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Technological order and technology transfer of the vaccine for COVID-19 in Brazil: a case study of the model used by AstraZeneca/Oxford and Fiocruz

Encomenda tecnológica e transferência de tecnologia da vacina para COVID-19 no Brasil: um estudo de caso do modelo utilizado pela AstraZeneca/Oxford e Fiocruz

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ABSTRACT

Introduction: The COVID-19 pandemic, caused by SARS-CoV-2, showed a rapid increase in the number of cases and deaths in the five continents, with a major impact in the public health and the economy of the countries. The effects of COVID-19 have highlighted an increase in existing inequalities in society. A global mobilization for the development and rapid production of vaccines was needed to meet the emergency demand caused by COVID-19. **Objective:** To discuss actions carried out by Fiocruz in the challenges imposed by the emergency to combat the disease, in addition to analyzing and discussing the partnership established between Bio-Manguinhos/Fiocruz and AstraZeneca, through Technological Order (ETEC), aiming at the verticalized Technology Transfer (TT) of the CHADOX1 NCOV-19 vaccine. **Method:** A documentary analysis of a descriptive nature and qualitative approach was carried out, based on the search for scientific articles on the subject, and institutional documents, as well as a thorough procedural analysis of ETEC, formalized between Fiocruz and AstraZeneca. **Results:** Although the National Policy for Technological Innovation in Health (PNITS) describes three viable legal instruments for formalizing partnerships, ETEC was the most adequate to meet the demands imposed by the health emergency of COVID-19, reinforcing the importance of using the State's purchasing power as an instrument for strengthening the State Health Care System (SUS) within the scope of the Health Industrial Complex. **Conclusions:** Even considering the health emergency caused by COVID-19, Bio-Manguinhos/Fiocruz managed to establish a partnership with AstraZeneca, aiming at the TT for the national verticalized production of the COVID-19 vaccine, for the attendance of SUS´s demand. The legal instrument chosen for the formalization of the partnership was ETEC, the first used in the public health area, which proved feasible to be reproduced in future partnerships aiming at the internalization of technologies of national interest. From the absorption of this technology, Bio-Manguinhos will be able to develop new vaccines of HM's interest using the same technology.

KEYWORDS: Technological Order; COVID-19 Vaccine; ETEC; Public Technology Procurement; Demand-side Innovation Policy

RESUMO

Introdução: A pandemia de COVID-19, provocada pelo SARS-CoV-2, mostrou um rápido aumento do número de casos e mortes nos cinco continentes, com marcante impacto na saúde pública e economia dos países. Os efeitos da COVID-19 evidenciaram um aumento das desigualdades existentes na sociedade. Foi necessária uma mobilização global para o desenvolvimento e produção rápida de vacinas para atender à demanda emergencial causada pelo COVID-19. Objetivo: Discutir as ações realizadas pela Fiocruz nos desafios impostos pela emergência ao combate à doença, além de analisar e discutir a parceria estabelecida entre Bio-Manguinhos/Fiocruz e a AstraZeneca, por meio da Encomenda

Tecnológica (ETECT), visando a Transferência de Tecnologia (TT) verticalizada da vacina CHADOX1 NCOV-19. **Método:** Foi realizada análise documental de natureza descritiva e abordagem qualitativa, realizada a partir da busca de artigos científicos sobre o tema e documentos institucionais, bem como uma análise processual minuciosa da ETEC, formalizada entre a Fiocruz e a AstraZeneca. **Resultados:** Embora a PNITS descreva três instrumentos jurídicos viáveis para formalização de parcerias, a ETEC foi a mais adequada para atendimento das demandas impostas pela emergência sanitária da COVID-19, reforçando a importância do uso do poder de compra do Estado como instrumento para o fortalecimento do Sistema Único de Saúde (SUS) no âmbito do Complexo Industrial da Saúde. **Conclusões:** Mesmo considerando a emergência sanitária provocada pela COVID-19, Bio-Manguinhos/Fiocruz conseguiu estabelecer a parceria com a AstraZeneca, visando a TT para produção nacional verticalizada da vacina COVID-19, para atendimento da demanda do SUS. O instrumento jurídico escolhido, para a formalização da parceria, foi a ETEC, a primeira empregada na área da saúde pública, que se mostrou factível de ser reproduzida em futuras parcerias visando a internalização de tecnologias de interesse nacional. A partir da absorção desta tecnologia Bio-Manguinhos poderá desenvolver novas vacinas de interesse do Ministério da Saúde utilizando a mesma tecnologia.

PALAVRAS-CHAVE: Encomenda Tecnológica; Vacina COVID-19; ETEC; Contratação Pública de Inovação; Política de Inovação do Lado da Demanda

INTRODUCTION

In 2019, contemporary history was made with the beginning of the pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS -CoV-2), whose first reports of Coronavirus Disease 2019 (COVID-19) appeared in the city of Wuhan, in the Hubei province, in China, in December, 2019[1].

The virulence characteristics observed for SARS-CoV-2 made it spread rapidly across five continents, victimizing a very large number of people. Considering the severity of the disease, the World Health Organization (WHO) declared, on January 30 of 2020, the epidemic of the new coronavirus as a Public Health Emergency of International Concern (PHEIC). On March 11, 2020, COVID-19 was classified by the WHO as a pandemic. According to data from the WHO itself, until April 27, 2022, about 507 million confirmed cases were reported with 6,219,657 deaths worldwide[2,3].

