ANVISA
Agência Nacional de Vigilância Sanitária

TECHNICAL NOTE No. 1/2022/SEI/COPEC/GGMED/DIRE2/ANVISA

Case No. 25351.902239/2022-81

Guidelines on completing the Clinical Trial Submission Form (FAEC) regarding the expiration date of medicines and products to be imported

for conducting clinical trials in Brazil, pursuant to RDC No. 9/2015.

1. Report

This document provides guidance to sponsors and their legal representatives in Brazil responsible for the submission of Clinical Development Dossiers of Medicines and Biological Products (DDCMs), Specific Clinical Trials Dossiers (DEECs) and Amendments to clinical protocols, on filling in field 70 of the Clinical Trial Submission Form (FAEC) regarding the expiration date of drugs and products to be imported for conducting clinical trials, pursuant to RDC No. 9/2015.

2. Analysis

According to RDC nº 9/2015, after the evaluation and approval of the DDCM, a single Special Communiqué (EC) will be issued mentioning all clinical trials to be conducted in Brazil and all drugs and products to be imported for each clinical trial. . For cases of DDCMs released due to expiry of term, pursuant to Art. 36 of RDC No. 9/2015, a Document for Importing Products (DI) or a Specific Special Notice (CEE) will be issued in the case of a clinical trial subject to the notification regime.

The CE, CEE or DI must be presented at the time of customs clearance, for the import or export of product(s) under investigation, necessary for the conduction of the clinical trial. The EC, CEE or DI must be updated due to new requests for modification of the DDCM for inclusion of Clinical Trials (planned and unplanned), quality change or amendment to the clinical protocol, if applicable.

The validity period described in the CE, EEC or DI, of each drug and/or product to be imported for the clinical trial, is one of the information provided at the time of customs clearance. The expiration date is also one of the most frequently updated information, generating constant inconsistencies and requests for clarification (requirements) to those responsible for importing drugs and products for clinical trials.

The importation of a product with a validity period different from the one informed in the EC, CEE or DI may be due to logistical / administrative issues, such as: due to the acquisition of comparators or placebos from different suppliers, whose deadlines may vary depending on each manufacturer; in the case of blind kits assembled for double-blind studies containing the experimental drug, for which the date of manufacture is adopted as

being the kit assembly date; different criteria for adopting the expiration date by different manufacturers, as in the case of the adoption of an expiration date shorter than the real one, to avoid using the drug at the limit of the expiration date; batches of drugs already manufactured, but not re-labeled, even after the expiry date has been extended, among others.

3. Conclusion

The definition of the expiration date of the investigational drug, comparator and placebo used in clinical trials should be based on data from stability studies carried out under accelerated and long-term conditions, available at the time of clinical trial authorization. For experimental drugs, placebo and comparators, whose recommended storage is at room temperature (between 15°C and 30°C), long-term stability studies must be performed under Zone IVb conditions (30°C±2°C/75% RH±5%RH). Stability studies can continue to be carried out in parallel with clinical trials, the results of which can be used to extend or reduce the initially approved shelf life.

Extending the shelf life and/or changing the conservation care of the investigational drug, comparator and placebo is considered a substantial modification when there is a change in the previously established stability evaluation criteria, such as the expansion of specification limits or exclusion of stability parameters/attributes, for example, and/or if the values are not within these limits or if the expiration date is defined based on reduced stability study plan models, such as clustering and matrixing, for example (ICH Topic Q 1 D Bracketing and

Matrixing designs for Stability Testing of Drug Substances and Drug Products, CPMP/ICH/4104/00, CPMP/ICH/4104/00; Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, EMA/CHMP/BWP/534898/2008 Rev. 2, 27 January 2022; Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials, EMA/CHMP/QWP/545525/2017 Rev. 2, 24 June 2021). In such cases, the interested party must submit the request to change the expiration date of the experimental drug through subject code 10849 – CLINICAL TRIALS – Modification of DDCM – Change of Expiration Date, and wait for the agency's manifestation.

Extending the validity period that does not involve any type of change described in the previous paragraph, and in cases of shortening the validity period of the API/active substance or investigational drug, without changing the conservation care, it is considered a non-substantial modification. In these cases, there is no specific petition subject, and this information must be attached to the Experimental Drug Development Safety Update Report (subject code 10825), according to RDC No. 9/2015. for those In these cases, in order for the CE, DI or CEE to be updated with the new validity period, the interested party must submit the Amendment to the Clinical Trial Submission Form (FAEC) through subject code 10823.

