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Regulations and institutional attributions for the evaluation of modified mosquitoes for the control of arboviruses in Brazil

Normas e atribuições institucionais para avaliação de mosquitos modificados para o controle de arbovírus no Brasil

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ABSTRACT

Introduction: New biotechnologies have grown rapidly with recent techniques for manipulating living beings. When combined with public health policies, these biotechnologies result in wide-scale interventions when creating, producing and disseminating new hybrid beings. A recent field of application of these biotechnologies lies in combating the epidemics of arboviruses caused by the *Aedes aegypti* mosquitoes. **Objective:** To analyze the regulatory trajectories of two new biotechnologies for the control of arboviruses transmitted by *A. aegypti*: the transgenic *A. aegypti* and the *A. aegypti* infected with the bacteria *Wolbachia*. **Method:** A qualitative analysis of publicly accessible documents made available by official organizations, in particular the Brazilian Health Regulatory Agency – ANVISA, the National Technical Commission for Biosafety – CTNBio and the Court of Justice of Distrito Federal, was carried out. in addition, an analysis of the legislation associated with these documents was performed. **Results:** Documents describe the different regulatory trajectories and the attempt to standardize the two biotechnologies in the country and present the gaps and controversies that involve the regulatory processes of these new artifacts. **Conclusions:** The difficulties presented to provide definitive registration for these new technologies have generated processes that last to the present day, highlighting gaps in the norms in terms of framework, definition of institutional competencies and path for the regulatory process. The importance of establishing a regulatory process for these technologies becomes evident by the scale of their implementation, by their accelerated pace of development, by the difficulty of reverting their implementation after release in the environment and by the need to guarantee participation and public debate.

KEYWORDS: Biotechnology; Regulation; *Aedes aegypti*; *Wolbachia*

RESUMO

Introdução: Novas biotecnologias tiveram rápido crescimento com as recentes técnicas de manipulação de seres vivos. Quando aliadas a políticas de saúde pública, essas biotecnologias resultam em intervenções de ampla escala ao criar, produzir e disseminar novos seres híbridos. Um campo recente de aplicação destas biotecnologias reside no combate às epidemias de arboviroses provocadas pelos mosquitos *Aedes aegypti*. **Objetivo:** Analisar as trajetórias de regulação de duas novas biotecnologias para controle de arboviroses transmitidas pelo *A. aegypti*: os *A. aegypti* transgênicos e os *A. aegypti* infectados com a bactéria *Wolbachia*. **Método:** Foi realizada uma análise qualitativa de documentos de acesso público disponibilizados por órgãos oficiais, em especial a Agência Nacional de Vigilância Sanitária (Anvisa), a Comissão Técnica Nacional de Biossegurança (CTNBio) e o Tribunal de Justiça do Distrito Federal, além da legislação associada a esses documentos. **Resultados:** Descrevem as diferentes trajetórias de regulação e a tentativa de normatização das duas biotecnologias no país e apresentam as lacunas e controvérsias

que envolvem os processos regulatórios destes novos artefatos. **Conclusões:** As dificuldades apresentadas para oferecer registros definitivos para estas novas tecnologias geraram processos que se prolongam até os dias atuais, evidenciando lacunas nas normas em termos de enquadramento, de definição de competências institucionais e de rito para o processo regulatório. A importância do estabelecimento de um processo regulatório para estas tecnologias se torna evidente por sua escala de implementação, por seu ritmo acelerado de desenvolvimento, pela dificuldade de reverter sua implementação após soltura em ambiente e pela necessidade de garantir a participação e o debate público.

PALAVRAS-CHAVE: Biotecnologia; Regulamentação; *Aedes aegypti*; *Wolbachia*

INTRODUCTION

Currently, daily life is permeated by products of biotechnosciences. The neologism biotechnoscience refers to the scientific paradigm defined by the production of interventions that modify the processes of life. The products of biotechnosciences are biotechnologies[2]. With the development of techniques for manipulating living beings, especially since the 1970s, new biotechnologies and fields of knowledge have grown rapidly, such as genetic engineering, molecular biology, and nanotechnology. Biotechnologies could then be defined as technologies based on multidisciplinary knowledge, which use biological agents to make useful products or solve problems[3].