These data include COVID-19 within the main pandemics reported throughout history, such as the Black Death, Smallpox, Spanish Flu, Cholera, Asian Flu, among others, which caused considerable impacts on society in each season[4,5].

In Brazil, the Health Ministry (HM) declared a PHEIC, due to the Human Infection by the new Coronavirus, on February 3, 2020, through Ordinance No. 188, which was revoked by the Ordinance No. 913, on April 22, 2022, because of the significant reduction in the number of positive cases and deaths resulting from COVID-19. The first case of COVID-19 in Brazil was registered on February 26, 2020, in São Paulo. The declaration of community transmission occurred in March, 2020, the month in which the first death from COVID-19 was also recorded[6,7].

It is worth noting the ability of SARS-CoV-2 to mutate. Since the first cases, back in 2019, variants with different transmission capacity and virulence were identified. SARS-CoV-2 variant B.1.1.529 was initially identified in South Africa and caused a rapid increase in COVID-19 cases. On November 24, 2021, the B.1.1.529 variant was named Omicron. This variant contains a large number of mutations, including 15 mutations in the receptor-binding domain (RBD)[8].

The dynamics of the pandemic caused by SARS-CoV-2 and its variants imposed a challenge for science, pharmaceutical industries, governments, and regulatory agencies. It was necessary a rapid mobilization, and combined efforts, to develop the necessary inputs to face the pandemic. The development of effective diagnostic kits, vaccines, and drugs, represented the first and most challenging efforts of the national and international scientific community[9,10].

In this scenario, the Oswaldo Cruz Foundation (Fiocruz), as a strategic scientific and technological institution of the State, linked to the HM, considering its historical and effective experience in dealing with health emergencies, was required to take effective actions, to provide the State Health Care System (*Sistema Único de Saúde* – SUS) with inputs and technologies to be applied in COVID-19.

In the field of development and production of vaccines for COVID-19, Fiocruz's main action was the establishment of an Agreement with the biopharmaceutical company AstraZeneca, aiming at the Technology Transfer (TT) and production, in Bio-Manguinhos/Fiocruz, of the vaccine against the new coronavirus developed by the University of Oxford. The Brazilian government's agreement with the United Kingdom was announced on June 27, 2020, by the HM, which was made possible by a legal instrument called Technological Order (*Encomenda Tecnológica* - ETEC)[11,12].

Throughout 2020, Bio-Manguinhos started to incorporate the technology to production of AstraZeneca/Oxford´s vaccine into the local production of the respective Active Pharmaceutical Ingredient (API). On January 7, 2022, Brazil's Sanitary Agency (*Agência Nacional de Vigilância Sanitária* – Anvisa) granted the registration for Bio-Manguinhos/Fiocruz to produce the vaccine in a vertical way, thus making Brazil autonomous in the production of this vaccine[13].

In Brazil, there was another initiative to internalize the technology for producing a vaccine for COVID-19. On September 30, 2020, the Butantan Institute and the Chinese pharmaceutical company Sinovac Life Science formalized a contract that

provided for the supply of 46 million doses of the CoronaVac vaccine, in addition to the TT for future production by the Butantan Institute[14,15].

In addition to the vaccines produced by Bio-Manguinhos/Fiocruz and Instituto Butantan, other vaccines were registered with Anvisa and made available for the National Immunization Program to use in the Brazilian population. However, the prices and volumes of acquisitions by the Brazilian HM in 2020 and 2021 were different[16].

The present study aimed to analyze and discuss only the partnership established between Bio-Manguinhos and AstraZeneca, through ETEC, aiming at the verticalized TT of the CHADOX1 NCOV-19 vaccine. However, this article will not discuss the safety and efficacy of vaccines registered by Anvisa.

METHOD

The present work was carried out using the exploratory methodology of document analysis of a descriptive nature with a cross-sectional design and qualitative approach, carried out from the search for scientific articles on the subject, as well as institutional documents. The main databases were consulted, such as Scientific Electronic Library Online (SciELO), Periódicos Capes, PubMed, Google Scholar and Arca. Keywords in Portuguese and English were used for the search: COVID-19, SARS-CoV-2, Variants, Vaccine, Pandemic, Technological Order and ETEC. Additionally, institutional documents were used, particularly to support the analysis of the contract established between Bio-Manguinhos/Fiocruz and the company AstraZeneca.

Initially, data were sought in the scientific literature on the dynamics of the pandemic, caused by SARS-CoV-2 and its consequences for global public health in terms of increased demand for health supplies used from prevention to treatment.

Subsequently, research was carried out in the literature of official documents on the partnership mechanism called ETEC, including where this instrument has already been successfully applied. The ETEC analysis established between Fiocruz and AstraZeneca was also evaluated. For this purpose, the analysis of the Contract established between Bio-Manguinhos and the Swedish pharmaceutical company was carried out, based on the literature review about subject and document analysis.

Based on the documents referring to the various stages of the process, the institutional obstacles, the legal restrictions, and the economic parameters involved, a critical analysis of ETEC was carried out. This analysis was used in the TT for the vaccine against SARS-CoV-2, and developed by AstraZeneca/University of Oxford, aiming at verifying the possibility of ETEC being used in the TT of other medicines of interest to the SUS.

