health policy universes are isolated from one another and do not have close, organic links.

In the scientific field, one sees a tendency for projects to be oriented by curiosity, for which legitimacy is sought by means intrinsic to the scientific community, as expressed in scientific publications. That is, even in a field with high social impact like vaccines, research is far more responsive to the internal logic of knowledge generation, for which the indicator of productivity is publication in specialized reviews. It is less directed to developing product and process technologies which are the way research results can most effectively be utilized by health policy.

The Scientific and Technological Development Support Program (*Programa de Apoio ao Desenvolvimento Científico e Tecnológico*) is a striking example in this regard. According to the survey carried out here, the second stage of the Biotechnology Sub-program (1991/1997) involved funding for 158 research projects in all fields (health, agro-industry and energy), 14 of which (9%) related to vaccine research, evidence of the priority given to this field. Despite the high scientific productivity identified in terms of publications, none of the projects has resulted to date in products and processes actually utilized (or even with prospects of being utilized in the next few years) in industrial production activities and, thus, by health policy. It is probable that in the third stage of this program (which began in 1998) the same situation will hold, given that no specific focus on research into vaccines of strategic importance in terms of public needs was identified in the call for projects of the Biotechnology Sub-program.

The disconnection between research and production is also evident in the health policy field. One first discovery by the survey was a total, and even surprising, absence of priorities, strategies and funding for vaccine development in the ambit of the Ministry of Health since the PNI was set up in 1973. The vigour of the immunization-related health policy never found expression in terms of stimulus for research and development for new or better vaccines, with no significant source of funding for basic and applied research in the field, despite the considerable funds involved in the vaccination programs¹⁵. Ministry of Health support for studies and research has been restricted solely to activities connected with short-term operational measures such as: conducting inquiries into vaccine coverage, evaluating the potency of different formulations and the corresponding level of serological response, surveys

¹⁵ As has been seen, vaccine purchases alone account for some US\$130 million.

of adverse events, evaluation of the cold chain and studies of health workers' training in syringe handling (PNI, 1998).

More surprising still is the fact that even the support given by the PASNI specifically to production (investments of the order of US\$150 million) did not involve funding for vaccine development, except for the hepatitis B vaccine. Actually, in conceptual terms, the program confused technological development – which must necessarily be built on a broad, complex research base – with obtaining operational production technology. As a consequence of this thinking, investment was concentrated in building work and equipment, while investment in research and development and in highly-skilled human resource capacity-building was relegated to the background. It is certainly this view that explains why self-sufficiency was never achieved, or even approached¹⁶, given that the research conducted internationally is forever raising new possibilities in terms of products and processes with which national agents have proven unable to keep pace.

Thus, from the science and technology point of view, there was great fragmentation and dispersion of efforts, which led to a lack of strategic focus, an accentuated academic slant and insufficient emphasis on industrial absorption of research results. On the health policy side, research and development activities were simply ignored as essential components of national vaccine strategy.

At the root of this divorce between the technical and scientific base and the requirements of health policy lies what can be identified as the weak structural link in the chain running from basic research to the provision of new vaccines to meet public needs: inadequate entrepreneurial capability and structures for vaccine-related technological development. As brought out in Figures 1 and 2, in the absence of industrial activity to mediate between research results and health policy needs, research efforts tend to disperse and to languish on the “shelf”, while health policy needs fail to find effective expression as guides for national research.

3 – Cases that illustrate the link between vaccine-related research and policy

In the course of the previous topics it was mentioned that, of the new vaccines, two – hepatitis B (HB) and *Haemophilus influenzae* type b (Hib) – have come to be used increasingly in national vaccination, and that these ally great importance for health policy and

¹⁶ Note that the target stipulated by the PASNI was self-sufficiency by 1990, at which time Brazil in fact imported more than 50% of the value of its vaccine purchases (Gadelha, 1990).

considerable research content. While the hepatitis B vaccine is the only one produced industrially in the world using genetic engineering techniques, the Hib vaccine is produced using advanced chemical conjugation and bioengineering processes for fermentation, purification and characterization of macro-molecules (Homma et alii, 1998).

