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The Butantan Institute and the Brazilian AntiCOVID Vaccine

Reinaldo Guimarães (https://orcid.org/0000-0002-0138-9594) [1]

Abstract *The text explores the theme of Brazilian sufficiency in vaccines. It presents the ways practiced in the two most important Brazilian institutions in the development and production of vaccines - the Butantan Institute and the Institute of Technology in Immunobiologicals (Bio-Manguinhos). These paths are the pure and simple purchase, the purchase of the product with technology transfer commitment, partnerships that include the fulfillment of phase 3 trials by the buyer, the new path announced by Instituto Butantan in which the partnership includes for the realization of trials in phases 1 and 2 and, finally, the invention, development and local vaccine production. The latter is only mentioned as a possibility currently not achieved. Finally, the text presents data on the chances of success in vaccine development.*

Key words *Vaccines, Technological development, Industry, Public Health*

[1] Núcleo de Bioética e Ética Aplicada, Universidade Federal do Rio de Janeiro. Rua Venceslau Brás 71, Campus Praia Vermelha. 22290-140 Rio de Janeiro RJ Brasil. reinaldo.guimaraes47@gmail.com

To Isaias Raw

In Brazil, there are five possible ways for a vaccine to reach the Unified Health System (SUS). In any of them, the product must have a registration with National Agency of Sanitary Surveillance (ANVISA) and have been incorporated by the National Commission for the Incorporation of Health Technologies in the Ministry of Health (CONITEC/MS).

The first way is to buy a finished product that is already being marketed by the company that invented, developed and produced it. In this case, it is a common commercial operation, whose effectiveness ends with the arrival of the product in the contracted quantities and its payment.

The second way is for a qualified national producer to buy the finished product under a contract that contains technological compensation clauses, currently called 'technological order'. This contract usually provides for a first stage of delivery of the finished product and, in subsequent stages, a growing appropriation by the buyer of retrograde local development and production operations. The contracts define deadlines, delivery schedule for the finished product and raw materials, eventual training of professionals, markets to be explored and royalties to be paid to the technology owner who, during the technology transfer, must be added to the price paid for the vaccines finished. In the current rules for the regulation of intellectual property, this type of operation, present in several contracts long signed by Butantan and Biomanguinhos / Fiocruz, is called 'voluntary licensing'. An alternative to voluntary licensing is 'compulsory licensing', which has been envisaged since 2001 in the World Trade Organization's rules for emergency situations or health crises. Until today it has not been used in the field of vaccines and an initiative sponsored by South Africa and India in 2020 has not managed to go ahead in opposition to the rich countries, with the regrettable adhesion of Brazil to this group.

The third path was used by the Butantan Institute in the agreement between it and the Chinese company Sinovac, for the development and production of the Coronavac vaccine. In this case, unlike the previous path, the production technology - inactivated virus - is largely dominated by the institute, which has been giving greater adherence to the terms of supply of the product to SUS. And there is a particularity regarding the realization of the Coronavac phase 3 trial. Sinovac did not elaborate a single protocol to be strictly followed by all countries that have established purchase agreements for their product. Each country, within certain general guidelines, carried out its protocol, which, among us, was carried out by Butantan himself, and the determination of the vaccine's efficacy was established after the consolidation of the results of the different trials carried out in several countries.

The fourth path is what guides the current debate. Butantan claims to have reached the formulation of the first 'Brazilian vaccine' and this has generated controversy, given that an important component of the vaccine was invented, developed and patented in the United States. This component is a modified virus that is harmless to humans, but capable of expressing the Sars-CoV-2 infective spike protein without the ability to penetrate human cells, but with the ability to produce antibodies against it. Other details of the contract are not currently known. What is original about the Butantan announcement is that the agreement with the patent holders involves the realization in Brazil of the initial stages of the clinical studies - phases 1 and 2 - that measure the immunogenicity in humans and the safety of the vaccine. In "normal" times, usually only phase 3 of clinical studies used to be outsourced abroad for reasons almost always related to resource savings.

The fifth path is the complete invention and development in the country, whose discussion deserves an exclusive text. According to the press, there are 16 projects in various preliminary proof of concept stages[1]. But, I advance that if we continue with the chronic financial shortening currently very aggravated and the institutional destruction by the federal government, at most we will make punctual a worthy effort by our scientific community. In 2019, Lo and Siah estimated the chances of success for 1869 vaccines against infectious diseases[2]. In summary, 76.8% of this total went from phase 1 to 2; among those who passed (1235), 58.2% were successful in phase 2 (42.1% of the initial 1869); among those that entered phase 3 (609), 85.4% were successful in this last phase. The aggregate chances of success were 33.4%. On 3/26/2021, the World Health Organization's vaccination overview for Sars-CoV-2 vaccines contained 83 vaccines developing human trials, 63 of which in phases 1 and 2 and 20 in phases 3 and 4[3]. It should be noted here that the readiness of the international scientific community to develop vaccines during the pandemic, until now, has increased "mortality" among the

candidates with a 7.5% success rate until phase 3, against 33.4% of the work already mentioned. But, it is necessary to consider that this race has not yet reached its end. In light of the numbers for Lo and Siah, the Butantan announcement elicits three comments. The first is that the risks of failure are not negligible; 57.9% according to those numbers (100 - 42.1). The second comment is evidence of the trust placed by the patent holders in the technical competence of the institute. It is difficult to believe that if this were not the case, this decentralization of development at an early stage of the clinical phase would have been achieved. The third is that Butantan, as in the partnership with Sinovac, once again invests in a safe technological route. If the candidate passes the three phases of clinical trials and goes into production, there will be no major difficulties, as it is through this route that the seasonal flu vaccine is already produced there (inoculation in Chicken eggs followed by inactivation of the virus).

The candidate vaccine announced by Butantan appears in the WHO database with developers Mahidol University / GPO (Thailand) and Icahn School of Medicine at Mount Sinai and the trial record that appears in ClinicalTrials.gov was last updated on 16 / 3/2021[4]. It is quite possible that there will be a new update and if the partnership with Butantan is carried out along the lines of the one made with Coronavac (each partner conducts its own protocol), a new trial registration may be necessary.

The debate about whether or not this is a 'Brazilian vaccine' cannot be answered in a binary way - it is or it is not. From the point of view of intellectual property, it is not. From the point of view of advancing the form of partnerships between national and foreign laboratories, it is undoubtedly a step forward. And from Brazil's point of view, risking another quality vaccine against Sars-CoV-2 is undoubtedly an extremely positive fact. And, let's imagine if, further on, given Butantan's technological commitment to walking on routes that it already dominates, it can reach a vaccine with five antigens. Three for influenza and two for Sars-CoV- 2 variants.

Congratulations to Butantan!

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