Issues related to the motivation of TT were analyzed to identify the aspects involved in the decision-making process, and the relevance and opportunity for the public sector to create technological knowledge in the production.

RESULTS AND DISCUSSION

National Policy for Technological Innovation in Health - Strategic instruments

The National Policy for Technological Innovation in Health (*Política Nacional de Inovação Tecnológica na Saúde* – PNITS) was established through the Decree No. 9,245, of December 20, 2017, aimed at regulating the use of the State's purchasing power in contracts and acquisitions that involve strategic products and services for the SUS within the Health Industrial Complex (*Complexo Industrial da Saúde* – CIS). Additionally, the Decree No. 9,245/2017 lines up the Executive Group of the Health Industrial Complex (*Grupo Executivo do Complexo Industrial da Saúde* – GECIS), and the Permanent Forum for Articulation with Society (*Fórum Permanente de Articulação com a Sociedade* – FPAS)[17].

Taking advantage of the improvements recently introduced in the Innovation Law (No. 10,973, of December 2, 2004), through the New Science, Technology, and Innovation Framework (Law No. 13,243, of January 11, 2016), the PNITS improves technological orders applied to the health area, offering more security and transparency to the contracts established between the government and the industry in the TTs of products that are essential for the SUS[17,18].

The PNITS allows the State to use three strategic instruments:

I. Partnerships for Productive Development (*Parcerias para o Desenvolvimento Produtivo* – PDP);

II. Technological Orders in the Health Area (*Encomendas Tecnológicas na Área da Saúde* – ETECS); and

III. Compensation Measures in the Health Area (*Medidas de Compensação na Área da Saúde* – MECS).

It is worth noting that the implementation criteria for each of these modalities will be different. Within the scope of PDP, there should be a selection through objective, transparent and simplified procedures to be defined by the HM. Compensatory measures result from contracts regularly submitted to the General Law on Public Tenders and Contracts, the application of which, however, will depend on criteria to be defined. However, ETEC, in its turn, may be signed through waiver of bidding[19,20].

Partnership for Productive Development

The PDP emerged in 2009 as an instrument of the industrial policy of the Health Economic-Industrial Complex (*Complexo Econômico-Industrial da Saúde* – CEIS), aimed at expanding the access to medicines and health products considered strategic to SUS[21].

The PDP is one of the Brazilian government's initiatives to use the purchasing power of the health sector for the execution of projects that associate access to quality medicines to the development of the CEIS. The articulated set of industrial sectors and service providers is capable of adding the economic and social dimensions of health. This initiative is coordinated by the HM

and was launched in 2009 at the GECIS meeting. It is a strategy that strengthens the model of a rational developmental economy, with the goal of increasing the technological and industrial productive capacity, with the active participation of the State, through the coordination of the initiative and the absorption of platforms for the effective manufacturing of strategic technologies, by public producers to meet SUS demands[22].

Despite the original 2009 date, the PDP were regulated in 2012, and redefined in 2014, when the criteria for drawing up the list of strategic SUS inputs were established. The Ordinance No. 2,531, of November 12, 2014 presents the PDP eight objectives, which seek the economic and technological sustainability of the country, fostering industrial development to reduce the vulnerability of the SUS, and expand the population's access to synthetic and biotechnological medicines, they are:

I. expand the population's access to strategic products and reduce the vulnerability of the SUS;

II. reduce productive and technological dependencies to meet the health needs of the Brazilian population in the short, medium and long term, following the constitutional principles of universal and equal access to health actions and services;

III. rationalize the purchasing power of the State, through the selective centralization of spending in the health area, with a view to the sustainability of the SUS, and the increased production of strategic medicines in the country;

IV. protect the interests of the Public Administration, and society, by seeking economy and advantages, considering prices, quality, technology and social benefits;

V. to encourage technological development and the exchange of knowledge for innovation within the scope of public institutions and private entities, contributing to the development of the CEIS and to making them competitive and qualified;

VI. promote the development and manufacture of strategic products for the SUS in the national territory;

VII. seek the technological and economic sustainability of the SUS in the short, medium and long terms, promoting structural conditions to increase the country's productive and innovation capacity, and contribute to reducing the CEIS trade deficit, as well as guaranteed access to health care; and

VIII. to stimulate the development of the public production network in the country, and its strategic role for the SUS[23].

Additionally, the contracts may provide, among other conditions, (i.) that, at the end of the partnership, the government must have an industrial plant, in the country, ready for the production of the strategic medicine/vaccine that was the object of the PDP; (ii.) the regulation of intellectual property rights arising from the PDP; and (iii.) that its parties will have the obligation to invest a minimum percentage in research, development and innovation in Brazil[17].

Compensation Measures in the Health Area

Since health is a strategic sector for national development and, with the State having a prominent role in the acquisition of products and services in this area, even though it is not the only buyer, the use of MECS adds to the instruments available for the regulation of use of public purchases' power as a tactic for strategic gain and overcoming the national technological delay[21]. MECS are used to regulate large volume purchases that have little competition. In addition to purchasing the product, the process may require a series of technological compensations to reduce the companies' monopoly and strengthen the domestic market.

