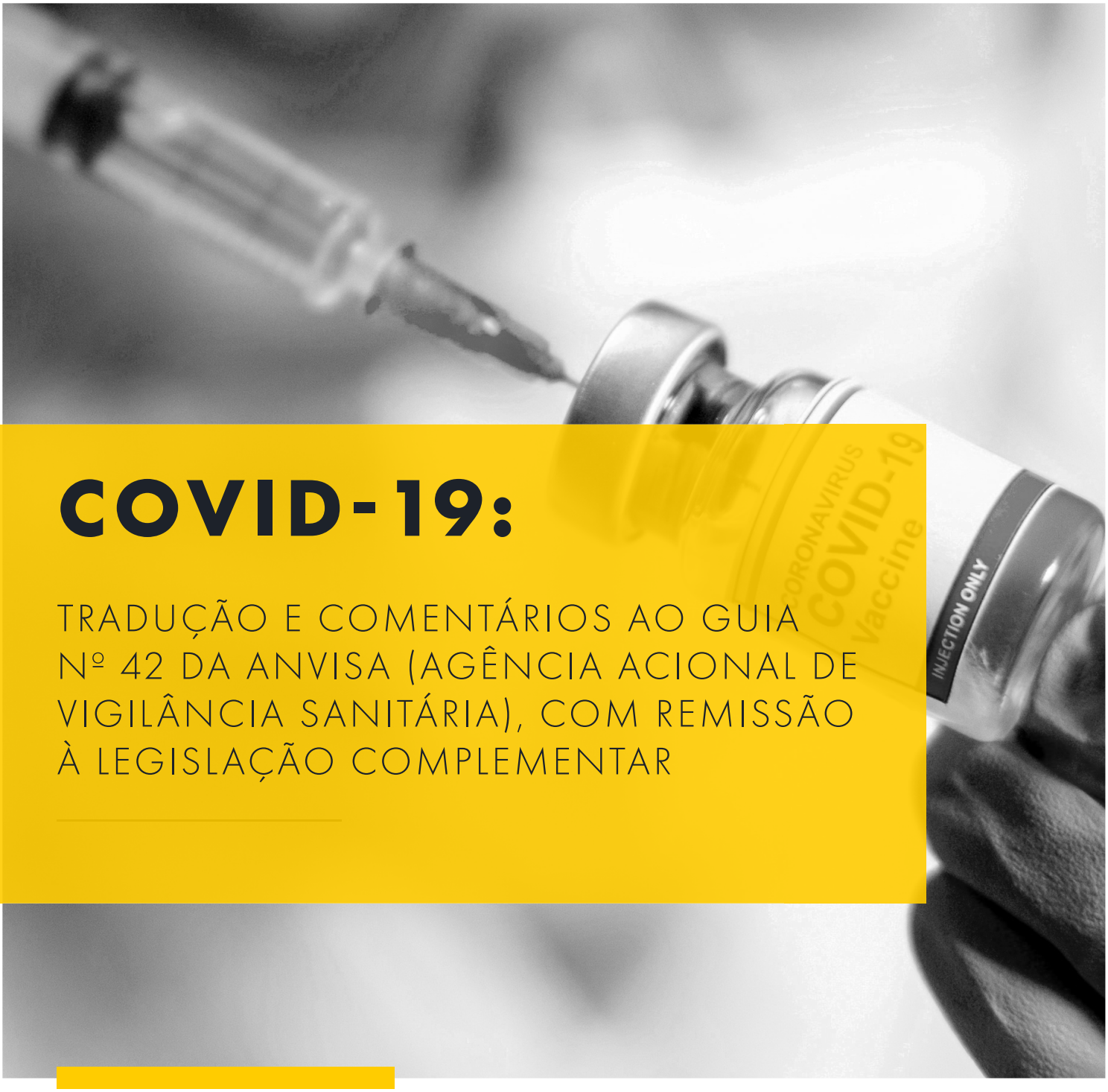

COVID-19:

