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Chapter

Developing Countries Can Innovate and Produce Vaccines: The Case of Butantan in Brazil

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Abstract

Since the introduction of vaccines, governments learn that they are the most efficient and inexpensive tool to avoid the spreading of infectious diseases. It resulted in the creation of public research institutes to develop new vaccines, which gave birth to the vaccine industry, that is, growing in size by acquisition of competitors, which estimate that in 2019 they will sell $58 billion, where developing countries represent 80% of the world population, submitted to be dependent of production and prices from large producers. Incapable or not willing to assume the responsibility to produce, accept to purchase vaccines in bulk for filling and labeling as "producers." Butantan, a public not for profit institute became the first producer of specific anti-venoms and anti-rabies sera. In 1985, Butantan Center of Biotechnology attracted 25 young PhD, which accepted to carry on inovations and technical developments, setting dedicated plants to produce vaccines at affordable cost, aiming self-sufficiency to distribute free through the Ministry of Health. This chapter describes problems and solutions that must be faced to produce vaccine at a cost that developing countries can afford.

Keywords: vacines control epidemics, developing coutries 80% of world population, developing countries self-sufficiency, Butantan from innovation to production, anti-venonms and anti-toxinas, encloses production plants, pertussis reduction by DTP vaccine, whole pertussis low in LPS, MPLA from B pertusis as adjuvant, MPLA adjuvant reduce ¼ influenza doses an price of vaccine, vitamines A,D,E, riboflavin as adjuvants, pneumococcus-PSAP3 reduce cost of pneumo vaccine, plasma fractions not for sale, lung surfactant saves neonatals

1. Institute Butantan—research, process development, and production

1.1 Antivenoms and antitoxins

Antisnake venoms were the strength of Instituto Butantan and its priority [1–4]. At the New York World Fair, Vital Brazil saved the life of an employee of the Bronx Zoo bitten by a rattlesnake, which induced President Theodore Roosevelt pay a visit to Butantan in 1915. In 1983, Butantan sera production situation was scary: venoms were collected from snakes and administered to horses. The horses were bled and their blood collected in rusted milk drums, precipitated

with ammonium sulfate, concentrated using a dirty towel, diluted and kept in large bottles until they "mature," and covered with mold! Probable other developing countries producers used the same ancient manufacturing process. Changing the production technology was the first goal of a recent Ph.D. group of researchers supported by the staff from the production laboratories under my supervision (**Figures 1–6**).

The first idea was to replicate the milk industry profile, creating a "hands-off" fully enclosed system using large stainless steel tanks and an industrial plate centrifuge. After snake venom inoculation, horse blood was collected in a 7-liter sterile bag with anticlotting solution, stirred, and kept in a cold room overnight. After plasma been removed, the settled cells were isotonic saline solution suspended and transferred to a connected-enclosed-4-liter bag to be returned to the same horse, characterizing plasmapheresis process and thus allowing repeated blood collection at short intervals.

The separated plasma was submitted to a complex process for immunoglobulin purification, began by precipitation by ammonium sulfate, followed by filtration, pepsin treatment (to remove the Fc portion of immunoglobulin to prevent complement activation), heath treatment, addition of caprylic acid to inactivate lipid-enveloped virus, finishing by an ion-exchange chromatography, which also removes viruses and other microorganisms. After sterile filtration, the final product was tested for neutralization potency and formulated to guarantee efficacy and safety.

Along 1985 to 2009, the production of antibothropic, anticrotalic, antielapidic, antilonomia, and combined antiarachnidic with other antivenomous insects sera reached about 700 million vials. The technology and the enclosed system were the model basis for the production of antitetanus, antidiphtheria, antibotulinic, and antirabic sera for human use. The antisera are usually presented in 40–100 ml vials diluted with isotonic sodium chloride solution, to be administered intravenously. Vials are kept refrigerated, and the freeze-drying process started to be introduced to avoid losses. Butantan supplies the demand of the Ministry of Health and began to export antisera to Latin America, some Africa countries, India, and even to attend the request of some countries in Europe and Australia. It was an unusual experience in learning by doing.