According to art. 15 of Presidential Decree No. 9,245/2017, the use of MECS in the health area aims to prioritize technological development and training in the country related to strategic products and services for the SUS. The MECS will have their application regulated in a joint act of the Ministers of Health (MS), Science, Technology, Innovation and Communications (*Ministério da Ciência, Tecnologia, Inovação e Comunicações* – MCTIC), Industry, Foreign Trade and Services (*Ministério da Indústria, Comércio Exterior e Serviços* – MDIC) and Planning, Development and Management (*Ministério do Planejamento, Desenvolvimento e Gestão* – MPDG), after hearing the Executive Group of the GECIS[17,24].

It is worth noting that MDIC is the acronym for the Ministry of Development, Industry, Foreign Trade and Services, which was extinguished through Provisional Measure No. 870 (art. 57), on January 1, 2019, later converted into Law No. 13,844, of June 18, 2019, which "Establishes the basic organization of the bodies of the Presidency of the Republic and the Ministries". The same Law also extinguished the MCTIC, which became a Secretariat of the Economy Ministry[25,26].

In this context, the MECS are anchored in a provision of the General Law on Public Tenders and Contracts (Law No. 8,666, of June 21, 1993) which allows requiring, from the Administration contracted for the supply of products and services, the promotion of commercial, industrial compensation measures, technological or financial. These measures can cover, for example, TT, human resources training, or investment in industrial and technological capacity building. In the health area, they should be used in purchases that involve large volumes and have little competition[17,19].

In any case, the application of the MECS will depend on a previous process that guarantees the competitiveness, transparency, and isonomy of the bidding. The operationalization of MECS follows a specific logic, established by its international use. However, its adoption in Brazil has its own characteristics. Unlike PDP and ETEC, which fit into the hypothesis of waiver of bidding, MECS are included in the bidding process, which even provokes criticism, since, normally, the practice of offset is carried out in a context of waiver of bids, in extensive negotiation with the bidders, part of which is the nature and volume of compensation.

Technological Order

ETEC is fundamentally a public purchase used when solutions to emergency demands are needed where there is still no consolidated technological solution and, therefore, the technological risk is high. ETEC is anchored in a legal framework initiated by Law No. 8,666/1993 (art. 24, item XXXI), art. 20 of Law No. 10,973/2004 and by section V of Decree No. 9,283, of July 2, 2018[18,19,27].

It is worth highlighting the definition of technological risk. According to Law No. 9,283/2018, technological risk is defined as: "possibility of failure in the development of a solution, resulting from a process in which the result is uncertain due to insufficient technical-scientific knowledge at the time when the action is taken". It is precisely the consideration of technological risk that differentiates ETEC from other initiatives provided for in PNITS[27].

The historical inexistence of a solution available in the market is a necessary condition for the establishment of ETEC, as this instrument constitutes an exception to the general rule of acquisition, where the State can assume most of the technological risk. In short, ETEC is flexible with the assumption of risk and, therefore, should be the last alternative deployed in the search for a solution. We emphasize, therefore, that ETEC was created to solve problems, and not simply to facilitate the technological development usually carried out by Universities and Research Centers.

Aiming at consolidating the main differences between the contractual instruments, now under study, Figure 1 was elaborated. It is possible to analyze the relevance of the criteria selected, regulatory framework, prioritization of large volumes and little competition, level of technological risk, need for bidding, and TT at PDP, MECS and ETEC.

Regarding ETEC, it is expected that it should be planned meticulously, as international experiences show that this prior planning phase consumes a relevant part of the time, as well as project resources[28].

This planning is precisely defined according to the form in which the problem needs to be solved, the existence of the solution in the market, the budget and availability, the technological risk, the general risks, the ways of hiring the technical committee, and the structure of ETEC. The contract must therefore contain all these definitions[28].

Anticipating all situations that may occur in the course of ETEC, even if they are apparently unlikely, reinforces the importance of the contract being prepared with attention to detail, and being widely discussed with the management team, the technical committee of experts, end users, and especially with potential suppliers[28].

The ETEC´s formalization will depend on the characteristics of the specific case. Therefore, it is necessary to consider what is most efficient regarding the desired objective. Thus, when dealing with public resources, the chosen structure needs to reflect the budgetary reality and the economic rationality involved.

Figure 2 outlines the main macro-steps that need to be considered until the ETEC is formalized, culminating in the signing of the Contract. A special emphasis should be given to the risk map and preliminary studies, as they form the basis of the decision-making chain at ETEC.

It is important to highlight an example of ETEC developed by the Brazilian Space Agency (*Agência Espacial Brasileira* – AEB), which started a project to acquire a technological solution, aiming at contracting the development of an Inertial Navigation System (*Sistema de Navegação Inercial* – INS). The difficulty in obtaining inertial navigation systems has been an obstacle to Brazilian research and development activities. This is due to

Instruments / Criteria	PDP	MECS	ETECS
Regulation Mark	Ordinance 2.531/2014	Law 8.666/1993	Law 10.973/2004
Prioritization high volume/ low competition	No	Yes	No
Technological Risk Level	Low	Low	High
Requires Bidding	No	Yes	No
Technology Transfer	Yes	Yes	Yes

Source: Elaborated by the authors, 2022.
PDP: Partnerships for Productive Development (*Parcerias para o Desenvolvimento Produtivo*); MECS: Compensation Measures in the Health Area (*Medidas de Compensação na Área da Saúde*); ETECS: Technological Orders in the Health Area (*Encomendas Tecnológicas na Área da Saúde*).

Figure 1. Comparison between the strategic instruments provided for in the National Policy for Technological Innovation in Health (PNITS).

Source: Adapted by the authors[28].