In Brazil, these vaccines have come not only to form part of the vaccination program but also to be produced locally. Brazil has mastered the entire technology cycle of hepatitis B vaccine production and is in the process of absorbing basic Hib vaccine production technology. This being the case, these two vaccines figure as the two most successful cases (at least potentially, in the case of Hib) of the utilization of research results by national production and by health policy. Analysis of this situation may suggest ways to approximate research activities and government strategies to combat transmissible diseases.

3.1. The Case of Hepatitis B Vaccine Development by the Butantan Institute

The Butantan Institute, a public organization connected with the São Paulo State government, was responsible for the development and production of hepatitis B vaccine in Brazil. The institute was set up in 1901 to support in combating the endemics that reached Brazil's port areas and was organized, among other activities, to carry out biomedical research and to produce sera and vaccines. From the second half of the 1980s onwards, encouraged by the National Program for Self-sufficiency in Immunobiologicals, the institute underwent a thorough process of modernization. Among the advances, the production and technological development area was individualized and organized into a format different from that of the more basic research activities. In this process, an effort was also made to attract a group of highly-skilled researchers to the Institute to work specifically in technological development, as part of a more general plan for capacity-building in research and development activities in health biotechnology.

As a result of this process, Brazil's main Health-related Biotechnology Centre was set up. Today it employs 40 researchers, 25 of whom hold doctorates, for the central purpose of developing products and processes, thus linking up research activities with those of industrial production. As basic lines of R&D, the centre initially prioritized serum and vaccine development, and more recently has engaged in research and development in biopharmaceuticals incorporating leading edge technology.

Two sets of determinants were decisive in Butantan's involvement in HB research and development. On the one hand, as has been seen, this was one of the first health products

developed on the basis of genetic recombinant technology, thus representing a natural interest for scientists whose aim was to pursue research activity directed to generating new products. There was thus a determinacy originating within the field of opportunities opened up by science and technology.

On the other hand, by the late 80s, viral hepatitis had become a prominent public health problem in Brazil, giving rise to a series of national health policy measures. The viral hepatitis monitoring system was introduced in 1992 and generated information as of 1993, when 42,321 cases were notified, the figures climbing to an even higher plateau in the two subsequent years (PNI, 1998). Mortality indicators showed that hepatitis B accounted for 20% of deaths, heavily concentrated in certain regions of Brazil. To meet this public health situation, the Brazilian government's vaccination policy evolved progressively, concentrating first on high-risk areas and certain specific population groups (health workers and drug users, for example) until nation-wide infant vaccination was introduced, as shown in the chart below.

Chart 2

Landmarks in the Introduction of Hepatitis B Vaccine into Health Policy

Year	Event
1991	Implementation and extension of hepatitis B vaccination in the western Amazon
1992	Introduction of hepatitis B vaccine for high-risk groups nation-wide
1993	Expansion of vaccination for the under-fives in Santa Catarina and Espirito Santo states and for government health workers
1994	High-risk, private sector health workers included
1996	National hepatitis B vaccination campaign involving schoolchildren and dentists
1997	Hepatitis B vaccine officially indicated for the under-ones nation-wide, and for the under-15s in areas of high prevalence (legal Amazon, Santa Catarina, Espirito Santo and areas of Paraná State)
1999	Hepatitis B vaccination implemented nation-wide for the under-ones. Routine vaccination for the whole population under 15 in regions where highly endemic: North Region and the states of Espirito Santo, Parana, Santa Catarina and the Federal District

Source: PNI, 1998

Thus, factors connected not only with the supply of scientific and technological knowledge, but also with health policy demands, acted in the decision to embark on a process of research and development and of absorption of essential know-how in order to produce this vaccine in Brazil. In the complex chain of determination, the present and prospective signs originating from control policy can be said to have been the most important in the process of

selecting the hepatitis B vaccine as a point of entry into advanced biotechnology research. In addition, economic factors also had considerable influence as the hepatitis B vaccination policy advanced causing importation costs to soar. In 1995, for example, HB purchases accounted for 73% of Brazil's spending on vaccine imports.