The term biotechnoscience, when applied to the field of health, refers to the "set of theoretical, technical, industrial, and institutional tools that aim to understand and transform living beings and processes, according to health needs and/or desires aiming at a general well-being of individuals and human populations"[1]. The use of biotechnologies in the field of health includes "any technological exploitation of biodiversity to solve human health problems"[4]. These definitions are broad enough to cover different fields and forms of action, not being strictly limited to techniques for modifying genetic material, but including other actions, such as biological or microbiological control. "Biological control can be defined as the release into the environment of a biological agent to control a given pest through mechanisms such as predation, parasitism, herbivory, or disease"[5].

In Brazil, when these artifacts are allied to public health policies, their presence becomes even wider in bodies and in the environment. The health area implements large-scale interventions and a recent field of application of biotechnological artifacts in Brazil is the control, in urban areas, of arboviruses that are transmitted by the *Aedes aegypti* mosquito.

Currently, Brazil lives with the circulation of three arboviruses of proven urban transmission (dengue, chikungunya, and Zika). The prevention actions are aimed at controlling its main vector, the *A. aegypti* mosquito, with the control of breeders and the use of larvicides and insecticides. Recent research on new technologies based on biotechnosciences has shown promise according to the World Health Organization[6], such as the transgenic *A. aegypti* mosquitoes from the company Oxitec and the *A. aegypti* mosquitoes infected with the bacterium *Wolbachia from Monash University, Australia. Both technologies are being implemented in Brazil and are transforming the strategies used to combat arboviruses.*

> As there is no available vaccine, insecticides are the key weapon used to kill *A. aegypti* and control dengue. That is changing though. A new paradigm that I term 'Rear and release' is being developed and tested for the control of dengue. And as the name implies, instead of spraying to kill mosquitoes and prevent dengue transmission, we will rear and release mosquitoes. [7].

Studying or creating these products in the laboratory is very different from understanding their functioning in the bodies of living beings or in the environment, as a lot can happen, and the risk assessment is uncertain[8]. Thus, the use of these technologies is accompanied by negotiation processes, being a mandatory point of passage, the governmental bodies of approval, such as the Brazilian National Health Surveillance Agency (Anvisa), the National Technical Commission on Biosafety (CTNBio), among others. These organizations are responsible for the evaluation of health products and genetically modified organisms, respectively, and, due to their legal attributions, they are involved in the process of regulating the technologies under study.

Transgenic mosquitoes, in Brazil, commonly known as *Aedes do Bem*, are part of a set of techniques called Release of Insects with Dominant Lethality (RIDL) and are the result of developments carried out at the University of Oxford, UK. In Brazil, the company Oxitec do Brasil Tecnologia de Insetos Ltda holds the patent for these mosquitoes and carries out their production in its own factories[10].

Initially, Oxitec produced the OX513A strain, a male strain of genetically modified *A. aegypti* which, when released into the environment, mate with local females, generating offspring of both males and females that die before reaching adulthood. As animals need to stay alive and fertile in the laboratory and, for some time, in the environment, their genetic construction makes it possible for a blocking mechanism to exist for their lethal gene. In the case of OX513A, this mechanism is the antibiotic tetracycline administered as a supplement in the feeding of insects in the laboratory. OX513A mosquitoes die between two and four days after being released into the environment. The OX513A mosquitoes were released in 2010, in the cities of Jacobina (State of Bahia), Piracicaba (State of São Paulo), and Juiz de Fora (State of Minas Gerais).

In 2018, the company Oxitec announced the creation of OX5034 mosquitoes, a second generation of transgenic mosquitoes, with

some differences in their action when compared to the OX513A. Males of OX5034 mosquitoes, when released into the environment, interbreed with local females, generating nonviable females and surviving males; therefore, male selection means an additional factor that would contribute to population suppression. The males that survive can mate with other local females, passing on the self-limiting gene for up to ten generations. Also, half of the males generated by mating with local females carry selected, unmanipulated genes that make them susceptible to insecticides, reducing the presence of resistant mosquitoes in the environment. This second strain had its first release in May 2018, in the city of Indaiatuba, in the State of São Paulo[11]. The company applied for commercial release of the OX5034 strain in May 2020[12]. Both strains and the strategies used have as their main objective the suppression or reduction of the *A. aegypti* population through releases of transgenic male mosquitoes in the environment.