Figure 2. Preliminary steps to be considered prior to the ETEC's formalization.

the embargoes imposed by international suppliers on products related to space and defense applications[29].

Another important initiative to formalize ETEC included the Federal University of Piauí (*Universidade Federal do Piauí* – UFPI), The Federal University of Delta of Parnaíba (*Universidade Federal do Delta do Parnaíba* – UFDPar), The Commerce Social Service (*Serviço Social do Comércio* – Sesc), The Regional Council for Physiotherapists and Occupational Therapists of the State of Piauí (*Conselho Regional para os Fisioterapeutas e Terapeutas Ocupacionais do Estado do Piauí* – Crefito-14), and The Federation of Industries of the State of Piauí (*Federação das Indústrias do Estado do Piauí* – FIEPI). In this case, the objective was to finalize the technology of a respirator, a fundamental activity for the necessary inputs in the development of the equipment to be acquired. Developed with accessible materials and built according to the standards of the Brazilian Medical Association (*Associação Médica Brasileira* – AMB), the respirator will revolutionize the health equipment market by not only meeting the needs for the pandemic, but reinventing the concept of a respirator, since its technology has connectivity and integration that allow telemedicine and health management by health professionals. The equipment will have a sophisticated user experience for healthcare professionals, a competitive price, and an artificial intelligence connection[30].

Technological Order – Vaccine for COVID-19

The term Technological Order was adopted in this paper based on the name used in the Contract established between Fiocruz and the pharmaceutical company AstraZeneca, in addition to being already used in papers dealing with the topic[15, 31]. However, it is worth noting that other terms such as Public Technology Procurement, Public Procurement of Innovation and Demand-side Innovation Policy have also been used internationally, for more than a decade, to refer to initiatives to encourage technological development[32,33].

The Fiocruz, an institution linked to the HM, understanding the health urgency caused by SARS-CoV-2, started actions early in 2020 to provide the SUS with the necessary inputs for the treatment, prevention, and diagnosis of COVID-19.

Considering the vocation of Bio-Manguinhos/Fiocruz in the development and production of vaccines and biopharmaceuticals, this technical-scientific Unit has centralized the responsibility of identifying the technology available at the time for the production of a vaccine that could be made in the industrial plant installed on the Fiocruz campus, in Rio de Janeiro, Brazil. In this sense, Fiocruz identified that the vaccine developed by University of Oxford/AstraZeneca would meet the institutional expectation of providing, as soon as possible, a safe and effective vaccine for the Brazilian population.

The instrument chosen to make the partnership between Fiocruz and AstraZeneca viable, considering the epidemiological scenario and also the necessary legal certainty for the process, was ETEC, as discussed above[31].

In addition to the specific issues involving the ETEC contracting process, aiming the TT of the candidate vaccine for COVID-19,

it is also important to describe the technical elements that justified the choice of this instrument as a technological solution in the segment of vaccines for COVID-19. In summary, the choice of ETEC was defined according to the following parameters: applicability and insertion in the technological route; technological risk and uncertainty; failure in the national and international market; Research and Development (R&D) interest in the national industrial sector; national technological maturity level of the system and its components; and the criticality of the subsystem and its components. The choice of ETEC was supported by articles 19 and 20 of the Law No. 10,973/2004 (Legal Framework for ST&I), and articles 27 to 33 of its Regulatory Decree No. 9,283/2018, which provides for the applicability of this type of contract, which is also part of the list of cases of waiver of bidding contained in art. 24, item XXXI, of Law No. 8,666, of 1993[18,19,27].

Another challenge for Fiocruz was to make the formalization of ETEC viable, taking all the steps foreseen in its training process, at a time of the health emergency. The alternative found was to establish a flow of activities in which some steps occurred simultaneously.

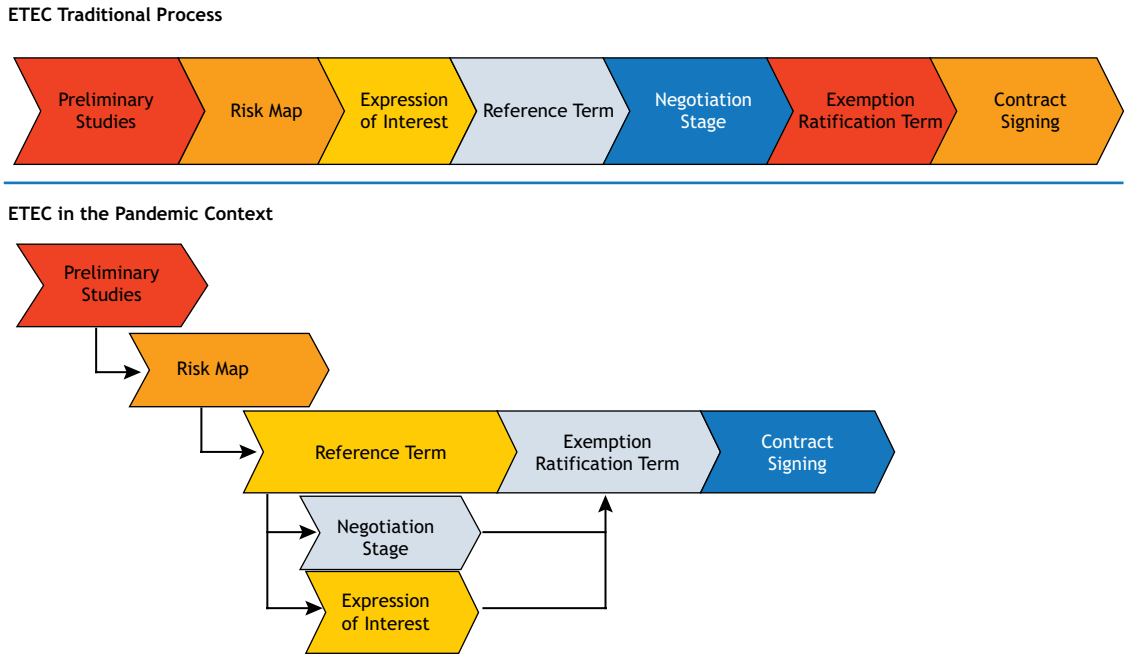
Figure 3 presents a comparative analysis between ETEC in a traditional context, where activities occur in a linear and sequential way; and the proposal to shorten the process, adopted by Fiocruz, for the pandemic context.