Figure 1.
Partial view of plasma fractionation production plant of antivenoms and antitoxins (Instituto Butantan Foundation).

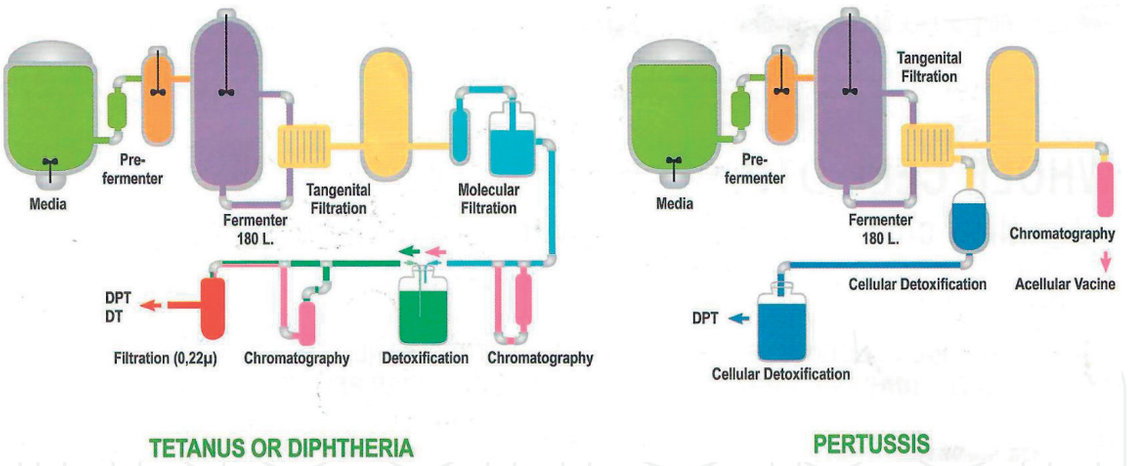


Figure 2.
Tetanus, diphtheria, and pertussis enclosed production systems.

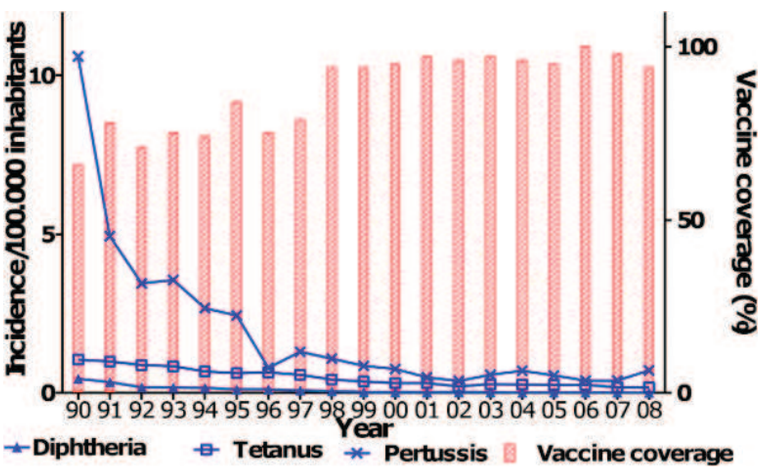


Figure 3.
Coverage of DTP vaccination and incidence per 100,000 inhabitants of pertussis, tetanus (except neonatal), and diphtheria in children below 1 year of age in Brazil from 1990 to 2008.



Figure 4.
Partial view of influenza production plant (Instituto Butantan Foundation).



Figure 5.
Partial view of the hepatitis B production plant (Butantan institute foundation).



Figure 6.
One of the larger chromatography columns of plasma fractionation plant (Instituto Butantan Foundation).

2. Diphtheria tetanus and pertussis (DTP) vaccine

The gained experience in innovation, clinical testing, production development, and full production of antisera pushed our team to move next step into vaccine development, maintaining the dedicated enclosed plants, which guarantee hands off from the production staff [5–10].

