



Long-term Stability Study for GERADOR-IPEN- TEC by IPEN-CNEN/SP

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1. Introduction

Radiopharmaceuticals are pharmaceutical preparations for diagnostic or therapeutic purposes which, when ready for use, contain one or more radionuclides. Radiopharmaceuticals include non-radioactive components for labeling with eluate from generator, radionuclides, including components extracted from radionuclide generators [1].

Resolution RDC No. 658, of March 30, 2022, which sets out the guidelines for Good Manufacturing Practices for Medicines (GMP) [2], and Normative Instruction IN No. 128, of March 30, 2022 [3], which sets out the complementary GMP for Radiopharmaceuticals, are the main ANVISA regulations applicable to the production of radiopharmaceuticals. Stability Study is one of the mandatory requirements for the production, registration and use of Radiopharmaceuticals and the requirements are defined in Resolution RDC No. 318 of November 6, 2019 [4].

Stability Study is the study designed to test and provide evidence that the variation in the quality of the Active Pharmaceutical Ingredient (API) or drug as a function of time, under the influence of environmental factors such as temperature, humidity, light, as well as other factors related to the product itself, such as the physical and chemical properties of the API and pharmaceutical excipients, as well as the pharmaceutical form, the manufacturing process, the type and properties of the packaging materials, with the aim of establishing the Shelf Life of the API or the Retest Life of the API and the drug.

RDC no. 318 describes all the types of stability relevant to medicines: Accelerated Stability Study, Follow-up Stability Study, Long-term Stability Study, In-use Stability Study, Reduced Stability Study. Stability Study must be carried out using an approved stability protocol.

Stability Study Protocol is the document which defines the stability study plan, including the tests and acceptance criteria, timetable, characteristics of the batch to be subjected to the study, quantity of samples, study conditions, analytical methods, and packaging material. Stability studies should be carried out on the medicinal product in the packaging proposed for marketing, including, as appropriate, the secondary packaging or intermediate wrapping. After all the tests have been completed, a Stability Study Report must be drawn up, which is the document presenting the consolidated results of the Stability Studies.

Technetium-99m is the most widely used radionuclide in nuclear medicine services because it has both chemical and physical characteristics making it the workhorse of radionuclide imaging [5].

^{99m}Tc has almost ideal physical characteristics: monoenergetic gamma ray of 140 keV, which is easily collimated and yields enough photons, half-life of 6.0 h long enough to obtain diagnostic information in many procedures and short enough to cause minimal radiation dose to the patient and operator [5].

The eluate obtained from an enclosed and sterile ^{99}Mo - ^{99m}Tc generator system does not need further processing or purification and can be directly administered or used for the preparation of ^{99m}Tc -radiopharmaceuticals. The ^{99}Mo - ^{99m}Tc generator has a glass column with loaded alumina (Al_2O_3). The amount of alumina varies from 5 to 10 g, depending on the total activity of ^{99}Mo . The ^{99}Mo is adsorbed on alumina as molybdate ($^{99}\text{MoO}_4^{2-}$) and to elute ^{99m}Tc radionuclide as sodium pertechnetate ($\text{Na}^{99m}\text{TcO}_4$), the column is washed with 0.9% sodium chloride solution (saline) [6].

Technetium is used to the preparation of a wide variety of ^{99m}Tc -radiopharmaceuticals for imaging of the brain, bone, liver, spleen, kidney, lung, thyroid, and blood-flow studies [5].

The aim of this work is to carry out a Long-term Stability Study (LT) for GERADOR-IPEN-TEC, produced and distributed by IPEN-CNEN/SP, to confirm the product's shelf life of 14 days when stored at room temperature.

2. Methodology

To carry out the Long-term Stability Studies on GERADOR-IPEN-TEC, a Protocol and Report were drawn up, in accordance with RDC 318. Table I illustrates the information that each document must contain.

Table I: Information about Stability Study Protocol and Report

STABILITY STUDY PROTOCOL	STABILITY STUDY REPORT
Name of the drug	Protocol version executed
Identification of the API by DCB and CAS	Name and address of the API manufacturer
Tests to be carried out	Batch number and size of the finished product
Specifications	Date of manufacture of the batch
Execution schedule	Batch and expiry date of the API used
Name and address of the API manufacturer	Batch of the bulk and/or intermediate product
Study conditions	Description of the primary packaging material
Name and address of the drug manufacturer	Study start date (day/month/year)
Manufacturing process, if there is more than one	Storage conditions
Batch size	Frequency of testing
Analytical Methods Indicative of Stability used for all tests	Stability specifications
Primary packaging material used	Identification of equipment used
	Production process, if there is more than one
	Test results (raw data)
	Statistical evaluation of results
	Conclusion

The LT Stability Study of GERADOR-IPEN-TEC was carried out on 3 batches of the product. To carry out the tests, a GENERATOR-IPEN-TEC was used, with an activity of 7400 MBq (2000 mCi), on the calibration date. The LT Stability Study of the GENERATOR-IPEN-TEC was carried out keeping the generator under controlled temperature and humidity conditions, $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / 35% UR $\pm 5\%$ UR. The tests were carried out at 5 different times within the proposed shelf life.