TRADUÇÃO E COMENTÁRIOS AO GUIA Nº 42 DA ANVISA (AGÊNCIA ACIONAL DE VIGILÂNCIA SANITÁRIA), COM REMISSÃO À LEGISLAÇÃO COMPLEMENTAR

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PANSIERI
ADVOGADOS

01. DISCLAIMER

This handbook expresses Anvisa's opinion and understanding of the best practices in procedures, routines, and methods considered to be adequate on complying with technical and administrative requirements established by the legislative and regulatory framework of the Agency.
This is a regulatory instrument of a non-normative nature, being recommendatory and nonbinding, remaining possible the use of alternative approaches other them those here recommended, if compatible with the prerequisites applicable to the case in practice. This document contains a series of comments made by the lawyers on our regulatory team, referencing also the sparse legislation and regulations regarding Anvisa's procedures.

02. INTRODUCTION

Considering the dispositions of Brazilian Law n. 6.360/1976, and Decree n. 8.077/2013, on the system of health regulation (to which medical products are subjected); Considering that the institutional goal of ANVISA is to promote the protection of the health of the population, according to its legal attributions defined in article 6º, III, VII and IX, and article 7º of Law n. 9.782/1999; Considering that on January 31 of 2020, following the recommendation of the Emergency Committee, the WHO declared a Public Health Emergency of International Concern (PHEIC), as a result of the suspect cases of human infection by the new Coronavirus (SARS-CoV-2); Considering the necessity of constant improvement on the activities of sanitary and health control, as a

consequence of the international epidemiological context, as well as the goal to speed up the availability of products that might help on the prevention, treatment, and relief of the individual and collective effects of the Covid-19 pandemic, ANVISA publishes this Handbook on the minimum requirements to apply for temporary emergency use authorization of covid-19 vaccines in an experimental nature.

ANVISA, as a regulatory agency of the Brazilian Federation, maintains the commitment to act for the benefit of the interest of public health. As such, ANVISA is committed to establishing regulatory guidelines to support the efforts against the pandemic caused by the new Coronavirus. In this context, ANVISA publishes the present handbook to guide the companies, which are developing vaccines, about the minimum requirements to apply for the temporary emergency use authorization for COVID-19 vaccines.

This handbook presents recommendations on the data and information essential to support the decision of ANVISA on the matter of the approval of the temporary emergency use authorization for vaccines in an experimental nature, aimed to prevent COVID-19 during the period of the public health emergency.

The pandemic of the new Coronavirus presents extraordinary challenges to public health and regulatory agencies all around the world. Until this moment there are no vaccines authorized by ANVISA1 to prevent COVID-19. There are four vaccines authorized by ANVISA to conduct clinical trials (phase 3) in Brazil, all of which were developed on different technological platforms, including adenoviral vector, inactivated virus, and RNA messenger.

In this context, this handbook is to be used only during the period of public health emergency related to COVID-19, declared by the Ministry of Health of Brazil on January 31 of 2020.

This handbook was implemented immediately after its publication but remains subject to commentary and revision in accord with the best regulatory practices of ANVISA. Thus, this guide describes minimum contemporary recommendations of ANVISA concerning the data and information essential to support the approval of the temporary emergency use authorization for vaccines of experimental nature, aimed to prevent COVID-19 during the period of the public health emergency.

Thus, for the application process, the Interested Party must present the data of the nonclinical and clinical trials of quality, good manufacturing practices, monitoring plans and control plans (risk management), and other administrative and regulatory information required.

The assessment by ANVISA on the matter of temporary emergency use authorization will be conducted in a case-by-case approach, and decided by the Board of Directors. ANVISA's decision shall consider the data presented on people demographically aimed, characteristics of the product, and results of the non-clinical and clinical trials. The decision shall consider any other scientific evidence that would be relevant on the product, which is the preliminary results of one or more clinical trials that meet the standards for efficacy and safety of use, leading to the conclusion that the benefits of the vaccine clearly and convincingly outweigh the risks. Besides that, to substantiate ANVISA's decision, the Interested Party must guarantee that the data on the manufacturing and stability of the vaccine is adequate to assure the consistency of its quality, according to the present technical requirements. Despite that, ANVISA might demand the fulfillment of additional requirements, considering the intrinsic characteristics of each vaccine as well as the national specificities.