The tetanus and diphtheria toxins production happened in enclosed large-scale cultivation systems as well as with the *Bordetella pertussis* strain (bioreactors 180–500 l). One observed particularity is that tetanus culture requires a vibromixer, a special device to promote the culture liquids shaking and not stirring. Bacteria were removed by tangential flow filtration, and toxins secreted in the media were purified by chromatography and finally detoxified basically following WHO recommendations.

A major concern was pertussis, a very common infant infection disease known as whooping cough. It can be fatal as a result of a variety of toxic substances from the classes of exotoxins and endotoxins. Among them, pertussis toxin, tracheal cytotoxin (that affect the respiratory epithelium), dermonecrotic toxin, and adenylyl cyclase (that inhibits phagocytosis) are the most studied and important.

We were able to select a strain of *B. pertussis* to produce an effective vaccine with mild reactogenicity and called it as whole cell pertussis (wP). After introduction of Butantan DTP vaccine (in between 1990 and 2009), the Ministry of Health reported that the incidence of pertussis infection had decreased from about 11/100.000 to 1/100.000, with practically no adverse reactions after vaccine administration. Around 70 million children were vaccinated.

The safety of Butantan's pertussis component of its DTP vaccine contrasted with the safety of DTP vaccine produced in Japan and in other countries. These vaccines are known as whole cell pertussis (wP). The development of an acellular pertussis (aP) vaccine based on purification of some virulence factors as pertussis toxin was a logical pathway. The acceptance of aP was achieved by most developed countries. These vaccines contained pertussis toxin, filamentous hemagglutinin (FHA), fimbria protein (FIM), and some pertactin. The aP vaccine required isolation and purification of all components, which raised its price from about US$ 0.16 to US$ 1.60, making it not accessible to the majority of the population from the developing countries. In 2013, CDC made a survey in the US and found that the aP confers a short protection, resulting in about 40.000 pertussis cases/year [11].

DTP vaccination scheme is usually carried out at 2, 4, 6, 18, and 48 months of age. One last booster occurred 10 years later. Thus, just for four DTP vaccine doses, replacing the DTwP by DTaP would represent an increase in cost of at least US$ 6.40 per capita, which is out of reach for poor countries. Even though a Brazilian publication [12] incited the use of aP for universal vaccination in Brazil at a "modest" cost of US$ 15,590 per life year saved, DTwP vaccination would cost 100x less.

There are other concerns for the use of aP [13]. Fetus and newborns may be exposed to pertussis infection before they are protected against it. Immunization occurs by three doses of DTP at 2–4–6 months of age. It is estimated that 45% of infant mortality occurs before they reach 5 years and is mainly concentrated before 6 months. This leads the idea to vaccinate pregnant women in the third trimester, generating maternal antibodies to be transferred to the babies by breast feeding. It is still necessary to fully investigate the safety of this type of vaccination to guarantee that there are no effects on the fetus [14–16].

Butantan has proposed an alternative for aP vaccine. It developed a process to remove the lipopolysaccharide (LPS), the most reactogenic component of the outer

membrane of most gram-negative bacteria, without breaking the bacterial membrane, producing a whole cell pertussis vaccine low in LPS (wPlow). This vaccine was retested at Nederland Vaccine Institute [8] and currently is under additional clinical trials, as required by the Brazilian regulatory agency, to replace wP in our DTP, without increasing cost. Furthermore, the isolated LPS can be hydrolyzed to obtain monophosphoryl lipid A (MPLA), a power vaccine adjuvant.

Other alternative for the vaccination of the newborn is BPZE1, a live genetically attenuated pertussis, developed by Pasteur-Lilly by inactivating pertussis toxin, tracheal cytotoxin, and dermonecrotic toxin [17–18]. This vaccine will be administered in newborns as a single-dose nasal vaccine. Its clinical assay is being proposed.

3. Hepatitis B

Butantan developed a recombinant hepatitis B vaccine by genetic engineering, based on the hepatitis B surface antigen (HBs) and expressed in the yeast *Hansenula polymorpha* with a good yield [19–25]. The vaccine was tested in adults, adolescents, and newborns with the cooperation of the Institute of Tropical Medicine, the Medical School in Campinas and Oswaldo Cruz Institute [19–22]. It was the first recombinant vaccine developed in Brazil, approved and accepted for newborns by the regulatory authority in 1997. A total of 260 million doses were produced between 1997 and 2009, delivered to the Ministry of Health that distributed to all States for free administration to newborns, children, and adults. No significant adverse events were reported. The potential use of hepatitis B vaccine or antibody to treat chronic hepatitis B must be explored in the future [23].