It also shows that the elaboration of the Reference Term was carried out in parallel with the process of expression of interest between the parties and the negotiation stage. It is also observed in the figure that the chaining of the macro steps took place in a linear format, with the Expression of Interest being the step prior to the Reference Term - and preceded by the Preliminary Studies, as well as a Risk Map.

The joint efforts of a multidisciplinary team from Fiocruz allowed the formalization of the ETEC, meeting all the procedural prerequisites, in a shorter time - more precisely, in 10 months, from the moment we chose both the technology and the international partner for the TT for the vaccine production in a vertical way, that is, including the production of the API.

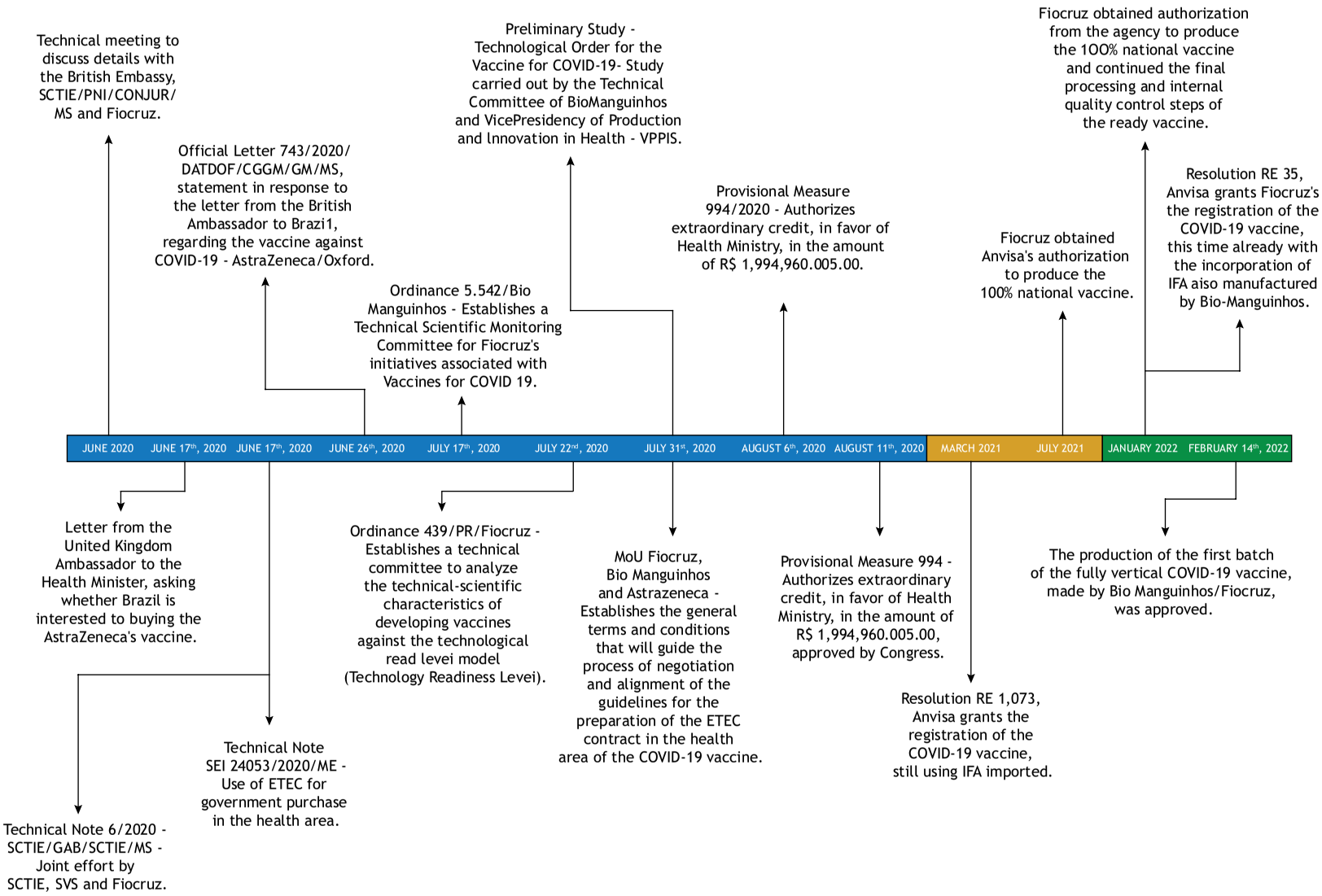
Figure 4 shows the timeline with the main events that have happened, from the beginning of negotiations with the Federal Government, through the formalization of the ETEC contract involving Fiocruz and AstraZeneca, until the production of the first batch of COVID-19 vaccine, fully, vertically manufactured by Bio-Manguinhos/Fiocruz. It is important to highlight that Fiocruz was the first institution to use this instrument for the development of a product for public health.

