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Pharmacovigilance capacity strengthening for WHO prequalification: The case of the trivalent influenza vaccine manufactured by Instituto Butantan

Marcelo E. Koike [a,*], Vera L. Gattás [a], Maria Beatriz B. Lucchesi [a], Mayra M. Moura de Oliveira [a], Tazio Vanni [a], Beatriz da C. Thomé [a], Olga Menang [b], Muriel Socquet [b], Alexander R. Precioso [a,c]

[a] Division of Clinical Trials and Pharmacovigilance, Instituto Butantan, São Paulo, Brazil
[b] Center for Vaccine Innovation and Access, PATH, Geneva, Switzerland
[c] Pediatrics Department of the School of Medicine of University of São Paulo, São Paulo, Brazil

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ABSTRACT

Instituto Butantan is a biomedical research center and vaccine manufacturer affiliated with the São Paulo State Secretary of Health in Brazil. In 2013, Instituto Butantan successfully licensed its trivalent influenza vaccine, in order to support the Brazilian National Immunization Program's influenza vaccination strategy, which was introduced in 1999. In order to respond to the increasing influenza vaccine demand worldwide, Instituto Butantan is undergoing prequalification of its trivalent influenza vaccine by the World Health Organization (WHO). A key requirement of the prequalification review was the submission of a pharmacovigilance plan, including an active surveillance evaluation, for the trivalent influenza vaccine, and proof of a functional pharmacovigilance system at Instituto Butantan. The aim of this paper is to describe the capacity strengthening process of the pharmacovigilance system at Instituto Butantan for the WHO prequalification of the trivalent influenza vaccine. This process was supported by PATH and the U.S. Federal Government Biomedical Advanced Research and Development Authority (BARDA). The key strategic axes for this capacity strengthening process included the improvement of organizational structure, human resources training, internal processes and procedures, appropriate documentation, and acquisition of an E2B compliant pharmacovigilance database. The project led to the establishment of a functional pharmacovigilance system compliant with international regulatory requirements.
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1. Introduction

Instituto Butantan is a biomedical research center and vaccine manufacturer affiliated with the São Paulo State Secretary of Health in Brazil. Currently, the institute is one of the major public producers of immunobiologicals in Latin America. Partnerships with public and private institutions for the manufacture of vaccines has successfully been one of Instituto Butantan's core endeavors to promote innovation and address public health demands regarding immunization in a timely manner.

An example of a successful initiative between Instituto Butantan and a private vaccine manufacturer was the technology transfer program for the trivalent influenza vaccine (inactivated split virion) established with Sanofi Pasteur (previously Pasteur-Mérieux) in 1999. The objectives were to produce 25 million doses of the trivalent influenza vaccine per year and to create a stockpile of H5N1 vaccine for use at the onset of a potential influenza pandemic [1]. The production capacity established in the technology transfer was based on the demand to promote immunization of the elderly population of Brazil at that time. By 2013, a trivalent influenza vaccine fully manufactured by Instituto Butantan was delivered to the National Immunization Program of Brazilian Ministry of Health (NIP). Instituto Butantan has since increased its influenza vaccine production capacity due to inclusion of new vaccination target groups defined by the NIP [2]. By 2017, Butantan delivered more than 45 million doses of trivalent influenza vaccine annually to the NIP.

To promptly and effectively respond to threats associated with potential pandemic influenza viruses, a concern that emerged from the advent of the pandemic caused by H1N1 influenza virus in 2009 [3], the World Health Organization (WHO) identified the need for vaccine producers to invest in innovative solutions

* Corresponding author at: Instituto Butantan, Division of Clinical Trials and Pharmacovigilance, Avenida Vital Brasil 1500, São Paulo 05503-900, Brazil.
E-mail address: marcelo.koike@butantan.gov.br (M.E. Koike).

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capable of increasing their production capacity and to prequalify their vaccines [4].

In 2015, Instituto Butantan began an initiative to prequalify its trivalent influenza vaccine. Toward this end, it established partnerships with PATH and the United States Assistant Secretary for Preparedness and Response (ASPR) Biomedical Advanced Research and Development Authority (BARDA) to provide technical assistance in order to meet the WHO standard recommendations on vaccine quality, safety and efficacy.