If the Interested Party (or any other affiliate) are developing clinical trials in Brazil, they shall continue the execution of these trials, gathering data in a controlled manner, for the maximum period possible, as to apply for the grant of definitive registration by ANVISA.

ANVISA does not consider that the availability of a COVID-19 vaccine, utilizing temporary emergency use authorization, is by itself ground to justify the cessation of any clinical trials currently in progress. An application for temporary emergency use authorization must include the implementation of strategies, by the Interested Party, to guarantee that the clinical trials ongoing are capable to assess the safety and efficacy of the vaccine on a long run basis.

It is vital that the Interested Party conducts a continual assessment on the risk-benefit analysis of the continuation of the product under temporary emergency use authorization, as well as having an adequate plan for the collection of data on the safety and efficacy of vaccinated individuals under the temporary emergency use authorization.

The temporary emergency use authorization in an experimental against COVID-19 is restricted to a pre-defined demographic region and does not substitute the grant of definitive registration by ANVISA.

ANVISA clarifies that only the grant of definitive registration is the adequate instrument to permit the expansion on using the vaccine in Brazil, according to the guidelines followed to guarantee the quality, efficacy, and safety of such products. However, the modality of temporary emergency use authorization might benefit determined and controlled groups, as an additional measure in the fight against the pandemic of the new Coronavirus.

The failure to meet these requirements established in this handbook must be previously subjected, and discussed with ANVISA, and justified by its data and shreds of evidence.

03. SCOOP

This handbook aims to guide companies on the regulatory scenario, involving the minimum technical criteria and the data required to apply for the temporary emergency use authorization for vaccines of experimental nature, aimed to prevent COVID-19 during the period of the public health emergency caused by the new coronavirus (SARS-CoV-2) pandemic.

04. SUBMISSION

The application must be presented by a company regularly registered with ANVISA.
The application for the temporary emergency use authorization for vaccines of experimental nature shall be submitted to ANVISA and labeled with the specific code (which denotes the subject). The application shall accompany reports on the data available on quality, safety, and efficacy of the vaccine, besides a conclusive report capable of demonstrating a positive coefficient on the risk-benefit analysis for the emergency use of the vaccine, according to the guidelines and regulatory requirements.
Before the formal application for the emergency authorization, the Interested Party shall schedule a pre-application meeting with the Gerência Geral de Medicamentos e Produtos Biológicos (General Management of Drugs and Biological Products – GGMED), for a presentation on the development of manufacturing process and clinical development of the vaccine, as well as sensitive information involving the application. A briefing must be sent in advance of at least two days, containing the subjects of the meeting.
The vaccine shall, preferably, be accompanied by a dossier Drug Clinical Development Dossier (DCDD) approved by ANVISA, and the phase 3 clinical trials in progress and conducted in Brazil.
If the COVID-19 vaccine is not being subject to clinical trials conducted in Brazil, it will fall on the Interested Party to present the strategy leading the clinical trials, demonstrating an intention of monitoring, for at least one (01) year, to assert the efficacy and safety of the participants of the pivotal trials. The strategy must include the assessment of enhanced respiratory disease (ERD), as well as guarantee that ANVISA is allowed to access the totality of the data generated, demonstrating also that the preclinical and clinical trials were conducted in compliance with the best practices recognized as such nationally and internationally (e.g. if the vaccines are manufactured in countries signatories of PIC/S, the guidelines of the ICH are to be followed), the research data gathered in other countries must also be able to apply to the Brazilian population (considering ethnic, socioeconomic and epidemiological data).
Before the submission of the application, the Interested Partner shall prepare a presentation including the aspects exposed in this handbook, to take place in the pre-submission reunion with ANVISA.
The Interested Party must commit to conclude the development of the vaccine in every aspect, presenting and discussing the results with ANVISA, to be granted definitive registration by ANVISA (as long as all of the regulatory requirements are met, according to the health legislation in effect).
Furthermore, for ANVISA's decision, the Interested Party must guarantee that the data on each phase of development, manufacturing, and stability are suitable to ensure the quality of the vaccine. Despite that, ANVISA might demand the fulfillment of additional requirements, considering the intrinsic characteristics of each vaccine as well as the national specificities.