A. aegypti mosquitoes infected with the bacterium *Wolbachia* are currently known in Brazil as Wolbitos and are the result of a project developed by the Monash University whose first funding came from the Global Health Initiative, an international call for proposals coordinated by the Bill & Melinda Gates Foundation and the National Institutes of Health (NIH)[13]. The program started in 2005, in Australia, at that time still with the objective of contributing to the control of *A. aegypti* by shortening the life of mosquitoes with the use of the bacterium *Wolbachia*[14]. Initially, it was called "Eliminate Dengue: Our Challenge" but has recently been renamed the World Mosquito Program (WMP).

The bacterium *Wolbachia* infects several insects in nature, developing inside their cells and establishing symbiotic relationships with different effects. For the creation of *Wolbachia* mosquitoes, the bacteria were transferred from the fruit fly to *A. aegypti* eggs through microinjections, after a few years of adaptation in cell culture[15]. Research on *A. aegypti-Wolbachia* symbiosis demonstrated that the resulting mosquitoes had different characteristics according to the strain of the bacteria used, such as shortening of life, transmission of bacteria to offspring by females, antiviral action, physiological changes, among others. The profile selected for release and testing in the environment has two central characteristics: cytoplasmic incompatibility; antiviral action against dengue viruses and other viruses such as Zika, chikungunya, and yellow fever[16].

The antiviral effect of the *Wolbachia* bacterium had already been studied in its association with other insects, such as the *Drosophila melanogaster*[17] and as of 2009, the literature presented results that confirm this action of certain strains of the bacterium when associated with *A. aegypti* [10]. In this sense, the studies affirm that the symbiosis resulting from *A. aegypti-Wolbachia* has its vectorial capacity compromised, failing to transmit diseases such as dengue, Zika, chikungunya, and yellow fever.

Cytoplasmic incompatibility can be defined as "the development arrest of insect embryos that results when females are mated to males that have a different infection status"[18]. Females infected with the bacterium when mated to males, whether infected or not, transmit the bacterium to their offspring. Males infected with the bacterium, when mating to uninfected females, produce nonviable eggs. After a certain number of releases, all (or nearly all) the local *A. aegypti* mosquito population would be infected with the bacterium *Wolbachia*. These two characteristics of the *A. aegypti-Wolbachia* symbiosis allowed the proposal of a strategy whose central objective is not population suppression or control, but the replacement of local mosquito populations with mosquitoes that are incapable of transmitting diseases.[18].

This study aimed to comparatively analyze, in the period from 2014 to 2020, the regulatory trajectories of these two new biotechnologies to control arboviruses transmitted by *A. aegypti*: the transgenic *A. aegypti* (OX513A) and the *A. aegypti* infected with the bacterium *Wolbachia*, both are currently being tested in Brazil. Therefore, the new biotechnologies proposed to combat arboviruses in Brazil were described, as well as the evaluation framework for these two technologies. In the end, the controversies, disputes regarding institutional competences, and the difficulties of framing these new artifacts in the current norms were debated.

METHOD

A qualitative, descriptive analysis was carried out of publicly accessible documents, made available on the websites of official government bodies involved in the regulatory process of the two technologies in the period from 2013 to 2020. The agencies surveyed were Anvisa and CTNBio. Documents were also collected at the 20th Federal Court of the Judiciary Section of the Federal District, as the regulatory processes at Anvisa were suspended due to a process under judgment in this instance.

At Anvisa, the Regulatory Agendas (RA) for the 2013-2016 and 2017-2020 periods and their monitoring documents were analyzed. The topics "Assessment of macro-organisms for biological control of vectors and pathogens in an urban environment" (RA 2013-2016) and "Regulation of disinfestant sanitizing products" (RA 2017-2020) were analyzed, as well as the processes linked to these topics. At CTNBio, the commission's documents relating to the commercial release of genetically modified *A. aegypti* mosquitoes – OX513A were analyzed, and the other processes of the company Oxitec do Brasil Tecnologia de Insetos Ltda – Oxitec were consulted. In the 20th Federal Court of the Judiciary Section of the Federal District, public documents referring to the lawsuit filed by the company Oxitec against Anvisa were analyzed.

Brazilian legislation and standards associated with the registration of health products and genetically modified organisms (GMO) were also identified.

