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 shelf life of drugs and products to be imported for conducting clinical trials in Brazil, under RDC No. 9/2015.

1. Report

This document provides guidance to sponsors and their legal representatives in Brazil responsible for submitting Clinical Drug and Biological Product Development Dossiers (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 shelf life of drugs and products to be imported for clinical trials, under RDC No. 9/2015.

2. Analysis

According to RDC No. 9/2015, after the evaluation and approval of the DDCM, a single Special Statement (CE) 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 DDCMs released due to expiry of term, under Art. 36 of RDC No. 9/2015, a Product Import Document (DI) or a Specific Special Statement (CEE) will be issued in the case of a clinical trial subject to the notification regime.

The CE, CEE or DI must be submitted at the time of customs clearance, for import or export of investigational product(s) necessary for the conduction of the clinical trial. The CE, 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 shelf life described in the CE, CEE or DI for each drug and/or product to be imported for the clinical trial is one of the information checked at the customs clearance. The shelf life is also one of the most frequently updated information, resulting in constant inconsistencies and requests for clarifications (requirements) to those responsible for importing drugs and products for clinical trials.

Importing a product with a shelf life different from that informed in the CE, CEE or DI may be due to logistical/administrative issues, such as: due to the acquisition of comparators or

placebos from different suppliers, whose terms may vary depending on each manufacturer; in the case of blind Kits assembled for double-blind studies containing the investigational drug, for which the date of manufacture is adopted as the date of assembly of the Kit; different criteria for adopting the shelf life by different manufacturers, as in the case of adopting a shorter shelf life than the actual one, to avoid using the drug at the limit of the shelf life; batches of drugs already manufactured, but not re-labeled, even after the shelf life has been extended, among others.

3. Conclusion

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

The extension of the shelf life and/or change in 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 extending specification limits or excluding stability parameters/attributes, and/or if the values are not within these limits or the shelf life is defined based on reduced stability study plan models, such as bracketing and matrixing (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 these cases, the interested party must submit the request to change the shelf life of the investigational drug through subject code *10849 – ENSAIOS CLÍNICOS – Modificação de DDCM – Alteração de Prazo de Validade* (CLINICAL TRIALS – Change of DDCM – Change of Shelf Life), and wait for the agency's response.

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

In cases of shelf-life reduction due to quality deviations or results of stability parameters/attributes outside the specification limits, in addition to submitting the Amendment to the FAEC, the justification for the reduction of the shelf life and information about the potential risks and respective measures to mitigate these risks must be submitted to the subjects of the clinical trial. In these 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 Submission of Changes, Amendments, Suspensions, and Cancellations.

3.1 Filling in FAEC field 70 about the shelf life

As of the publication of this Technical Note, the sponsor or company designated by it **is authorized** to fill in field 70 of the FAEC, shelf-life field of each product, with the maximum shelf life of the product to be imported (*up to XX months*), according to the model below. Thus, any variation of the shelf life 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 shelf life motivated by quality deviations, as mentioned above.

For 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 its manufacture. In the Import Licensing (LI) document, the date of manufacture and validity of the kit must be informed, as a single item. However, field 70 of the FAEC (which will also appear in the CE, DI or CEE) must detail each component of the kit and their respective shelf lives, 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 shelf lives of each component individually detailed in the FAEC (and in the CE, DI or CEE), it is recommended that a clarification on this divergence be inserted 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 (FAEC) Template

70. Drugs and Products to be imported to conduct the clinical trial				
Products with their respective presentations	**Route of administration**	**Storage Conditions**	**Shelf Life**	**Controlled**
Anvisex	*Oral*	*Between 15 °C and 30 °C*	*Up to 36 months*	*( ) YES ( ) NO*
Faex	*Injection (IV)*	*Between 2 °C and 8 °C*	*Up to 24 months*	*( ) YES ( ) NO*

References:

1. MANUAL FOR SUBMISSION OF CHANGES, AMENDMENTS, SUSPENSIONS, AND CANCELLATIONS, 5th Edition, 2021.
2. MANUAL FOR SUBMISSION OF QUALITY DATA REGARDING THE INVESTIGATIONAL PRODUCTS USED IN CLINICAL TRIALS, 3rd Edition, 2019.
3. MANUAL FOR SUBMISSION OF QUALITY DATA REGARDING THE INVESTIGATIONAL PRODUCTS USED IN CLINICAL TRIALS – SYNTHETIC AND SEMI-SYNTHETIC 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. Brazilian Health Regulatory Agency. RDC Resolution No. 09, of February 20, 2015. Provides for the regulation for conducting clinical trials with drugs in Brazil. Official Federal Gazette; Executive Branch, of March 03, 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:

- 28/Jan/2022: New.