05. PEOPLE DEMOGRAPHICALLY AIMED

The Interested Party shall indicate which kind of people are demographically aimed for the vaccine, considering the available data on its safety and efficacy.

06. OBLIGATORY DOCUMENTS

The Interested Party must present, at least, the following data, preferably in CTD format, to accompany the application for temporary emergency use authorization for vaccines of experimental nature against COVID-19. It is expected of the data, information generated for the emergency use to be detailed, and that the Interested Party follows the national technical guidelines, as well as the international requirements recognized by ANVISA, such are the guidelines of the WHO, FDA-US, EMA-EU, and ICH.

I – Description of the product and its intended use;
II – Record of interactions of the Interested Party with ANVISA;
III – Description of the status of approval of the vaccine in the international community;
IV – Justification for the emergency use of the vaccine, considering the public health situation in Brazil;
V – Risk assessment demonstrating a positive coefficient in a risk-benefit analysis;
VI – Information on the quality of the pharmaceutical technology applied on the active substance as well as on the final product, including at least:

a) Record, qualification, and quality control of the cell banks, virus banks, and identification of all materials obtained or derived from animals for cell and virus culture, including the characterization of the antigen expressed (for vaccines which induce the triggering of antigen production);
b) Plan for the mitigation of potential adventitious agents;
c) Characterization of the active substance;
d) Detailed description of the entire manufacturing process utilized for the production of the lots destined for emergency use, starting at the manufacturing of the active substance until the final phases of the manufacture of the final product, accompanied by a flowchart, identifying the critical stages of the process, the critical attributes of quality and the tests and controls applied in the process;
e) Record of the development of manufacturing process and the strategy for quality control, including the alterations introduced during the phases of development, clinical and commercial, as well as data for the analysis of comparability of lots manufactured on the different processes of fabrication. Also must be present data on for liberation and supplementary characterization, for the assessment of the impact of the alterations on the attributes of quality and investigative studies, assessment and definition of the limits of the impurities on the active substance, and on the final product.
f) Tabular list of all the clinical trials, specifying the lot number of the vaccines used in each one of the trials, including the genealogy of the active substance tracing back from the master cell bank and master viral seed bank, the processes and location of manufacturing, as well as the certificates of analysis (CoAs) for every lot used in the clinical trials;
g) Qualification/Validation for all of the tests for the liberation, quality control, and stability, including a test of purity, identity, and potency of the vaccine, demonstrating they are suitable for the intended purpose;
h) Stability plan, including test indicative of stability and safety of the active substance and the final product, data on the stability available on every lot in development, clinical and commercial. Data to support the short-term stability of the vaccine in use, pointing out the conditions of storage during transport and distribution to the vaccination grounds and covering the time and conditions since the preparation of the dose until the administration of the vaccine.
i) Specification of quality, accompanied by its justification, grounded on the record of the lots produced, including every clinical lot;
j) Data to support the consistency of the quality of the vaccine among the manufacturing plants in case of more than one manufacturing plant for the active substance and/or the final product.

VII – Report on the safety and immunogenicity during the phase of preclinical stage.
VIII – Report on the immunogenicity, containing the results of the immunologic parameters analyzed during clinical trials;