Other new developments have been planned like the vaccine association with the adjuvant MPLA to reduce its concentration/dose (at least by fourfold as some assays have showed). These results consequently increase the vaccine's potential installed capacity without increasing the vaccine cost. A new genetic construction to express the preS antigen (the N-terminal polypeptide in the large (L) HBs antigen associated with virus attachment to the host cell receptor and membrane fusion during entry) was implemented considering the about 10% of nonresponsive adults. The use of the regular vaccine and the preS vaccine to treat chronic infection was also considered, but it was not yet tested. The success of the regular vaccine to protect newborns postponed the materialization of the last proposal.

Recently, a study was conducted in Brazil revealing that hepatitis B is not the prevalent strain causing hepatitis, with variation in different regions. Hepatitis A represents 58.7% followed by hepatitis D and F (23.4%), while B, C, and G are minor[23-24]. In a world overview, B/C relation represents 60% [24]. It is estimated that there are 5.000 cases of hepatitis C. The Ministry of Health is trying to cure with a patented drug that inhibits replication of the virus, sofosbuvir combined with daclatasvir, at a cost of about US$ 9000 per patient. The Instituto Oswaldo Cruz is trying to market a generic drug for four times less. The right of the Brazilian Ministry of Health to be able to supply the drug for all is being questioned by the patent holders, although it was accepted during the AIDS epidemics.

4. Butantan legacy, influenza, and adjuvants

Butantan assumed a national leadership in vaccine production in 2007, with dedicated plants for diphtheria, tetanus, pertussis, and hepatitis B [26–32]. Going from the innovation all the way to production, Butantan provided the

Society's demand to control wide spread infections, delivering vaccines free of charge to all population at risk, at acceptable cost to the resources of the Ministry of Health.

The public memoir goes back to 1918 when the "Spanish flue" reported 116.777 cases in city of São Paulo and killed 5.330 people. Those who could afford or have family elsewhere fled the country, leaving the streetcars to transport bodies to be buried in common graves. Government and Society respected the translation of "innovation" into vaccines and sera, safe, and efficient. Developing and manufacturing vaccines were different from buying bulks from large companies to formulate, fill, and label as made in the other countries. This situation was named at WHO meetings, the "coca-cola" model: buy bulk, dilute, and label made in the countries.

With the few vaccines and antisera mentioned, between 1985 to 2009, Butantan was able to produce about 720 million doses of effective and safe vaccines, representing 80% of the vaccines really made in Brazil, receiving for this about 40 honors, medals, and public grants. This was made possible by creating Butantan Foundation, a not-for-profit body that could operate as a private organism, by passing the Government rules, which would make impossible to buy reagents, supplies and equipment, maintain or built new labs and dedicated production plants, hire, and trend in service, the staff, to operate the plants, without the constrains of public rules, which were not adapted to solve public emergencies.

The next priority was flu epidemic risk. The "Spanish flu" reached Brazil in 1918 killing about 35,000 people. US-Barda realized, as pandemic spreads, that the total world production vaccine plants against flu could not supply the demand for vaccines, as the virus serotypes change each year and stocks could not survive and be used for the next epidemics.

Butantan seasonal or pandemic flu first action experience was to set a pilot laboratory to maintain and replicate influenza strains certified by WHO and CDC for production, and to train the staff for produce. A control lab to test and certify vaccines was installed. The State and Federal Government granted 10 million dollars to build the production lab, ordered when possible custom-made equipment (like the machine to destroy the infected shells that was built in Brazil). A central formulation plant was constructed and equipped with a modern automated filling line, to wash and sterilize vials, fill cap, and label vials, with filling capacity of 28,000 vials per hour, containing 10 doses each. A second automated filling system was added to cover for all the vaccines produced. Flu vaccine was cultivated in fertilized chicken eggs and, after extensive purification steps, was transferred for formulation and filling. C. Merrieux (latter Sanofi) extended its help to Butantan, following the plant construction and installation, and inspecting to be sure of our suppliers of chicken eggs comply the rules established by WHO.