The R&D process began in 1993 with the hiring of an independent researcher from the former Soviet Union, who was to be entitled to a fixed share of the value of future sales. A Biotechnology Centre working group specifically designed to obtain the product was coupled to the basic know-how contributed by this researcher. Laboratory trials were concluded in 1996 and followed by the scale-up, a stage which – it should be stressed – involves a significant research and development effort. Field studies in humans were then begun in 1998, and the following year the Butantan Institute was able to offer the Ministry of Health 5 million doses, with plans to raise the supply to 10 million doses by the year 2000.

The process by which support was obtained for this project was also rather revealing. One of the most important factors to stress in the Butantan Institute's strategy was the hiring of a senior researcher who would lead its technological strategies. This researcher, an authority in the field of biomedical research, also engaged in political activities, which had led to his being forced in exile during the military dictatorship. Throughout that period, he pursued his scientific activities at world centres of excellence in biomedical research, among them the University of Harvard and the Massachusetts Institute of Technology. With re-democratization, and formulation of the PASNI in 1986, this researcher was invited to enter the Institute, by virtue of his specific capability - given by his background - to articulate research activities with political activities, particularly in the fields of health, and science and technology.

Under the leadership of this researcher who to this day plays an outstanding role in the institute, Butantan managed to forge a network of alliances in both the health and science and technology areas. In the former, of the laboratories that formed part of the PASNI, it was the only one that managed to raise substantial funding for R&D activities. In addition, it was always intensely active among the formulators of the national immunization policy, to ensure government commitment to purchasing the vaccine the moment it had been successfully developed. In the science and technology domain, also as a result of its leaders' activities, Butantan managed to raise funding from government agencies at the federal (Finep and CNPq) and state (FAPESP) levels to finance vaccine development activities at the Biotechnology Centre. The Butantan Institute can be claimed to have anticipated health policy

demand on research activities and, in fact, to have prompted that demand by way of its political links.

This said, two explanatory factors were crucial to the project's success: the presence of a scientific leader who bridged between scientific activities and health policy requirements, and mobilized the stakeholders in these two universes, and the setting up of a technological development structure capable of serving as the material link among research, production and transmissible disease control policy.

The results of this process of research, development and absorption of technology included the following:

- a drastic fall in the price of vaccines purchased by the Brazilian government (from US\$ 8.00 to US\$ 0.80 a dose) even before Butantan went into production, because the international producers that supplied Brazil perceived the threat from local production;¹⁷
- the biotechnology Centre gained the legitimacy necessary to continue receiving support from State and Society with a view to developing new vaccines and other products of strategic importance to health;
- foreign exchange savings were made at a moment when Brazil was in balance of payments difficulties; and
- technological capacity was consolidated that would make Brazil more competitive in high technology health products.

The overall philosophy guiding the institute's activities – and which explains this success – includes the clear perception that research in the technology field can only become workable in terms of industrial production and utilization by health policy if, from the outset, it is coupled to an entrepreneurial structure for technological development. Only when there is close interaction between research, development and production is a concrete link established between academic activities and health policy. It is in this way that technology is conceived within a broader context that links research to national development.

The basic ideas that guided the Butantan's R&D activities are expressed in the institute's information leaflets, which contain the following assertions evidencing the necessary, systemic links among research, development and production:

¹⁷ Note that other factors connected with the maturity of the product technology cycle also influenced the fall in international prices.

“National vaccine production is not just an economic problem. Without production there is no development; without development there is no research. If you do not research, you will continue under-developed and dependent.”