This paper aims to describe the process of enhancing the capacity of Instituto Butantan's pharmacovigilance system for the prequalification of its trivalent influenza vaccine. The key strategic axes for this capacity strengthening process included the improvement of organizational structure, human resources training, internal processes and procedures, appropriate documentation, and the selection and acquisition of an E2B compliant pharmacovigilance database.

2. Safety monitoring of the Instituto Butantan's trivalent influenza vaccine: Initial activities

With the publication of Directive Resolution RDC No. 4 of February 10th, 2009 by the Brazilian Health Regulatory Agency (ANVISA) [5], post-licensure safety monitoring became mandatory for all Marketing Authorisation Holders (MAH) of medicines for human use in Brazil. To comply with this regulation, Instituto Butantan implemented pharmacovigilance activities of its products through the creation of a Pharmacovigilance Department as part of the Division of Clinical Trials and Pharmacovigilance.

Since 2013, the department has been conducting passive safety surveillance of Instituto Butantan's trivalent influenza vaccine. Activities related to this surveillance are described in multiple Standard Operating Procedures (SOPs) developed by the Pharmacovigilance Department as part of local Pharmacovigilance Practices and Good Manufacturing Practices. It is relevant to state that local regulation does not describe the pharmacovigilance processes as thoroughly as the prequalification program requirements, whilst, e.g., European regulation has a number of very specific guidelines that support the marketing authorisation holders. Moreover, local regulation predates the most recent updates in the international pharmacovigilance system, and important aspects such as Post-Authorisation Safety Studies and E2B requirements, are uncovered by local regulation. Therefore, although the pharmacovigilance activities satisfactorily met local regulation, improvements were required to comply with the WHO prequalification program for vaccines.

3. Prequalification by WHO supported by PATH and BARDA

In 2016, Instituto Butantan initiated prequalification of its trivalent influenza vaccine by submitting the Product Summary File (PSF) [6] to WHO. From a pharmacovigilance perspective, WHO evaluation of the clinical experience of Instituto Butantan's influenza vaccine triggered the request to improve post-authorisation safety surveillance of the trivalent influenza vaccine as well as conducting active surveillance of the vaccine. WHO also requested a more robust and functional pharmacovigilance system at Instituto Butantan. The Institute was able to address WHO's requests with the support of a BARDA-funded project to address Chemistry, Manufacturing and Control (CMC) and Clinical Trial Technical Support, and technical assistance provided by PATH to improve the Institute's pharmacovigilance capacity by implementing active pharmacovigilance activities and establishing a robust pharmacovigilance database. Technical assistance with regards to pharmacovigilance followed a two-pronged approach: activities related to the safety surveillance of the trivalent influenza vaccine and activities related to the improvement of the pharmacovigilance system.

3.1. Risk management plan and active surveillance of the trivalent influenza vaccine

Implementation of an active surveillance for the Instituto Butantan's trivalent influenza vaccine was a mandatory requirement from WHO for prequalification. With guidance from PATH, Instituto Butantan developed a risk management plan (RMP) document for the trivalent influenza vaccine, using the EU-RMP template [7] to comply with the prequalification program requirements. A post-authorisation safety study (PASS) was included as additional pharmacovigilance activity. It is worth mentioning that the Pharmacovigilance Department already had processes and procedures compliant with local regulation to manage risks.

The PASS protocol was developed according to the Guideline on Good Pharmacovigilance Practices (GVP): Module VIII – Post-authorisation safety studies [8]. WHO provided recommendations on the draft protocol and a final protocol was submitted to WHO and the Pharmacovigilance Division of ANVISA prior to study implementation.

The PASS was an observational, prospective cohort study aimed at identifying and evaluating Adverse Events Following Immunization (AEFI) in five high-risk groups: (1) children aged 6 months to under 5 years, (2) pregnant women, (3) postpartum women, (4) health care professionals, and (5) elderly, who received Instituto Butantan trivalent influenza vaccine during the 2017 and 2018 national immunization campaigns (ClinicalTrials.gov registry numbers: NCT03057483 and NCT03392207). A total of 942 participants were recruited and followed for 42 days post vaccination. The study confirmed that the vaccine was safe and well tolerated among all five study cohorts, as discussed in a separate manuscript in preparation by the Division of Clinical Trials and Pharmacovigilance.