The first formulated vaccines produced were taken to Merrieux's laboratory to be inspected and tested for the demanded requirements of the European Community. Butantan transported the vaccines using cold trucks to the central stock of the Ministry of Health in charge to vaccine distribution to all the state centers, which transfer them to municipal facilities during vaccination. To attend actual Brazilian yearly demand, about 100 million flu vaccine doses are necessary and it is not an easy task to achieve. It took a few years until the regulatory agency approved Butantan's vaccine, while Sanofi assumed an agreement to meantime supply the vaccine in bulk for formulation at Butantan. We reached, in 2017, the production of 60 million doses of flu vaccine given to children, young adults,

pregnant women, and people above 60 years or with special health problems, doctors and nurses.

About 5 million Brazilians live above the equator line and, by mistake, they received the same Southern vaccine, in the same date. It was clear that they were vaccinated after the top of the flu season was over, and they were not protected [25]. The solution was to use part of the year to produce Northern flu vaccine to supply the population in the North. As the sole production plant in Latin America (other than a Sanofi plant that provides bulk to Birmex in Mexico), the excess vaccine production should be offered to PAHO rotating fund, solving the demand of vaccine influenza for Venezuela, Colombia, and Central America (some countries use North and other Southern vaccines).

Butantan became interested in using adjuvants for vaccine production, if they would guarantee more vaccines doses using the same facilities and thus reducing their costs. The first attempt, in 2002, was to use a formulated vitamin A in oil as a potential adjuvant to DTP [5]. The production of flu vaccine allowed Butantan to look into adding adjuvants to reduce antigen/dose, increasing the plant capacity and reducing the purchase of fertilized eggs. A ready formulated adjuvant was offered by one of the large producers of vaccines, but that would give to this company the control of the Brazilian market. We considered formulating our adjuvant using squalene as a component, but the supplier advertised that squalene was restricted to competitors. Squalene plus tocopherol (adjuvant system ASO3) resulted in some cases of narcolepsies in Scandinavia and China, attributed to a deficiency of hypocretin secretion by hypothalamic neurons [27–28]. ASO3 comes in two formulations, $ASO3_A$ with 11.86 mg/dose and $ASO3_B$ with 5.93 mg/dose [30]. In our assays, testing vitamins as adjuvants [29], we also included and studied tocopherol present in several multivitamins sold over the counter, and known to be toxic to monkeys. We developed the production of *Bordetella pertussis* monophosphoryl lipid A (MPLA), as a byproduct of the production of the low reactogenic pertussis vaccine (Plow). This MPLA has been shown to be a powerful adjuvant. We also tested vaccines with vitamins as adjuvants, which are produced in large volume as nutritional compounds. Testing 27 adjuvant combinations [5, 31–32], we concluded that the most promising was MPLA with the classical $Al(OH)_3$ [33]. Riboflavin and folic acid may act as a bridge to mucosal-associated invariant T cells (MAIT) and the major-histocompatibility-complex-related molecule MR1 [34]. We tested riboflavin combined with MPLA and a trivalent influenza vaccine, and we found a high increase in antibody titers [31].

We found that addition of adjuvants to influenza vaccine allowed a decrease in the usual dose of 15–3.75 μg. The adjuvant addition increased the vaccine production by 4-fold per egg, for the four split virus: A H1N1, H5N1, H3N2, and even H7N9, a new serotype spreading present in the vaccine. We also developed a whole virus vaccine technology in 2010 [35], recently being tested by several large-scale vaccine producers. Whole virus represents more than double production of vaccine/egg, as compared with split virus, and may decrease production cost by a factor of 2-to 5-fold, which would make preventive influenza vaccination affordable to developing and poor countries. In the whole virus, nucleoprotein is present, and they activate toll-3, toll-7, and toll-9 receptors of the host cell, explaining the higher immune response, but also produces antibodies that cross react with hypocretin receptor 2, which will require careful investigation before whole virus influenza vaccine is approved. There are results suggesting that the role of vaccine adjuvants like vitamin A and E increases the IgG1 response as high as squalene. Vitamin D was shown to modulate influenza immune response [35].