3. Results and Discussion

The LT Stability Study tested all the quality attributes that may have a potential impact on quality, efficacy, and safety, and which may change due to the influence of time, temperature, humidity or any other exposure factor.

The tests for radiochemical purity (Fig. 1), pH, radionuclide purity, product description and radionuclide identification were carried out at 5 different times on alternate days, starting with the first eluate obtained on the day of production, within the proposed shelf life. The preliminary radionuclide purity test was carried out in two daily elutions, with a minimum interval of 6 hours between them. For all the eluates obtained, the chemical purity test was carried out to determine aluminum. The sterility and bacterial endotoxin tests were carried out on the initial day (day of production) and the final day (last day of validity).

Table II shows the tests carried out and the acceptance criteria for GERADOR-IPEN-TEC, according to the Brazilian Pharmacopoeia, 6th edition 2019.

Table II: GENERATOR-IPEN-TEC: Tests carried out and Acceptance Criteria

Testing	Specification
Radiochemical purity	$\geq 95\%$
Product description	Clear; colorless appearance
Radionuclide identification	Detecting the photopic in 140 keV
Radionuclide purity	$^{99\text{m}}\text{Tc} \geq 99.99\%$. $\leq 0.15 \text{ kBq } ^{99}\text{Mo} / \text{MBq } ^{99\text{m}}\text{Tc}$; $\leq 0.05 \text{ kBq } ^{131}\text{I} / \text{MBq } ^{99\text{m}}\text{Tc}$; $\leq 0.05 \text{ kBq } ^{103}\text{Ru} / \text{MBq } ^{99\text{m}}\text{Tc}$; $\leq 0.01\%$ for adding impurities
pH determination	4.0 – 8.0
Chemical purity (Al)	$\leq 5 \text{ ppm}$
Preliminary radionuclide purity test	$\mu\text{Ci } ^{99}\text{Mo} / \text{mCi } ^{99\text{m}}\text{Tc} \leq 0.15$
Sterility	No microbe growth
Bacterial endotoxins	$\leq 175 \text{ UE/V}$, where $V=6\text{mL}$

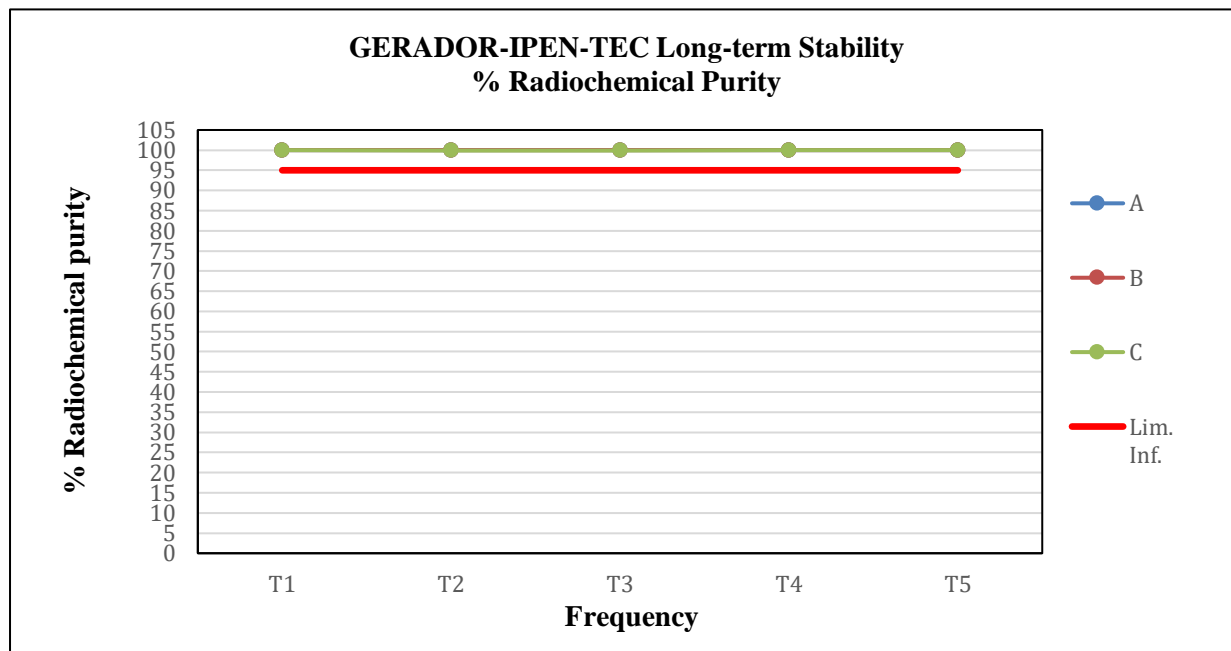


Figure 1 – GERADOR-IPEN-TEC Radiochemical purity

4. Conclusions

The eluates from the 3 batches of GERADOR-IPEN-TEC analyzed showed results that met the radiopharmaceutical's specifications, confirming its shelf life of 14 days when stored at room temperature (15 to 30 °C).

References

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