The set of documents was analyzed in order to enable the description and comparison of the regulatory trajectories of the two technologies, as well as the identification of gaps and controversies related to these trajectories.

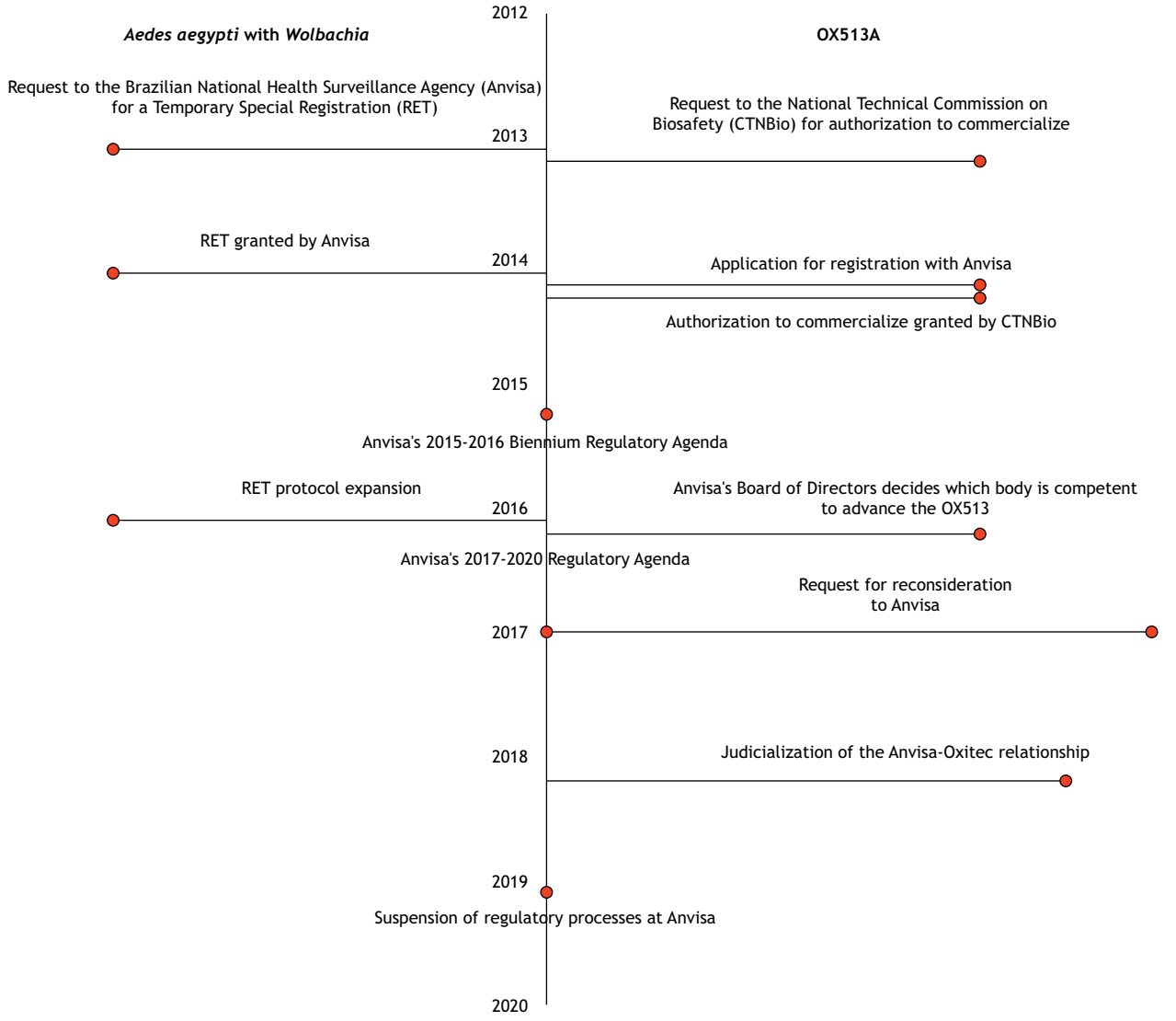
RESULTS

The two biotechnologies being implemented in Brazil, despite sharing the paradigm of "rear and release" mosquitoes for the control of arboviruses, differ in terms of their path in the country's regulatory framework. The transgenic mosquitoes of the company Oxitec are entities that fall within the legal framework that takes care of GMOs, while the mosquitoes infected with *Wolbachia* are new entities, created based on technologies not yet provided for in our legal framework; that is, without framing. Despite the difference, the two biotechnologies fall into regulatory gaps and generate intertwined processes. Both regulation paths can be seen in the Figure.