The starting point for the discussions, addressed at the development and production of the vaccine developed by the University of Oxford/AstraZeneca, took place in June 2020; and it involved teams from the *Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos* (SCTIE/HM), Legal Consultancy (*Consultoria Jurídica* – CONJUR)/HM, National Immunization Program (*Programa Nacional de Imunização* – PNI)/HM, Fiocruz, and British Embassy in Brasília. The importance of this strategic meeting was reflected in a letter from Mr. British Ambassador to Mr. Minister of Health of Brazil informing AstraZeneca's interest in partnering with Fiocruz, aiming at the production of the COVID-19 vaccine[34].



Source: Adapted by the authors[28].

Figure 3. Activities involved in the formalization of the traditional Technological Order, and in the pandemic context.



Source: Elaborated by the authors, 2022.
SCTIE: Secretaria de Ciência, Tecnologia, Inovação e Insumos Estratégicos; PNI: Programa Nacional de Imunizações; CONJUR: Consultoria Jurídica; MS: Ministério da Saúde; DATDOF: Divisão de Análise Técnica de Documentos Oficiais; CGGM: Coordenação-Geral do Gabinete do Ministro; GM: Gabinete do Ministro; SVS: Secretaria de Vigilância em Saúde; ETEC: Technological Orders in the Health Area; MoU: Memorandum of Understanding.

Figure 4. Timeline of the Technological Order.

The choice of AstraZeneca was preceded by a broad effort of technological prospection and discussion of strategies, carried out by both Fiocruz and the HM, which culminated in the issuance of Technical Note No. 6/2020-SCTIE/GAB/SCTIE/MS, signed by the SCTIE/MS, by the Secretary of Health Surveillance (*Secretaria de Vigilância em Saúde* – SVS), by the Executive Secretary of the Ministry of Health, and by the President of Fiocruz. It can be seen in the analysis of the Technical Note No. 6/2020, that the candidate vaccine, developed by the Oxford University and licensed to the AstraZeneca company, was the one that best suited Fiocruz's needs, both because of the stage of development it was in, and for the compatibility with the production facilities of Bio-Manguinhos[34].

The decision was also taken, based on the opinions of experts in the legal and technical areas of Fiocruz, in compliance with Decree No. 9,283, which regulates the Innovation Law. When dealing with the TT, the Decree states that the public agency will be able to create a technical committee of experts to advise the institution in the definition of the object of the order, in the choice of the future contractor, and in the monitoring of the contractual execution, among others[27].

Thus, Fiocruz published Ordinance No. 5,542, of July 17, 2020, which established the Technical-Scientific Monitoring Committee of Fiocruz's initiatives associated with Vaccines for COVID-19, with renowned internal and external members, to advise the presidency and evaluate such initiatives, especially all the potential risks inherent to products in the final stage of development. The committee is responsible for: (1) evaluating technical-scientific documents on the technological development of the vaccine, clinical trials, and the technology incorporation process; (2) evaluate the acquisition or absorption of technologies from other possible partners, or the development of collaborations or partnerships for the development of technologies related to the fight against COVID-19; and (3) to prepare technical-scientific opinions, to support the Fiocruz Presidency on these topics[29].

Subsequently, Bio-Manguinhos also published Ordinance No. 439, of July 22, 2020, which established the Technical Committee for the Analysis of Technological Readiness for vaccines for COVID-19. The objective of the Bio-Manguinhos Committee was to analyze the technical-scientific characteristics of the vaccines under development against the Technology Readiness Level model, as well as the necessary elements for the technological order proposal aimed at the introduction of the Vaccine for COVID-19 by Fiocruz, considering the potential risks inherent to products in clinical development stages.

The HM, through the Official Letter No. 743/2020/DATDOF/CGGM/GM/MS, appointed Fiocruz as the public laboratory in charge of incorporating AstraZeneca's vaccine production technology. For this purpose, the Fiocruz, the HM, and AstraZeneca signed a Memorandum of Understanding (MoU) on July 31, 2020, which laid the foundation for the Agreement between the laboratories on the transfer of technology and production of 100 million doses of the vaccine against COVID-19, if its efficacy and safety were proven. The MoU established the general terms and conditions that guided the negotiation process and establishment of guidelines for the partnership between the parties.

As per MoU's terms, Fiocruz and AstraZeneca decided to structure the relationship between the parties in two contractual instruments: the ETEC Agreement, and the Technology Transfer Agreement (*Contrato de Transferência de Tecnologia* – CTT) for the production of the API of the COVID-19 Vaccine[31].

The ETEC in question was made possible through the Technical Note SEI 24053/2020/ME, which authorized the use of this instrument for government procurement in the health area. This act confirms the importance of articulated actions between the various spheres of government[35].