“(…) research to develop, develop to produce, produce to research.”

3.2. Prospects for Development of the *Haemophilus influenzae* type b Vaccine by the Oswaldo Cruz Foundation

Packaging of Hib vaccine in Brazil began in 1999, and the whole technology cycle is expected to be mastered by the year 2003. The institution responsible for this initiative is the Oswaldo Cruz Foundation (Fiocruz), through Bio-Manguinhos, its technical unit responsible for producing immunobiologicals. The Foundation is a complex public organization connected to the Ministry of Health which, like the Butantan Institute, originated at the start of the century to provide technical and scientific support for combating infectious and parasitic diseases. At present, it is quite a broad, diversified institutional complex comprising 13 technical units, and involving biomedical and social research, teaching, quality control, production and care service provision.

Decisive landmarks in production activities at Fiocruz include, firstly, the creation of Bio-Manguinhos in the second half of the 70s, as a separate unit (in terms of research activities) for producing vaccines and diagnostic reagents and, secondly, the investments allocated by the PASNI, which made it possible not only to modernize overall infrastructure and to improve production quality, but to install the largest final vaccine processing plant in Latin America and one of the 10 largest in the world, according to information provided in the interviews. In this process, it proved essential to hire a leader with practical and technological know-how in the field of private industry and who, at the same time, identified the research and technological development base as the critical factor for the activity to continue dynamic in the long-term.

From the end of the 80s and in the 90s, the Fiocruz began to prioritize vaccine technology development activities, although these may still be modest compared with those of the Butantan Institute. Mobilization by certain international organizations (particularly the PAHO/WHO and the CVI) played an important role in creating an awareness of the importance of technological development to meeting the new health policy needs dynamically. On the basis of this perception, Bio -Manguinhos began to structure a department

specifically directed to product and process development and to the absorption of research results. At present it has some 15 researchers of whom around 3 hold doctorates.¹⁸

The planning to embark on the process of absorbing and researching the Hib technology depended essentially on two types of conditioning factors. In the first place, from the health policy point of view, international organizations, particularly the PAHO, WHO and CVI, are increasingly recommending that less-developed countries use the Hib vaccine in their immunization policies, because of its high impact on health conditions. In Brazil, in particular, contagion by *Haemophilus influenzae type b* is the most frequent cause of meningitis in childhood, incidence of which is high (around 0.5% of the child population), as is the impact on child mortality, in addition to meningitis being responsible for nervous system complication. On the basis of these indicators, and despite the high cost (around US\$ 2.5 a dose), Hib was introduced in 1998 into routine child vaccination in Brazil.

In the second place, from the science and technology standpoint, absorption of the Hib technology could constitute a gateway to leading edge technology, and make it possible to leverage the institution's internal research and development capacity-building. Note that Hib is one of the most modern and effective bacterial vaccines, produced employing advanced fermentation technology and chemical conjugation between a polysaccharide of the bacteria and a purified protein that enables immune response to be triggered in children under 4 years old, which was not possible with the non-conjugate vaccine.

The fact is that the unit had already been investing in R&D activities, with a view to producing high quality bacterial vaccines by fermentation (meningitis B, C and A/C, and others). This, on the one hand, constituted an important base from which to absorb leading edge technology, but, on the other hand, would yield results in too distant a future to be of use to health policy in the short term. Thus, the decision to absorb technology from an international partner can be seen as a strategic "short-cut" in an endogenous R&D effort and to leveraging the Fiocruz's future capacity to generate and absorb new technologies.