"Rear and release mosquitoes" at CTNBio

As they fit the definition of GMO according to Law n° 11.105, of March 24, 2005, transgenic mosquitoes from Oxitec had the CTNBio as the first passage point of its regulatory trajectory; on the other hand, mosquitoes infected with *Wolbachia* do not fit this definition and were not submitted to CTNBio evaluation.

In Brazil, GMOs are defined as organisms whose genetic material, deoxyribonucleic acid (DNA)/ribonucleic acid (RNA), has been modified by genetic engineering techniques[19]. CTNBio, created in 1995 and restructured in 2005, linked to the current Ministry of Science, Technology and Communication, concentrates decisions on safety and risks associated with GMOs and their derivatives. It is an advisory and deliberative collegiate body composed of 27 members, of which: 12 are chosen from a triple list drawn up with the participation of scientific societies in the areas of human, animal, plant and environmental health; six are chosen from a triple list drawn up by civil society organizations in the areas of consumer protection, health, environment, biotechnology, family farming and workers' health; and nine are representatives of Ministries. CTNBio is seen as a scientific body, both



Source: Elaborated by the authors, 2021

Figure. Regulation, *Aedes aegypti* with *Wolbachia* and OX513A.

due to the level of training and the professional activity of its members; nevertheless, its operating rules allow the participation of other actors, either through its composition or through the public hearings it holds[20].

CTNBio's role is to:

> [...] provide technical support and advice to the Federal Government in the formulation, updating and implementation of the National Biosafety Policy - PNB, with regard to GMOs and their derivatives, as well as in the establishment of technical safety standards and technical opinions regarding authorization for activities involving research and commercial use of GMOs and their derivatives, based on the assessment of their zoophytosanitary, human health, and environmental risk[19].

Among the services offered by the Commission are authorizations for the planned release into the environment and commercialization of GMOs and their derivatives.

So far, the only planned releases and commercialization of genetically modified animals analyzed by CTNBio were related to transgenic mosquitoes from Oxitec. The first approved commercial release of genetically modified animals refers to OX513A mosquitoes, in 2014[21]. In May 2020, the company Oxitec requested an authorization from CTNBio for the commercial release of the strain OX5034[12], which was obtained in May 2020.

Like the first release of a genetically modified plant, the first commercial release of a genetically modified animal generated (and still generates) strong controversies about biosafety. The main actors involved in this controversy are CTNBio, Oxitec (applicant for the release and owner of the patent), the Brazilian Association of Collective Health (ABRASCO - association that brings together institutions and professionals of collective health in the country) and researchers in the field of genetics who affirmed the ability of transgenic mosquitoes to transfer genes to local mosquito populations[21,22].

The release of Oxitec transgenic mosquitoes also generated controversies regarding its regulatory process. CTNBio's authorization is a necessary condition for a GMO to obtain commercial clearance and be released into the environment. After CTNBio's authorization, it is necessary to send the process to the competent bodies so that they can perform the functions of registration, inspection, and other related actions, as provided by law:

> Art. 16. It will be up to the registration and inspection bodies and entities of the Ministry of Health, the Ministry of Agriculture, Livestock and Supply and the Ministry of the Environment, and the Special Secretariat for Aquaculture and Fisheries of the Presidency of the Republic, among other attributions, in the field of their competences, subject to the technical decision of CTNBio, the deliberations of the CNBS and the mechanisms established in this Law and in its regulation:
>
> [...]
>
> II - to the competent body of the Ministry of Health to issue authorizations and registrations and inspect products and activities with GMOs and their derivatives intended for human and pharmacological use, household cleaning, and related areas, in accordance with the legislation in force and according to the regulation of this Law[19].

In the case of Oxitec transgenic mosquitoes, the OX513A, Anvisa, linked to the Ministry of Health, assumed this competence[24].