3.2. Strengthening the pharmacovigilance system at Instituto Butantan

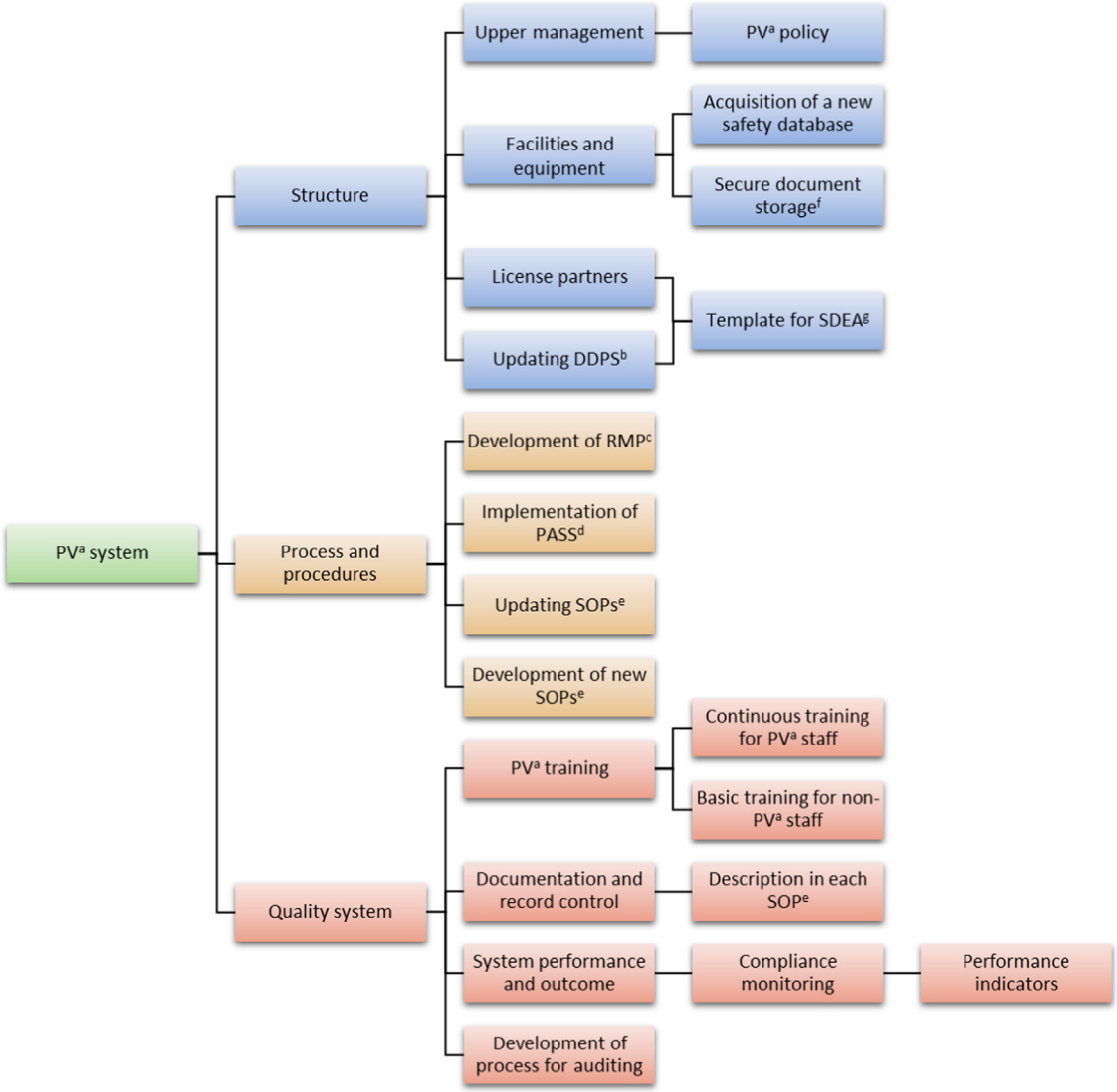
In the fourth quarter of 2016, PATH initiated an assessment based on the pharmacovigilance guidelines of European Medicines Agency (EMA) to identify gaps in the pharmacovigilance system at Instituto Butantan. The assessment was questionnaire-driven and covered the main aspects of a pharmacovigilance quality system, including organizational structure, qualified person responsible for pharmacovigilance, human resource and training, computerized systems and databases, pharmacovigilance processes, compliance management, audit, documentation, and additional record keeping [9].