Vaccine	Age	Produced by
Hepatitis B	birth: 1, 6 months	Butantan
BCG intradermal [BCG-S1pertussis]	birth	Ataulfo Paiva Butantan
DTwP + HiB [DTwPlow + HiB]	2, 4, 6 months	Imported Butantan
Oral polio	2, 4, 6, 15 months	Biomanguinhos/GSK
[Rotavirus]	2, 4 months	Imported Butantan-NIH
Pneumococcal conj 10 valente	2, 4, 6, 10 months	Imported Butantan
Meningitis C conj	3, 6, 15 months	Imported
Yellow fever	9 months	Biomanguinhos

[vaccine]: under development.

Brazilian vaccination schedule.

5. New vaccines under development at Butantan

5.1 *Haemophilus influenza B*

Vaccines against *Haemophilus influenza B* are based on polysaccharides. The technologies for the production and the conjugation of the polysaccharides with the carrier protein were developed by Butantan, from 2007 to 2012. It is ready to move to full-scale production [36–38]. This product will allow to simplify vaccination of newborns, by combining in a single vial a pentavalent vaccine, DTwPlow, Hepatitis B and H. influenza B, all produced with our own technology, which depends on building a GMP-dedicated lab for *Haemophilus* production, evaluating trials and registration.

5.2 Rotavirus vaccine

An agreement NIH-Butantan authorized Butantan to produce the pentavalent rotavirus vaccine. Butantan was the first to produce experimental lots for a clinical trial phase I, which was conducted with good results [39]. The phases II and III trials were not yet authorized by Anvisa, but opened for the GSK tetravalent vaccine, using Biomanguinhos as an importer. This occupied the Brazilian public market for about six years. A new vaccine trial comparing with the GSK vaccine was planned with NHI, but the previous Butantan board of directors and management did not act.

5.3 Dengue vaccine

An agreement with NIH allowed Butantan to start a pilot production of dengue vaccine. Trials at School of Public Health of Pennsylvania were successful, but the clinical trial of Butantan vaccine was delayed 2 years by ANVISA, while allowed Sanofi to test their tetravalent vaccine in Brazil. After two years delay, Butantan is conducting the clinical tests in different regions of Brazil, using pilot-scale vaccines produced by Butantan. Clinical tests about to finish slowed down by an unusual decrease in the incidence due to unexpected weather changes. Production plant building is about to be completed by 2019. Meantime, Sanofi vaccine tested in Brazil will not be used and was not approved by any other countries due to serious adverse reactions. Even so, the Brazilian State of Paraná purchased the Sanofi dengue vaccine, while Philippines sued Sanofi for its adverse events.

5.4 DTwPlow and MPLA

The production plants developing antigens diphtheria and tetanus were supposed to be renovated to comply with WHO recommendations and requirements by ANVISA. Thus, at the moment, the production has been stopped. Meantime, we invested in the development of large-scale technology for MPLA from *B. pertussis*, expected to be used as an adjuvant for influenza and hepatitis B vaccines.

5.5 Pneumococcal vaccine

To replace a mix of 13 to 20 serotypes of pneumococcus, Butantan developed a vaccine based on recombinant pneumococcal surface protein A (PspA) from three different strains, making production easier and less expensive [40–42].

5.6 Modified BCG

By genetic engineering, a BCG expressing pertussis S1 protein was obtained. It was shown to be more immunogenic than the regular BCG and more effective in a mouse model of bladder papilloma. With this, new BCG Butantan intends to perform proper human trials and return to produce BCG to take place at Ataulfo Paiva Institute that is closing its operation [43–47].