"Rear and release mosquitoes" at Anvisa

The beginning of the regulatory processes at Anvisa for *A. aegypti* with *Wolbachia* and OX513A took place in 2013 and 2014, respectively. These processes were reflected in the institution's Regulatory Agenda (RA). A revision of the "Regulatory Agenda Quadrennial Cycle 2013-2016" resulted in the inclusion of a new topic from the document "Biennium 2015-2016", in the Sanitation area, topic 54/Subtopic 54.1: "Control of urban pathogen vectors/Assessment of macroorganisms for the purpose of biological control of vectors and pathogens in an urban environment". The topic emerged as a result of internal dialogue and was justified by a regulatory gap that provides for the regulation of sanitizers with only chemical actives and microorganisms[25]. The development of this theme defined and classified both OX513A mosquitoes and mosquitoes infected with *Wolbachia* as organisms (macroorganisms or biological agents) for the purpose of biological control of vectors and pathogens in an urban environment.

At a meeting of Anvisa's Collegiate Board of Directors, held on September 27, 2016, the process of preparing Anvisa's RA for the period 2017-2020 (RA 2017-2020) and approval of the Guiding Document[26,27]. RA 2017-2020 includes 147 themes organized into 15 macro themes. One of the themes refers to the "Regulation of Sanitizing and Disinfesting Products"[28].

The new biotechnologies were framed as household sanitizers, insecticides. Household sanitizers are defined as "substances or preparations intended for cleaning, disinfection, or disinfestation at home, in collective and/or public environments, in places of common use and in water treatment". Insecticides are those sanitizing products "intended to combat, prevent and control insects in houses, enclosures and places of public use and their surroundings", according to the Medicines Law, Law nº 6.360, of September 23, 1976[29].

Sanitation products are those used for cleaning and conservation of environments and, as they present certain associated risks, they are subject to regulation. Sanitizing products are classified as detergents, disinfectants, desinfestants, rodenticides, insecticides, and repellents. Also, as sanitizing agents, biological products used in septic systems are included[30]. Regulations already exist for chemical-based products and for products involving microorganisms. In Anvisa's view, the gap would be in products with similar functions involving macroorganisms.

While the regulatory theme was being developed, requests for authorization and registration of new technologies continued to be processed at Anvisa. In the case of the *A. aegypti* mosquitoes

infected with bacterium *Wolbachia* its classification was carried out based on Annex III of the Joint Normative Instruction No. 25, of September 14, 2005, which includes in the list of products to be analyzed:

> Biological control agents, microbiological agents, as defined in specific standards, except those obtained through genetic engineering techniques; Biological control agents, natural enemies, such as parasitoids, predators, and nematodes, as defined in specific norms, except those obtained through genetic engineering techniques[31].

The *A. aegypti* with *Wolbachia* were then able to obtain a Special Temporary Registration (RET). The RET is an instrument defined as "a private act of a competent federal body, intended to grant the right to use a pesticide, component or similar for specific purposes in research and experimentation, for a determined period, being able to confer the right to import or produce the quantity necessary for research and experimentation"[32]. By its very definition, it is a temporary registration for the inspection of research activities and experimentation of pesticide products with analysis by the Ministry of Agriculture, Livestock and Supply (MAPA), the Brazilian Institute of Environment and Renewable Natural Resources (Ibama) and Anvisa[33].

The research and experimentation activities in which the RET can be applied are defined in three different phases: preliminary phase, initial phase, and final phase. The preliminary phase, whose registration lasts for a maximum of 3 years, has a maximum area of implantation (1,000 m^2 in land surface or 100 m^2 in water). The initial phase has the same duration time limit, but its deployment area can be expanded (5,000 m^2 on land surface or 1,000 m^2 on water). The preliminary and initial phases must be carried out in accredited stations or with greater possibility of control, such as: laboratories, greenhouses, tanks, or closed ponds. The final phase, on the other hand, does not provide for a definition of validity period or maximum area for experimentation and allows the implementation in third-party areas, public or private[31].

Regarding the mosquitoes infected with the *Wolbachia* bacterium, the RET obtained in 2014 and its updates seemed to constitute the appropriate regulatory path until the theme "Regulation of Sanitizing and Disinfestant Products" (RA 2017-2020) by Anvisa was fully developed.

