NORMATIVE INSTRUCTION (IN) No. 139 OF 30 MARCH 2022

Provides for the Good Manufacturing Practices complementary to the reference and retention samples.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, item III of Law no. 9,782 of 26 January 1999, and item VII, paragraphs 1 and 3 of Article 187 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Normative Instruction, as decided upon in the Extraordinary Meeting – RExtra 6, held on 30 March 2022, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Article 1. This Normative Instruction has the objective of adopting the guidelines on Good Manufacturing Practices related to the reference and retention samples of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), as complementary requirements to be followed in the manufacture of medicinal products, in addition to the General Guidelines on Good Manufacturing Practices for Medicinal Products.

Section II

Scope

Article 2. This Normative Instruction applies to companies that carry out operations involved in the manufacture of medicinal products, establishing the requirements for the collection and safekeeping of reference samples of raw materials, packaging materials, or finished products; and of retention samples of finished products.

Section III

Definitions

Article 3. For the purposes of this Normative Instruction, the following are adopted definitions:

I – reference sample: samples from a batch of raw materials, packaging material, or medicinal product in its primary packaging, which are stored for the purpose of analysis, if necessary, during the shelf-life of the product; and

II – retention sample: samples of a fully packed batch of a medicinal product, with all its components required for sale to the consumer, such as secondary presentation packaging, labeling, package inserts, variable data recordings, which are stored for identification purposes.

CHAPTER II

GENERAL PROVISIONS

Section I

Introduction

Article 4. In cases where there is enough stability, reference samples must be stored for critical intermediates that require analysis and release, or for intermediates that are transported out of the establishment.

Article 5. In the case of finished products, in many situations the reference and retention samples have the same presentation and may be considered interchangeable.

Article 6. The manufacturer, importer, or batch release site must keep reference and/ or retention samples for each batch of finished product, and the manufacturer must keep reference samples from batches of raw materials and/ or intermediates.

Article 7. Each packaging site must keep reference samples from each batch of primary and printed packaging materials.

Sole paragraph. The provision of printed packaging materials as a constituent part of reference and/ or retention samples of the finished product is acceptable.

Article 8. Reference and/ or retention samples are a record of the finished product batch or raw materials and may be accessed in situations, such as concentration-related complaints, questions related to compliance with marketing authorization or related to packaging/ labeling, or in pharmacovigilance reports.

Article 9. Records regarding the traceability of use and storage of samples must be kept and be available for review by the health authorities.

Section II

Storage duration

Article 10. The reference and/ or retention samples of each batch of finished product must be kept for at least one year after the expiry date.

Paragraph 1. The reference sample must be contained in the primary packaging or in packaging made of the same material as the primary packaging in which the product is commercialized.

Paragraph 2. For large volume parenteral solutions and polyelectrolyte concentrates for hemodialysis, the storage period referred to in the caption of this article is thirty (30) days after the expiry date.

Article 11. Samples of raw materials other than solvents, gases, or water used in the manufacturing process of a medicinal product must be retained for at least two years after the medicinal product batch is released.

Sole paragraph. This period may be reduced if the stability of the material, as indicated in the relevant specifications, is lower.

Article 12. Samples of the packaging materials must be kept during the validity period of the medicinal product in which they were used.

Section III

Quantity of the reference and retention samples

Article 13. The reference sample must be of a sufficient size to allow two complete analytical controls of the batch to be performed on separate occasions, in accordance with the health marketing authorization of the country where the manufacturing site is located.

Paragraph 1. Quantities must be planned so that analytical tests can be performed from unopened packages.

Paragraph 2. Any exception to the provisions in the caption and in Paragraph 1 of this article must be technically justified and approved with the competent health authority.

Article 14. The reference samples must be representative of the batches of raw materials, intermediate products, or finished products from which they were taken.

Sole paragraph. Additional samples may be required to monitor stressful stages of a process, such as the beginning and end of a process.

Article 15. When a batch is packed in two or more distinct packing operations, at least one retention sample must be taken from each individual packing operation.

Sole paragraph. Any exception to this requirement must be technically justified and agreed upon with the health authority.

Article 16. The maintenance of an analytical capability readily available must be ensured to perform the specified tests for a period of up to one year after expiration of the last batch manufactured.

Section IV

Storage conditions

Article 17. The storage conditions must be in accordance with the health marketing authorization of the country where the manufacturing site is located.

Section V

Quality agreements

Article 18. In cases where the marketing authorization holder is not the same establishment responsible for releasing the batch, the responsibility for the collection and storage of reference and/ or retention samples must be defined by means of a technical agreement between the parties.

Sole paragraph. The provisions in the caption of this article also apply to the cases where any manufacturing or batch release activity is performed by an establishment other than the one with overall responsibility for the batch.

Article 19. The person delegated by the Pharmaceutical Quality Management System to release a batch for sale must ensure that all relevant reference and retention samples are accessible within a reasonable time frame.

Sole paragraph. When applicable, the provisions regarding the access provided for in the caption of this article must be defined in the contract.

Article 20. In situations where more than one establishment is involved in the manufacturing of the product, written agreements must be available for the control of withdrawal and location of reference and/ or retention samples.

Section VI

Generalities regarding reference samples

Article 21. The reference samples have an analytical purpose and, consequently, must be conveniently available to the laboratory that holds the validated methodology for their test.

Paragraph 1. In the case of reference samples of raw materials and packaging materials used in the manufacture of medicinal products, the storage must correspond to the manufacturing site of the medicinal product.

Paragraph 2. In the case of reference samples of finished products, storage must correspond to the original manufacturing site.

Section VII

Generalities regarding retention samples

Article 22. The retention sample must represent the batch of the medicinal product as it has been released for consumption, so that it may be analyzed with a view to verifying compliance with nontechnical requirements of the health marketing authorization or applicable legislation.

Article 23. The retention samples must preferably be stored in the establishment where the batches are released for sale.

Sole paragraph. The health authorities must have free access to this location.

Article 24. When more than one establishment is involved in the manufacturing chain, packaging, analysis, import, and final release of batches, the responsibility for the collection and storage of retention samples must be defined in a contract between the parties involved.

Section VIII

Management of reference and retention samples in case of termination of a manufacturer's activities

Article 25. If batches of unexpired medicinal products manufactured by a company that has terminated its activities remain, the manufacturer must make arrangements for the transfer of reference and retention samples, and of the pertinent Good Manufacturing Practices documentation to an entity authorized before Anvisa.

Article 26. The manufacturer must assure the competent authority that the storage arrangements are satisfactory and that samples may, if necessary, be readily accessed and analyzed.

Paragraph 1. When there are situations preventing compliance with the provisions, the necessary measures may be delegated to another manufacturer.

Paragraph 2. The holder of the product marketing authorization is responsible for delegating and providing all required information to the health authority.

Article 27. The holder of the product marketing authorization must, with regard to the adequacy of the proposed measures for the storage of reference and retention samples, consult with the health authority of each country in which any batch within the expiry date has been placed on the market.

CHAPTER III

FINAL PROVISIONS

Article 28. Non-compliance with the provisions contained in this Normative Instruction constitutes a health infraction, pursuant to Law no. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 29. Normative Instruction – IN No. 48 of 21 August 2019 is hereby revoked.

Article 30. This Normative Instruction enters into force on 2 May 2022.

ANTONIO BARRA TORRES