In this process, two movements of negotiation and inter-linking proved central: choosing a holder of the technology able and willing to transfer it and the Ministry of Health's intervening to guarantee future purchases, given the size of the Brazilian market. As regards the international partner, the process was difficult because the technology is dominated by a small group of major transnational pharmaceuticals corporations that generally do not negotiate know-how, but products. In this case, it was possible to obtain the technology only

¹⁸ The figures are not precise because some researchers are also connected with other units that devote their efforts more to basic research.

as a result of the size of the national market and the installed capacity for final processing (one of the largest in the world, as mentioned above) which guaranteed bulk purchases from the technology supplier during the transfer period. It was thus possible to reach a trade agreement tied to a technology transfer agreement to run for 5 years. The Ministry of Health's intervention was critical in that only the PNI's undertaking to purchase the vaccines could guarantee that they would be sold during and after the technology absorption period, thus justifying the investment by both parties.

Fiocruz can thus be said to have shown skill in articulating health policy with an agreement for the transfer of leading edge technology.

The relationship between research and policy in this process suggests the inverse of the linear model mentioned in topic 1. In fact, the point of departure for the process of planning the research activity was an evaluation of the immediate needs of the policy for control of transmissible diseases, which determined the decisions on production and technology absorption which, at a later stage, leveraged vaccine research activities conducted in Brazil. Health needs influenced decisions on production and technology absorption which, at a later stage, leveraged vaccine research activities conducted in Brazil. This was so much so that the process of technology acquisition itself began with the final activities (formulation, packaging and lyophilization) and ended with the transfer of the more complex know-how that called for a greater research contribution (conjugation, fermentation of bacteria and purification).

The most striking results of this process include the following:

- 7.5 million doses were packaged and supplied to the PNI in the first year, the projection being to reach 15 million doses in the year 2000, thus meeting the entire national demand and enabling Brazil to make foreign exchange savings;
- transfer was completed of the leading edge technological know-how with scope for spill-over into R&D activities connected with vaccines produced by fermentation and by conjugation techniques;
- it was demonstrated that it is feasible to take research and development shortcuts by means of a model of technology transfer of a modern immunobiological;
- the national production unit made economic gains, which enabled more funding to be contributed for investment in R&D;

- national research potential was leveraged in a strategic area, considering that a large part of the future bacterial vaccines will be conjugate vaccines; and
- the possibility of establishing a vaccine combination strategy (combination of Hib with DTP and Hepatitis B, for example) was increased, thus boosting the effectiveness of the PNI.

As a general philosophy running through the Fiocruz's strategic decisions in this area, it can be said that it gave greater weight than the Butantan Institute to large scale, industrial production activities. Even though it incorporated lower technological and research content at the initial stage, the absorption of international technology was seen as one way of using the opportunities that presented themselves at the time, stemming from the immunization policy, and of achieving competitiveness in the long term by progressively internalizing a research process of greater density.

The following assertions made during the interviews evidence the philosophy that was adopted, which subordinates the application of research results to the issue of industrial production:

“In order for there to be technology, there has to be industrial production, large scale production.”

“There is an under-utilized scientific base. That base must be drawn in.”

“Application starts only when the industrial issue is solved.”

4- Conclusions and Lessons

In the course of the foregoing topics a number of conclusive remarks have been made which apply to each specific part of the study. More generally, this study of the relationship between research and health policy in a field that involves the development of products and processes prompts the following main conclusions:

1 - The Brazil's experience with vaccine shows that the dichotomy between health policy and science and technology policy has to be overcome in order to enable the public to make wider use of product and process research. On the one hand, the science and technology domain has neglected health policy priorities, which was evidenced by the absence of more precisely focussed research activity, even when the aim was explicitly to develop products

and processes and to give them industrial use. On the other hand, the health policy formulators are, to a large extent, ignorant of the logic of scientific development and the factors that condition the transformation of this knowledge into usable technologies. As has been shown above, even at the heart of a sizeable program of investments in vaccines designed to boost local production, the strategic component of scientific and technological development was largely ignored.