IX – Report on the clinical trials, including the results of the interim or conclusive results of the primary endpoints of phase 3 clinical trials, demonstrating at least a 50% efficacy. The statistical success criteria must be that the inferior limit of the confidence level (adjusted to alpha) is higher than 30%, or, in the case of alternative parameters, that these were preapproved by ANVISA. The reports must contain, at least:

a) Criteria for inclusion and exclusion;
b) Detailed description of the demographic characteristics of each trial, and other characteristics considered important to the assessment of the efficacy and safety of the product (e.g. the presence of subjects affected by comorbidities, that were under concomitant treatments, and subjected to other vaccines).
c) Detailed description of the outcomes and on how each one of the outcomes was assessed during trials, including the definitions of the cases of Covid-19 and the scale utilized to assess the severity, symptoms considered to define the necessity sample collection for viral confirmation, procedures that were taken to monitor subjects symptoms, the period of days, maximum and minimum, from the first of the symptoms, until the collection of samples for the serologic confirmation;
d) Average monitoring time of the subjects after the administration of the entire vaccination schedule for the demographic, for safety and efficacy analyses;
e) Listing of the data necessary to support the critical analyses: individual results of base serology, prior diagnoses of Covid-19 with the results of the test performed, the individual result of the outcomes on immunogenicity, date of collection, number of samples collected, and results for the tests on viral confirmation of the Sars-CoV-2 infection for each one of the symptomatic subjects in the trials.

X – Report of validation of the bioanalytical tests utilizer to evaluate the outcomes of phase 3 clinical trials.
XI – Safety data gathered on phases 1 and 2, focusing on serious adverse events, adverse effects of special interest, and severe cases of Covid-19, accompanied by the respective detailed narratives, and the plan for monitoring and detection of late adverse events, justifying the period proposed;
XII – Safety data gathered on phase 3, regarding the average period of at least 2 months after the last immunization, and the establishment of a preliminary security profile for cases of severe adverse effects, of adverse effects of special interest, and cases of enhanced respiratory disease (ERD). The data must accompany the detailed narratives on the serious adverse events, adverse effects of special interest, and severe cases of Covid-19.
XIII – Data relating to the efficacy and safety analyses on subgroups, by the status of prior infection e by age group.
XIV – List containing each of the manufacturing plants (currently operational, or to become operational), as well as the following documents related to the Current Good Manufacturing Practices (CGMPs)2:

a) Site Master File (SMP)3;
b) Inspection report emitted by authority member of PIC/S;
c) Validation process;
d) Cross-contamination risk management, due to the inclusion of the product in the production line;

XV – Information on the validity period, precautions regarding the conservation of the vaccine, and on the capability of the Interested Party in maintaining such conditions until the administration;
XVI – Information on the probable amount of the final product available for importation and disponibility;
XVII – Text of the inner vial label, and outer label. It's recommended the utilization, as reference, the Resolução da Diretoria Colegiada – RDC nº 400/2020.
XVIII – Risk management plan for the identification of problems derived from the use of the vaccine, including measures to be taken; XIX – Vaccination consent form4 must be signed by the patient and filled with the specific data of the vaccine proposed. It's recommended the utilization, as a reference, the model utilized by the United Kingdom (https://www.gov.uk/government/publications/covid-19-vaccination-consent-form-and-letter-for-adults).

ANVISA might, at any moment, require data and additional information that judges necessary to verify that the benefits of the emergency use of the vaccine outweigh the risks involved. The Interested Party must inform whatever documents are missing on the application, considering the specific legislation for the registration of vaccines in Brazil, and discuss the impact of the absence of said documents on the report on the risk assessment of the vaccine (item V). The risk assessment report shall be presented 3 months after the concession of the emergency use authorization for vaccines of experimental nature, aimed to prevent COVID-19, as dictates article 18 of Instrução Normativa – IN n. 63/2020.
In case of vaccines register or approved for emergency use in other countries, it must be presented a technical report of assessment by the respective regulatory authority, if available.
In the case of vaccines that were not clinically developed, partially or fully, in Brazil, the protocols of every one of the clinical trials conducted with the vaccine must be presented.
The outer label of the vaccines shall bear the expression: "Uso Emergencial" (emergency use).
To prove the Current Good Manufacturing Practices (CGMPs), the establishments involved in the manufacturing of the vaccine must comply with the requisites of certification stated by Resolução da Diretoria Colegiada-RDC n. 346/2020, which defines the temporary and extraordinary criteria and procedures for the certification on Current Good Manufacturing Practices for registration purposes and post-registration changes of the active pharmaceutical component (API), drugs and health products related to the international public health emergency of the new Coronavirus.