5.7 Rabies vaccine for human use

Rabies vaccine was produced by Butantan for many years, using basic Pasteur process and using suckling mice to isolate brains [48–49]. The rabies virus inactivation used an ultraviolet lamp. This type of production was abandoned as the Ministry of Health requirement was to immunize each year about 42,000 domestic dogs. A new process was developed using Vero Cell in a serum-free media, followed by inactivation, to be used in human who had been bitten by suspected dogs [48–50]. The production and control of this vaccine limit the production to a few producers, being an expensive vaccine. Butantan invested in a large plant to where production is expected to be transferred in 2019.

6. Other process and products under development at Butantan

6.1 Plasma fractionation

According to the Brazilian Constitution, blood cannot be purchased from donor, nor its fractions sold; thus, plasma fractionation must be a public not-for-profit operation. Butantan did not have access to the plasma, but developed a process for hemoderivatives obtaining from human placenta extracts, establishing technologies to separate a series of proteins at high purity. The process allowed to isolate and purify albumin, immunoglobulin G, and some enzymes of potential interest for medical use [50–54]. When we got access to bags of human blood, we developed the purification process of factor VIII [55].

Butantan has worked in the development of a modern plant, replacing the Cohn method by sequential chromatographic steps, thus avoiding denaturation of fractions with potential clinical use caused by ethanol precipitation. The State of São Paulo with a few other states collected a large part of the human plasma collected in Brazil.

The Government of São Paulo provided funds to build a plant and purchase special equipment. The plant was built and part of the equipment acquired. It was planned to be an automatized facility, and a company with expertise was contracted to design a computerized central of control system that would direct the simultaneous steps of the process. This has already represented a partial investment of about US$ 200 million, while we maintained a small pilot plant to test every step of the complete process for purification of albumin, immunoglobulin, and coagulation factors. The scientific project started at Butantan in collaboration with Pharmacia, which was willing to participate in developing a plant to process about 150,000 l/year, purifying about ten different proteins.

Among other reasons, the project stopped after Pharmacia was sold to GE, which lack expertise and did not have the same interest in this project, which could be transferred to other countries, and Butantan would open its plant to train operators. A second impediment became the interest of a few large-scale plasma fractionation foreign companies, which would like to process Brazilian plasma in their existing plants, where Cohn method was utilized to supplement final purification by chromatography. There was an old precedent trying to establish a plasma fractionation plant in Brazil, expecting to produce albumin to rescue wound soldiers in the field, who were participating in the Second World War in Europe. This did not happen, but later opened the possibility for installation of a plant fractionation by a known company, which did not test the plasma to produce albumin, spreading hepatitis B in Brazil. Recently, there was a negotiation to open Butantan plant for a public private partnership, legally prohibited by the Constitution. Meantime, Butantan developed a chromatographic process to isolate as a first step the factor VIII, following with the isolation of IgG to be used to control infections, which are more specific for the country [53].

6.2 Lung surfactant

Each year, about 150,000 newborn dies by suffocation few minutes after the delivery. Most are premature, too small, do not cry after delivery, and do not open the alveoli. This can be corrected by administering to the newborn a lung surfactant. We assemble a team of investigators, including pediatricians from the Medical School of the University of São Paulo, which helped to develop a process for isolation of natural lung surfactant from pig lungs in an enclosed system and test in unborn piglets just after cesarean intervention [56–60]. The project was supported by grants of FAPESP and by a large meat producer, which supplied the pig lungs. A multistate clinical trial was carried out in public maternities with very good results, including cases of meconium aspiration. These good results supported the drug registration by the national regulatory agency.

The process initially developed extracted the crude lung surfactant with the solvent trichloroethylene, which was removed and recovered by evaporation under vacuum. The final surfactant is then lyophilized. As a byproduct of the surfactant production, we recover aprotinin, used in the surgery to replace stands. The process of isolation of the lung surfactant was redesigned to use less trichloroethylene and guarantee full removal during freeze-drying.

A large company on meat market in Brazil showed interest in funding the new plant in Butantan and expects to distribute lung surfactant for free to other countries like Congo where 100,000 newborns die each year. In contrast with Brazil where most deliveries occur in maternities, the introduction of surfactant in some countries with untrained mid-wife may only administer the surfactant as aerosols using a portable inhaler. The use of surfactant aerosol containing tobramycin is in our agenda, to treat cystic fibrosis and to speed up the recovery from postinfluenza among elder people.