2 – The lack of interest from the private sector in carrying out R&D and productive activities in Brazil forced direct entry by the State, in response to a crisis in supply of essential immunobiologicals for immunization programs that had been expanding at a growing rate since the 70s. Although politically the moment was quite unfavourable to the State's entering the production field, its entry proved the only possible way of internalizing activities with high technology content in Brazil and establishing links between research activities and health policy, by intervening in the fragile structural link of the relationship between research and policy: by setting up a structure for technological development and industrial production in a backward, dependent country. Local private enterprise simply proved incapable of operating in this field for lack of technology. The large multinational corporations, which have advanced R&D structures, were not interested in pursuing these activities in a country with a less developed S&T base. As a general lesson, it can be said that the state has a critical role to play in backward countries' entering into research and production of high technology products.

3 - In the two cases analyzed in greater detail, R&D activities benefited from an external contribution, evidence that in the backward countries activities directed specifically to prospecting scientific and technological knowledge and to absorbing research results are an essential, critical element in carrying out and utilizing research and development. Seen another way, the existence of an endogenous research and development base proved an essential condition for absorption of the results of research conducted in the more advanced countries. There is thus no dichotomy between domestic development and the absorption of research results generated in the more developed countries. These cases of success show a dynamic interaction between setting up a domestic R&D base and the ability to select and absorb knowledge generated internationally as a short cut to accelerate the introduction of new vaccines into national programs.

4 – A conspicuous role was played by the leaders of those institutions most successful in having their research results utilized. This was particularly so in the relationship they managed to establish with S&T policy and health policy actors. As a result of the poor

interaction between these two groups, these leaders' action made it possible to forge links between the scientific world and social needs. By mobilizing the stakeholders in this field, it was possible to bring together the requirements of the immunization policy and vaccine research and development activity. In this type of action, it is clear that, in addition to technical and scientific proficiency, the leaders of health product research and development programs must act as veritable entrepreneurs to link up the world of science with those of industrial production and health policy.

5 – In the cases where a successful relationship was established among research, production and policy, the planning of research activities can be said to have been decisive by incorporating both a prospective view of health policy needs given by vaccine purchase trends and, at the same time, a strategy for capacity-building in, and absorption of, new technologies. Rather than planning a specific activity for a given product, planning was directed to laying solid organizational foundations for research and development in response to social needs. As a result, it was possible to set strategies for progressively increasing the knowledge content of the activities pursued, and to open up promising prospects of capacity-building in Brazil in research and development in latest-generation vaccines with high impact on health conditions.

6 – The signals emitted by national immunization policy were decisive to the successful cases of vaccine research in Brazil. It was the eruption of a critical situation in the supply of essential immunobiologicals in the first half of the 80s which triggered a steady process to interlink vaccine research efforts with health policy needs. The linear model that links research to health policy (Figure 1) was inverted, evidencing the systemic, interactive nature of the process as regards high technology health products. In the case studied, the point of departure was the introduction of a new product into health policy, which induced a strategy to set up a local production base, and only later were research activities of any density carried out. Health research policy should thus be coupled to a policy for the production of high technology products in the field in accordance to health needs.

7 – The dispersion and fragmentation of research efforts connected with product and process development tends to lead to a general low rate of research result utilization, as was shown by the science and technology programs analyzed. The cases of success show that selecting strategic foci connected with the national health context – as was the case with the two vaccines considered – is an appropriate means of ensuring that research activities (even when fundamental) produce an effect and of spreading essential knowledge that can be applied to a considerable range of products, thus legitimating the activity of health research in the backward countries. In the vaccine field the present and prospective signals emitted by the

policy for control of immunization-preventable diseases and by national epidemiological conditions must constitute the guide for focussing research efforts into new health products and processes, to ensure industrial application of results originating from scientific research. In this area, the attention of policy makers and state intervention must contemplate, simultaneously, the march of science and technology, of the industrial base and of health policy.