From this gap analysis, Instituto Butantan and PATH developed an improvement and corrective action plan. Main areas of improvement consisted of redefining the organizational structure; training of pharmacovigilance staff; streamlining internal processes, procedures and appropriate documentation; and implementing an E2B validated global safety electronic database.

PATH provided technical support through a combination of onsite visits and remote assistance with the purpose of consolidating a fully functional pharmacovigilance system in accordance with local and international standards for pharmacovigilance (Fig. 1).

4. Organizational structure and pharmacovigilance policy

The creation of the Pharmacovigilance Department in 2010 marked the start of the passive pharmacovigilance activities at Instituto Butantan. The pharmacovigilance system was



[a] PV: Pharmacovigilance.

[b] DDPS: Detailed Description of the Pharmacovigilance System.

[c] RMP: Risk Management Plan.

[d] PASS: Post-Authorization Safety Study.

[e] SOP: Standard Operating Procedure. Updated and developed procedures are described in Table 1.

[f] Storage of documents with controlled access and water/fire proof.

[g] SDEA: Safety Data Exchange Agreement.

Fig. 1. Critical findings in the gaps assessment of the pharmacovigilance system of Instituto Butantan and corrective actions.

already described in the Detailed Description of the Pharmacovigilance System (DDPS), according to regulation of ANVISA [5].

Changes made to the organizational structure included:

- An institutional policy on pharmacovigilance that met stringent international standards was established and disseminated to the upper management and all employees of Instituto Butantan. This policy describes the objectives of the pharmacovigilance system, roles and responsibilities of the pharmacovigilance system within the organization, the quality system for pharmacovigilance and company-wide training on pharmacovigilance awareness [9].
- An internal process for exchange of safety data with partners was established in collaboration with the Legal Department and a template for Safety Data Exchange Agreements (SDEA) was validated.
- The DDPS was updated to reflect the current state to the pharmacovigilance system after the strengthening process.

5. Training on pharmacovigilance

According to GVP module I [9], all personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training as related to the roles and responsibilities of the personnel.

The Pharmacovigilance Department had implemented a training plan for the pharmacovigilance personnel that included local regulation on pharmacovigilance, internal processes and procedures. However, there was no strategy for continuous education in pharmacovigilance nor for pharmacovigilance training of non-pharmacovigilance personnel. According to GVP module II [10], besides the pharmacovigilance department staff all other Institute staff should be trained as they may also receive safety reports.

As a corrective action, an SOP on pharmacovigilance training was developed to describe initial and continuous education of the pharmacovigilance personnel. This SOP also described a company-wide basic pharmacovigilance awareness training with support from Human Resources Department on its coordination and implementation.

6. Internal processes and procedures

A pharmacovigilance system is characterized by all appropriate processes and procedures required to produce outcomes that are relevant to the objectives of pharmacovigilance. It shall cover all aspects of product safety and shall be aligned with the quality system of the institution to ensure its proper accomplishment [9].

Prior to the evaluation, Instituto Butantan had existing SOPs that described several critical pharmacovigilance processes such as management of adverse events and periodic update safety reports. However, some of these SOPs did not explicitly describe the procedures and there were no processes in place for critical pharmacovigilance activities such as signal management and safety communication. Therefore, procedures consistent with local and international norms and standards required updating or development (Table 1). The main improvements are discussed below.

6.1. Collection and management of safety data

The main sources of spontaneous safety data for the Pharmacovigilance Department are the NIP and the Customer Service Department of Instituto Butantan. Other data sources include scientific medical literature and the lay media.

At the time of evaluation, the process of data collection and management was described in a main SOP, and specific points inherent to the clinical trials and scientific medical literature were documented in complementary specific SOPs. However, some procedures were not adequately performed or described. For example, follow-up procedures, especially related to exposure during pregnancy were not optimal, as was the process of duplicate check.

Table 1
Procedures updated or developed by Instituto Butantan in order to comply with EMA† standards.

Updated procedures	Developed procedures
• Collection and management of safety data • Collection of safety data from scientific medical literature • Operation of the electronic safety database • Preparation of periodic safety reports to regulatory authorities • Procedure for updates to the labelling • Submission of serious adverse events from clinical trials to the regulatory authority	• Audits and inspections of the pharmacovigilance system • Collection of safety data from lay media • Company-wide pharmacovigilance policy • Safety concerns management and communication • Detection and management of safety signals • Preparation of risk management plans according local regulation • Training on pharmacovigilance

†EMA: European Medicines Agency.