Not all Butantan's projects were successful, even with the partnership of important laboratories in advanced countries. This has been the case of leishmaniosis, which affects Brazil and many countries in Africa and Asia. Visceral and cutaneous leishmaniosis infect dogs and are transmitted to man by mosquitos. It is increasing even in the developed state of São Paulo. New antigens are also been studied.

Difficulties are being faced also due to the reduction of funds to research institutes and even the closing of international research institutions where the developing world could find scientific support.

Butantan has proven the feasibility of public production of good quality biopharmaceuticals in developing countries, contributing to world science and innovation, translating the research into affordable vaccines for the population.

7. Conclusions

The Brazilian Constitution defines as role of the State to provide public health, specially controlling the infectious diseases where a few cases can spread the infection as epidemics to the whole population. The most effective program is to vaccinate, which should be affordable to the Government and then available for all.

In the early developments, advanced countries' governments invested in focused research, by creating public institutes and recruiting outstanding scientists to solve the needs for public health. They innovate and assay their developments for efficacy and safety, which requires an additional step going from the lab into developing production technology, which lead those scientists to create large-scale production facilities to make biopharmaceuticals available to the society. This was not the role of public institutes, and soon, large companies were created to supply, not just the national market, but developing countries, which represent 80% of the world population.

Soon, the public health motivated scientists were replaced by managers that measure their achievements not by saving lives but by volumes of sales, not responsible for public heath affordability. In recent time, producers of vaccines invested in innovation. Many public research institutes lost government support and some international health research institutes are closing. Developing countries lost support to receive technologies and to train scientists, so that they would be dependent forever and could not contribute to knowledge.

This brief description of scientific and industrial developments to answer to public health priorities represents the efforts of members of Butantan to convert innovation not only in publications, but also in vaccines and other biopharmaceuticals at costs that the national public health system can afford. This is easy to state, but in most countries difficult to achieve. As Butantan was able to provide to the society through the government some vaccines and other biologicals at affordable costs, we became recognized by our population, while considered by the large industries in developed countries as a bad example to other developing countries, becoming a target to be absorbed by the international large producers, not to produce to the government but to receive bulk, fill vials, and label as local production.

Also, some of the few local producers in developing countries were purchased to be closed. Offers for a public private partnership were not real, as both parts did not plan to implement, as large pharma had no intention to transfer recent technologies, while the local public producers, to avoid efforts and responsibilities, replace local production by buying bulks at costs dictated by the real for local filing. The large vaccine producer changed the goals, in part by transferring the leadership from scientists at service of the society to skilled managers, which measure success in terms of sales and profit, imposing their politics to developing countries market.

Buying smaller pharma in developing world, in most cases does not represent local production at affordable prices, but simply removal of competition.

There was an attempt to buy Butantan production units. In recent years, the institution has been suffering political and economic interferences that led to an undue stop of most of the production plants, pretending to be for major renovations. Instead, functional plants were destroyed, while purchasing the vaccines from large pharmas, without any concerns for our population or to provide affordable vaccines for the Ministry of Health.

Rebuilding Butantan and recover the expertise of the staff are not easy tasks and will require major investment. For other Latin America countries to begin without help is practically impossible. An interim plausible solution is to use a large unfinished Butantan's building to house a joint Latin American biotechnology center, while its plants are recovered to produce and train younger graduates participating in innovation international team, how to produce vaccines and they could take back with them the technologies developed at Butantan and maybe share with us clinical trials, avoiding the present prohibitive costs.

We think Butantan must go on with its public mission recovering good early Brazilian health public experiences and efforts. The case of AIDS pandemic was emblematic. It was partially controlled with new drugs, which were denied to poor countries, until Brazil challenged the patent. Same thing is in process to be repeated with the drug for treatment of hepatitis C, sold for $US 9000/person. And many other health public problems must be considered as neonatal syphilis is back to Brazil, even though it could be controlled with penicillin G, the first antibiotic discovered. The reason for the lack of penicillin is that its price became so low that private pharma lost interest in producing, illustrating the need of careful public health attention and decisions.

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