The requests from Oxitec to Anvisa occurred after the CTNBio authorization to commercialize OX513A mosquitoes, in April 2014. The company Oxitec asked Anvisa about the appropriate regulatory path for OX513A mosquitoes. Such questioning by Oxitec initiated the Administrative Proceeding nº 25351.444810/2014-42[24]. As transgenic mosquitoes are a new biotechnology and the paths for their registration and inspection remain uncertain, the questioning of Oxitec gave rise to internal discussions at Anvisa regarding competence and how to classify these mosquitoes. Even before the approval of OX513A mosquitoes by CTNBio, Anvisa was already discussing the need to regulate these mosquitoes[24].

After two years of internal discussion and contacts with Oxitec, in 2016, the Board of Directors decided that OX513A mosquitoes should be regulated by Anvisa with regard to risks to human health and effectiveness. The need to develop the topic on the regulatory agenda and to develop an adequate rule for the OX513A mosquitoes to have their situation regularized through an instrument similar to the RET were confirmed. OX513A mosquitoes cannot obtain a RET under current legislation because Annex III of the Joint Normative Instruction No. 25/2005 excludes biological agents obtained through genetic engineering techniques of this type of registration[31].

In 2017, almost a year after the decision of Anvisa's Collegiate Board, Oxitec continued without obtaining an instrument analogous to the RET and without specific regulations to the evaluation of macroorganisms for biological control of vectors and pathogens in an urban environment. Faced with this scenario, Oxitec requested reconsideration from Anvisa on its competence in regulating the commercialization of OX513A mosquitoes, which was denied[24]. Oxitec, then, filed the lawsuit on January 12, 2018, and the action 1000746-35.2018.1.01.3400 initiated in the Federal Court of the Federal District. On March 20, 2018, the court granted an injunction to Oxitec determining the suspension of the registration processes and authorizing the commercialization of OX513A mosquitoes at Anvisa. The process rendered a decision, on May 7, 2019, determining that the assessment of OX513A is the responsibility of CTNBio and that Anvisa "should have observed the technical decision of CTNBio and promoted the registration of the product". The process is currently under appeal[34,35].

Administrative Proceeding 25351.136014/2015-13, initiated in March 2015, brought the proposal for the standardization of the evaluation of macroorganisms for the purpose of biological control of vectors and pathogens in an urban environment, with the General Management of Sanitizing Products as responsible. The process sought to establish regulation for these alternative vector control methods. The problem is defined by Anvisa as:

> There is ongoing research involving the use of biological agents for vector control, e.g., the use of populations of *Aedes aegypti* infected with bacteria (*Wolbachia*), the use of male sterile technology for the control of *Aedes aegypti*. Currently, there are no regulations for the evaluation and regularization of such techniques, which deprives society of access to less toxic methods than the chemical disinfestants currently in use[36].

The attempt to standardize these products, within the scope of Anvisa, brought together both mosquitoes infected with *Wolbachia* and transgenic mosquitoes in a single process. When the justice system suspends the regulation of OX513A mosquitoes, it also suspends the regulation of mosquitoes infected with *Wolbachia* and any other biotechnology that involves macroorganisms for the control of vectors and pathogens that arise, at least within the scope of Anvisa.

DISCUSSION

Both biotechnologies discussed in the present work are being implemented on an ever-increasing scale. In the case of Oxitec, its transgenic mosquitoes were released in the cities of Juazeiro (two neighborhoods) and Jacobina (one neighborhood), two cities in the State of Bahia; in the city of Piracicaba, in the State of São Paulo (12 districts); and in the city of Juiz de Fora (three districts), in the State of Minas Gerais. Also, OX5034 mosquitoes were released for study purposes in the city of Indaiatuba, in the State of São Paulo, in 2018-2019[37]. In the case of mosquitoes infected with the *Wolbachia* bacterium, they were released in the State of Rio de Janeiro, in the cities of Rio de Janeiro (30 districts) and Niterói (34 districts). With support from the Ministry of Health, the WMP began its expansion to the cities of Campo Grande/State of Mato Grosso do Sul, Petrolina/State of Pernambuco, and Belo Horizonte/State of Minas Gerais, with releases already in 2020[38]. The Brazilian Unified Health System finances the implementation of these biotechnologies, ensuring the scale of their use. A first reason to look for a way to register these biotechnologies, either as a product or as a service, is their establishment on an increasing scale in cooperation with local governments or the national government.