07. COMPANYS MONITORING COMMITMENT

The Interested Party shall:

I – Verify the validity period, and establish mechanisms to safeguard the general conditions and quality of the vaccines;
II – Inform and guide the health services and patients about the use and precautions for the conservation of the vaccine, as well as how to notify the Interested Party of any technical complaints and adverse events related to the product;
III – Establish mechanisms for monitoring the post-distribution e post-administration of the vaccine by the health services, enabling that technical complaint and adverse events identified will be informed to ANVISA, via information system;
IV – Accept the obligation to recall the vaccine if and when determined by ANVISA. The Interested Party, an applicant for emergency use authorization for vaccines of experimental nature, shall guarantee that the health professionals, which administer the vaccine approved for emergency use, are informed of the following aspects:
I – That ANVISA authorized the emergency use of the product (including the name of the vaccine, and an explanation on the proposed use); and II – About the benefits, significant and known risks, and potential risks involved that accompany the use of the vaccine, and to what extend the benefits and risks are unknown. The Interested Party, the applicant for emergency use authorization for vaccines of experimental nature, shall guarantee that the patients are informed of the following aspects:
I – That ANVISA authorized the emergency use of the product;
II – About the benefits, significant and known risks, and potential risks involved that accompany the use of the vaccine, and to what extend the benefits and risks are unknown;
III – That the patient has the option of accepting or refusing the vaccine approved for emergency use; and
IV – Of whatever alternatives available other than the vaccine, and the risks and benefits of such alternatives.

The patient or his legal representative must sign the vaccination consent form, which shall be complete with the specific data on the vaccine object of the authorization for emergency use.
The Interested Party, an applicant for temporary emergency use authorization for vaccines of experimental nature, aimed to prevent COVID-19 during the period of the public health emergency, is subject to the same sanitary and legal obligations as those who hold a definitive registration granted by ANVISA, being subjected to pharmacovigilance actions as defined in RDC 406/2020
Any serious advert events, related to the vaccines object of this handbook, must be reported to ANVISA within 24 hours.

The notification of serious advert events shall be made within the system e-SUS Notifica. If unable to access the platform, the notification shall be made within the Vigimed system (https://www.gov.br/anvisa/ptbr/assuntos/fiscalizacao-emonitoramento/notificacoes/vigimed); if not registered on the platform, the following system must be used: reporting – https://primaryreporting.whoumc.org/Reporting/Reporter?OrganizationID=BR.
The notification of technical complaints shall be made in the System of Notifications of Vigilância Sanitária, available at http://www.anvisa.gov.br/hotsite/notivisa/index.htm.

08. DEADLINES

In the cases of application for the temporary emergency use authorization for vaccines of experimental nature, with phase 3 clinical trials conducted in Brazil, and authorized by ANVISA, ANVISAs analyses of the application shall be made in the maximum of 10 days.
In the cases of application for the temporary emergency use authorization for vaccines of experimental nature, with phase 3 clinical trials conducted outside Brazil, ANVISAs analyses of the application shall be made in a maximum of 30 days.
In the case of technical requirements, the deadline for the analyses will be interrupted, and the Interested Party shall comply with said requirements within 48 hours. The deadline for the presentation of any new data and any clarifications by the Interested Party shall be within 3 days before ANVISAs deadline indicated above.

09. EMERGENCY AUTHORIZATION

The lots of vaccines authorized for emergency use, of experimental nature, shall only be cleared for administration after the appraisal by the National Institute for the Quality Control in Health5, which shall follow the procedures defined in Resolução da Diretoria Colegiada – RDC n. 73/2008.
At any time, the temporary authorization for emergency use may be modified, suspended, or revoked by ANVISA, for technical and scientific reasons that alter the cost/benefit relation or based on information provided by the control and monitoring system for the vaccines authorized for emergency use.
The conditions for the approval of the authorization for emergency use, of temporary nature, shall be published on ANVISAs website.

5 Instituto Nacional de Controle de Qualidade em Saúde (INCQS)