In cases of reduced shelf life due to quality deviations or results of stability parameters/attributes outside the specification limits, in addition to the submission of the FAEC Amendment, the justification for the reduction of the validity period and information about the potential risks and respective measures to mitigate these risks must be presented to the participants of the clinical trial. In such cases, the company must assess whether there is a need for additional submission of substantial quality modification and proceed according to RDC No. 9/2015 and Manual for Submissions of Modifications, Amendments, Suspensions and

Cancellations.

3.1 Filling in FAEC field 70 about the expiration date

As of the publication of this Technical Note, the sponsor or company designated by it is allowed to fill in field 70 of the FAEC, expiry date field of each product, with the maximum validity period of the product to be imported (up to XX months) , according to the model below. Thus, any variation of the validity period up to the maximum period informed will not impact the clearance process at the time of customs clearance, except in cases of reduction of the validity period motivated by quality deviations, as mentioned above.

In the case of drug kits used in double-blind studies, in which the components of these kits cannot be identified to protect the blinding of the clinical trial, it is up to the importer to consider the kit assembly date as the date of manufacture. In the Import Licensing (LI) document, the date of manufacture and validity of the kit must be informed, as a single item. However, in field 70 of the FAEC (which will also appear in the CE, DI or CEE) each component of the kit and their respective expiration dates must be detailed, approved by the technical area.

In these cases, as there may be a discrepancy between the validity period of the kit, informed on the invoice, and the expiry dates of each component individually detailed in the FAEC (and in the CE, DI or CEE), it is recommended that a clarification be inserted about this divergence in the product description field in the LI. Clarify that the shelf life of each component is duly supported by stability studies under appropriate conditions, in addition to informing and justifying the criterion for choosing the component used to define the shelf life of the kit.

Clinical Trial Submission Form Template (FAEC)

70. Medicines and Products to be imported for conducting the clinical trial				
products with your respective presentations	way of management	conditions of Storage	Term of Shelf life	Controlled
anvisex	Oral	Between 15 and 30ºC	Up to 36 months	( ) YES NO
faex	Injectable (IV)	Between 2 and 8ºC	up to 24 months	( ) YES NO

References:

1. MANUAL FOR SUBMISSION OF MODIFICATIONS, AMENDMENTS, SUSPENSIONS AND CANCELLATIONS, 5th Edition, 2021.
2. QUALITY DATA SUBMISSION MANUAL REGARDING PRODUCTS UNDER INVESTIGATION USED IN CLINICAL TRIALS - BIOLOGICAL PRODUCTS, 3rd Edition, 2019.
3. MANUAL FOR SUBMISSION OF QUALITY DATA REGARDING PRODUCTS UNDER RESEARCH USED IN CLINICAL TRIALS - SYNTHETIC AND SEMISSYNTHETIC DRUGS, 3rd Edition, 2019.
4. ICH Topic Q 1 D Bracketing and Matrixing designs for Stability Testing of Drug Substances and Drug Products, CPMP/ICH/4104/00, February 2002.

5. BRAZIL. ANVISA National Health Surveillance Agency. Resolution RDC No. 09, of 20 February 2015. Provides for the regulation for conducting clinical trials with drugs in Brazil. Official Diary of the Union; Executive Branch, of March 3, 2015.
6. EUROPEAN MEDICINES AGENCY. Committee for Medicinal Products for Human Use (CHMP). Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials. EMA/CHMP/BWP/534898/2008 Rev. 2, 27 January 2022. Available at: https://www.ema.europa.eu/en/documents/scientific guideline/guideline.

Change history:

1/28/2022 : New.

Document signed electronically by Gustavo Mendes Lima Santos, General Manager of Medicines and Biological Products, on 01/28/2022, at 5:04 pm, according to Brasília official time, based on § 3 of art. 4 of Decree No. 10.543, of November 13, 2020 http:// www.planalto.gov.br/ccivil_03/_ato2019-2022/2020/decreto/D10543.htm.

Document electronically signed by Claudiosvam Martins Alves de Sousa, Coordinator of Clinical Research in Medicines and Biological Products, on 01/31/2022, at 4:22 pm, according to Brasília official time, based on § 3 of art. 4 of Decree No. 10.543, of November 13, 2020 http://www.planalto.gov.br/ccivil_03/_ato2019-2022/2020/ decreto/D10543.htm.

The authenticity of this document can be checked on the website https://sei.anvisa.gov.br/autenticidade, informing the verification code 1756102 and the CRC code CBF5C81D.

Reference: Case No. 25351.902239/2022-81 **SEI No. 1756102**