One of the characteristics of these biotechnologies is their fast pace of development. Oxitec announced that, as of 2018, it would replace the use of OX513A mosquitoes with OX5034 mosquitoes, which have had a planned release allowed since 2016 by CTNBio[39], with field tests started in 2018 and with the commercial release approved in 2020[12]. With respect to mosquitoes infected with *Wolbachia*, different strains of the bacteria produce different effects on mosquitoes. WMP researchers seek new associations of *A. aegypti* with other strains or even with combinations of *Wolbachia* strains to propose future releases. Other research involving pathogen vectors applicable in agriculture or health is under development. In CTNBio's 21-year history, since the first commercial release of a GMO, there have been more than 150 releases. Over time, approvals for commercial release increased, with 64% of these approvals taking place in the last 5 years[40]. New mosquitoes, and perhaps other modified animals, will come and Brazil needs to have normative paths that make it possible to assess risks and allow or not their use.

These technologies present difficulties related to control or suppression of the environment of new mosquitoes after their release. Although Oxitec guarantees that its OX513A mosquitoes would only live for two to four days, there are doubts raised by ABRASCO concerning this period[23] and studies have already identified parts of the genome of these mosquitoes in local populations of *A. aegypti* [22]. Its new creation, the OX5034, doesn't have this lifetime limitation in the environment[11,37]. Mosquitoes infected with *Wolbachia* use the technology's irreversibility feature as an advantage in controlling arbovirus transmission, that is, after the introduction of a certain number of mosquitoes infected with *Wolbachia* in a certain location, all or almost the entire population of local mosquitoes will be infected. Therefore, the newly released mosquitoes will live for long periods (or forever) with the communities in which the technologies are implemented[15].

The question of who is involved in making decisions about the use of these biotechnologies is relevant. These are decisions about what level of risk our society will assume and with what principles and values these judgments will be guided[41]. In the case of transgenic mosquitoes, CTNBio, the technical and regulatory body, has some level of social participation, either through its composition or through the public hearings it holds. In the case of mosquitoes infected with *Wolbachia*, official assessments have so far been restricted to the bodies responsible for issuing the RET, which have a regulatory and technical function, but do not include broader participation by society in this specific process. Public debate must be guaranteed by the legal framework for regulating these technologies.

Making a parallel with GMOs, the first transgenic seeds began to enter Brazil, in the 1990s, through Argentina and were planted without the need for approval, as the Biosafety Law dates from 1995. The first GMO release by CTNBio, in 1998, was Monsanto's Roundup Ready soybean, which generated a series of controversies that culminated in a lawsuit brought by sectors of organized civil society. Monsanto lost the suit, however, without strong enforcement, GM seeds continued to be planted. The context was very favorable to the results promised by transgenic seeds: lower production costs for farmers and greater insertion of Brazilian agriculture in the international scenario. This scenario contributed to a "permissive illegal diffusion of genetically modified seeds"[42].

In Brazil, in the case of modified mosquitoes, either by RNA/DNA manipulation or bacterial infection, not even a normative framework exists. Its implementation, like the introduction of transgenic seeds, has strong allies at this historic moment. For over 100 years, *A. aegypti* has been considered an enemy of humanity and there is still no control over the epidemics of which the mosquito is a vector. In addition to dengue, yellow fever, and chikungunya, the recent Zika epidemic opened up space for encouraging and funding these new biotechnologies. The material concreteness of the diseases, which are experienced, and the relative invisibility of risks, which can only be recognized by scientific knowledge, contribute to a greater acceptance of these technologies[43]. However, these are new products, the first of many to come, to be used on a large scale and often irreversibly without a defined or adequate regulatory path.

CONCLUSIONS

Despite the fact that, since 2014, mosquitoes infected by *Wolbachia* rely on RET from Anvisa and OX513A mosquitoes, from Oxitec, obtained CTNBio authorization for commercialization, the difficulties presented in offering definitive registry for these new technologies generated processes that continue to the present day, evidencing gaps in the norms in terms of framing, definition of institutional competences, and rite for the regulatory process.

The importance of establishing a regulatory process for these technologies is evident due to their scale of implementation, their accelerated pace of development, the difficulty of reversing their implementation after release into the environment, and the need to ensure participation and public debate.

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Author's Contributions

Turco CS - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. Paiva EN - Conception, planning (study design), and writing of the work. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.