8 – In the field of vaccines and, more generally, of industrialized health products and processes, the application of research results depends on prior structuring of an entrepreneurial technological development capability. That is the base that enabled the link to be forged between the worlds of science and of production, thus concretely allowing health policy to make use of research. The favourable context for vaccine research in Brazil, as concerns both health policy and science and technology policy, led to the application of research results only when an entrepreneurial technology development base was structured. Whenever research initiatives towards generating new vaccines or processes occurred in isolation from a technological development and production structure, the results were confined to scientific publications and to increasing knowledge, but were not put to use in vaccination programs. Thus, the problem in the relationship between research and policy in backward countries was seen to be fundamentally structural, and not solely behavioural. The absence of an endogenous production and technological development base hampers stakeholders' efforts to forge links between research and health policy, even when the intentions of the scientific community and policy makers are favourable to such linking. The structure of the economy (especially the lack of technology-intensive sectors) really is critical to a successful relationship between research and policy, when this relates to industrial products and processes. From the policy standpoint, there is a need to solve the issue of industrial production, without which the relationship is limited. The cases of success demonstrate that only when the State took a hand in the issue of industrially-based technological development did prospects for concrete application of vaccine research emerge.

9 - In the backward countries, of the territorial and economic proportions of Brazil, the existence of a local health products research base proves essential for fundamental reasons of two orders. In the first place, considering the research bias at the world level, the impact of health product research and production on equity and quality of life will be greater the more these activities relate to local epidemiological needs. In the second place, in the less-developed countries, the development process itself, and thus overall health conditions, is closely tied up with the constitution of an endogenous base for research and innovation. Just

as health policy needs must serve as a focus for induced health research efforts, it should be stressed that health policy on product and process development has to consider the rationale of the economy and technology. As shown by a number of authors in the field of economics (Dosi, 1984; Freeman, 1995; Marx, 1983; Schumpeter, 1985, and many others), innovation is the wellspring of development in the long term. No country has developed without an aggressive product and process innovation policy. Poor countries' major health problems can be said to be underdevelopment and the lack of an endogenous innovation capability. Health policy research, therefore, must be interlinked with a national development strategy, otherwise poor countries' health problems tend to be perpetuated down through time. There is no developed country without an advanced S&T base in high technology sectors. In accordance to this more general perspective, vaccine may be seen as a "window of opportunity" for the Brazilian innovation and development policy.

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Annex

List of Interviewees*

- Akira Homma - Chief Technology Officer of Technology of the Oswaldo Cruz Foundation.
- Gilberto Hauagen Soares - Federal Study and Projects Funding Agency (*Financiadora de Estudos e Projetos*, FINEP).
- Guilherme Augusto de Barros Pinho Junior- The Scientific and Technological Development Support Program (*Programa de Apoio ao Desenvolvimento Científico e Tecnológico*, PADCT).
- Hisako Gondo Higashi - Director of the Butantan Institute.
- Isaias Raw - President of the Butantan Foundation (and Former Director of Butantan Institute).
- João Quental - Former Director of Bio-Manguinhos / Oswaldo Cruz Foundation.
- Laura Dina B. S. Arruda - Immunobiologicals Self-Sufficiency Program (*Programa de Autosuficiência em Imunobiológicos / PASNI*).
- Mara E. Moreira de Oliveira - Immunobiologicals Self-Sufficiency Program (*Programa de Autosuficiência em Imunobiológicos / PASNI*).
- Maria de Lourdes de Souza Maia - Coordinator of the Immunobiologicals Self-Sufficiency Program (*Programa de Autosuficiência em Imunobiológicos / PASNI*) and of the National Immunization Program (*Programa Nacional de Imunizações / PNI*).
- Marco Antônio El Corab Moreira - Immunobiologicals Self-Sufficiency Program (*Programa de Autosuficiência em Imunobiológicos / PASNI*).
- Marcos Mandelli - Science and Technology Department / Ministry of Health.
- Sandra de Almeida Carvalho- Federal Study and Projects Funding Agency (*Financiadora de Estudos e Projetos*, FINEP)

* Some of the people were interviewed before the COHED project along the author routine line of investigation