The ETEC Contract was prepared based on the model draft prepared by the Permanent Chamber of Science, Technology, and Innovation of the Federal Attorney General's Office (*Advocacia Geral da União* – AGU) and negotiated between the parties. Therefore, the contract signed included the following services: scaling (development of the process on an industrial scale) of the production of the API, aiming at the production of the amount of COVID-19 Vaccine agreed by the parties. During the Pandemic Period, the commercialization territory of the COVID-19 vaccine by Fiocruz will be the Brazilian public market, to meet the needs of SUS. For the post-pandemic period, the Parties may, in good faith, assess the possibility of extending the territory, under the terms of a new specific instrument to be signed by the parties[36].

Carrying out the contracted object, AstraZeneca is committed to making every effort, including the allocation of qualified professionals with appropriate technical knowledge, providing the appropriate facilities, materials, equipment, and technologies.

The ETEC Contract, as well as the MoU signed between the parties, established some provisions that were observed in CTT. Under the Agreement, AstraZeneca made available the license of patents in Brazil to Fiocruz for its term, as well as the right to use the technical information used in the activities of registration, production, and commercialization of the vaccine in the Brazilian public market, to meet the demand of SUS. CTT also provided for the supply of working cell banks to support production by Bio-Manguinhos, as well as for the future production of its own bank of working cells, in addition to the supply of working seed lots to guarantee autonomous production by Fiocruz of the API.

An important milestone that enabled ETEC was the approval by the parliament of the Provisional Measure (*Medida Provisória* – MP) No. 994, on August 11, 2020, corroborating with the need for urgency in the negotiations and the necessary procedures to obtain ETEC. Provisional Measure No. 994 ensured the necessary resources for compliance with the targets established in ETEC[37].

In July 2021, the production of the national API began, a necessary input for the COVID-19 vaccine to be 100% produced in Brazil. After finishing the first batches of API and stages of internal controls of Bio-Manguinhos, the input also followed, in October 2021, to the stages of external quality control, including international ones, for comparability tests between foreign and national

APIs, guaranteeing that the input produced in Fiocruz presented the same standards of the original product.

In this context, the strategic role that Anvisa played in this process needs to be highlighted. The Agency clearly exercised its mission of promoting the protection of public health by thoroughly examining all technical documentation related to requests for registration of vaccines against COVID-19, with the agility and promptness that the topic deserved. Thus, in relation to the vaccine produced by Bio-Manguinhos/Fiocruz, we can mention, as a starting point, the publication of RE No. 1,073, of July 7, 2021, which granted the registration of the COVID-19 vaccine, still using the imported API[38].

At the same time that Bio-Manguinhos produced the vaccine using the imported API to meet SUS demand, the research and development team was developing the API production technology on a pilot scale, and later on an industrial scale. Subsequently, in January 2022, Anvisa issued RE No. 35/2022, which granted Bio-Manguinhos/Fiocruz the registration of the COVID-19 vaccine, this time with the incorporation of the API also manufactured by Bio-Manguinhos[39].

Finally, on February 14, 2022, the first batch of COVID-19 vaccines manufactured 100% in Bio-Manguinhos was released by the internal quality control of Bio-Manguinhos. Since this event, Fiocruz has been aligning with the HM the distribution agenda of national COVID-19 vaccine batches, produced by Fiocruz.

CONCLUSIONS

The health urgency experienced in the course of the COVID-19 pandemic, caused by SARS-CoV-2, imposed on the world the need to develop new models and dynamics for technological development, network activities, relationship with Regulatory Agencies, in addition to legal models capable of enabling partnerships for the development and transfer of technology.

In Brazil it was no different. The country with more than 210 million inhabitants has seen the rapid evolution of COVID-19 cases in its territory, causing hundreds of thousands of deaths. Fiocruz, as an institution directly linked to the HM, and assuming its century-old role in the struggle for Brazilian public health and, also, taking advantage of the scientific-technological training already in place, has been mobilized since 2020 to provide the SUS with inputs and technologies to face the COVID-19 pandemic.

In this context, the technology to produce a vaccine against COVID-19 that is safe and effective, and capable of being produced in Bio-Manguinhos/Fiocruz, was quickly identified. At the same time, the legal instrument capable of guaranteeing legal certainty for Fiocruz and the partner holding the technology to produce the vaccine against COVID-19, AstraZeneca, was evaluated.

The legal instrument chosen for the TT for the COVID-19 vaccine was the ETEC, successfully used for the first time in Fiocruz. ETEC allowed Bio-Manguinhos/Fiocruz to meet society's expectations to produce and distribute a vaccine 100% manufactured in Brazil, which was incorporated by the PNI in the fight against COVID-19. Additionally, from the absorption of the technology passed on by AstraZeneca, Bio-Manguinhos will be able to develop new vaccines of interest to the HM using the same technology.

In the specific case of the partnership established between Fiocruz and AstraZeneca, ETEC proved to be an instrument capable of meeting the emergency needs, imposed by the pandemic, for the development and production of the COVID-19 vaccine. Evidently due to the sanitary urgency, some steps foreseen in the process had to be carried out in a customized way. Thus, the success of this process showed that the ETEC, respecting all its procedural peculiarities, can be used by the Executive Power in the formalization of future partnerships, aiming at the incorporation of technology of national interest, including in the health area.

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Author's Contributions

Dantas SI, Amaral LFG, Costa JCS - Conception, planning (study design), acquisition, analysis, interpretation of results and writing of the work. All authors approved the final version of the work.

Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.