As corrective actions, the SOP on case management was updated to include new procedures and to amend existing processes to reflect current practices, with related flowcharts for better visualization.

With regard to monitoring of the scientific literature, screening was restricted to a single online database of scientific literature, and there was no systematic screening of lay media sources. In collaboration with the Library of Instituto Butantan, a more robust search string was created and screening was extended to additional major global databases (Medline, Scopus, Web of Science, SciELO and LILACS). In collaboration with the Communications Department, a process for screening lay media was also established and documented.

6.2. Causality assessment

Assessment of causality is a regulatory requirement and it is critical to the benefit-risk assessment [5,11]. At the time of evaluation, the Pharmacovigilance Department performed causality assessment according to WHO-UMC System for Standardised Case Causality Assessment [12], but the process was not described in any SOP. As corrective action, the process was described in the SOP for data collection and management.

After the submission of the PSF [6], WHO recommended the use of the WHO manual on Causality Assessment of an Adverse Event Following Immunization, which is more specific for causality assessment of vaccine-related safety events [13]. However, this algorithm is not applicable to other biologics (e.g., heterologous sera) manufactured by Instituto Butantan. Moreover, implementing this algorithm conflicted with the WHO-UMC System for Standardized Case Causality Assessment used during clinical trials safety assessment as required by the local regulation.

To avoid using two different methods of causality assessment, an algorithm was developed that combined these guidelines. This algorithm is currently being tested and validated in collaboration with the Clinical Trials personnel of Instituto Butantan.

6.3. Safety signal management

Signal management to identify new risks associated with a medicinal product or whether known risks have changed, and management of new risks are critical points in pharmacovigilance [14], and it is critical to the benefit-risk assessment. Previously, signal management was not systematically performed at Instituto Butantan. A procedure for signal detection, including both a qualitative and quantitative approach, was established and steps for signal management (i.e., signal validation, evaluation, and risk assessment) were defined and documented in a SOP.

6.4. Safety communication

Safety communication is a critical pharmacovigilance process which enables timely provision of evidence-based information on the safe and effective use of medicines to patients, healthcare professionals, and Health Authorities. This is essential to assess, communicate and minimize previously known or unknown risks of medicines which have or could have an impact on the benefit-risk, assuring protection of the patients [15].

Previously, Instituto Butantan was capable of performing safety communication, but did not have a systematic procedure described. As a corrective action in the second quarter of 2019, the process was systematically described in a SOP. This SOP covers the identification and management of safety concerns, internal communication within the institution including the upper management, and communication to the Health Authorities.

6.5. Audits and inspections of the pharmacovigilance system

According to GVP module I [9], audits and inspections of the pharmacovigilance system must be part of the quality system's audit strategy. Previously, the Instituto Butantan Quality Assurance Department had a process for audits and inspections of the pharmacovigilance system, but there was no specific SOP explicitly describing it. As corrective action, the process for auditing the pharmacovigilance system was described in a new SOP compliant with regulation of ANVISA [5] and GVP module IV [16].

7. Implementation of a new global pharmacovigilance electronic database

An important aspect of a functional and reliable pharmacovigilance system is the existence of a consistent global pharmacovigilance database that enables proper storage, handling, analysis and submission of safety data to regulatory authorities.

The electronic database that was used for by Pharmacovigilance Department did not have all the properties of an EMA and E2B compliant pharmacovigilance database. Therefore, courtesy of the project, Instituto Butantan acquired a new electronic database. The acquisition process started in the second quarter of 2018, and was fully implemented early in the second quarter of 2019.

8. Final remarks

The pharmacovigilance strengthening project described in this report has resulted in the establishment of a functional pharmacovigilance system that is in compliance with international regulatory requirements. The WHO prequalification process for the trivalent influenza vaccine mandated the establishment of active post-authorisation safety surveillance for the trivalent influenza vaccine and triggered the strengthening of the Institute's pharmacovigilance system. An independent pharmacovigilance system audit carried out at the end of the project concluded the improvements were satisfactory. These improvements will successfully support the prequalification of the trivalent influenza vaccine by the WHO, and support pharmacovigilance activities relevant to all other products of the Institute to ensure that important safety-relevant information is properly identified and Health Authorities are notified in a timely manner.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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