PhD THESIS EVALUATION REPORT

the Thesis entitled
«Development of a radiopharmaceutical based on Lu-177 labelled elagolix for therapy and diagnosis», submitted by **Gurin Andrey Nikolaevich**
for PhD Degree in 6D060600 – «Chemistry»

Every year there are novel approaches to the therapy of cancerous tumors. In recent years, drugs have been used to target cancer cells. Targeting helps to get rid of various cancers, including breast cancer.

Radionuclide therapy is a modern technique, the principle of which is the introduction into the human body of special medications that contain radionuclides. Such pharmaceutical preparations go directly to the lesion sites, due to which the irradiation is of a targeted nature (it does not affect the entire body, but acts specifically on oncological foci). A unique achievement of radionuclide therapy is the radiopharmaceutical ^{177}Lutetium. This medication had been developed for the treatment of severe prostate cancer, destruction of neuroendocrine neoplasms in the gastroenteropancreatic zone.

Actuality and practical importance of Thesis Research is determined by the need for creation of domestic pharmaceuticals, in particular radiopharmaceuticals, for the diagnosis and treatment of breast cancer; as well as the need to deepen and expand theoretical concepts related to solving the problems of studying the processes of obtaining ^{177}Lu with high and appropriate specific activity, labeling DOTAELA ^{177}Lu, developing a technology for obtaining a chelate complex ^{177}Lu-DOTAELA that meets the requirements of a pharmaceutical.

The Thesis Research was performed and supported within the framework of the grant funding project of MES of Republic of Kazakhstan AP 05134384 "Determination of the optimal technological parameters for preparation of a novel radiopharmaceutical for diagnosis and therapy of thrice-negative breast cancer (TNBC) with an elagolix-177Lu of antagonistic mechanism of action "(2018-2020).

The results received by a candidate for PhD Degree are following:

1) The conditions for the activation of ^{176}Lu by neutrons have been developed and ^{177}Lu with high and appropriate specific activity has been obtained;

2) The optimal technological parameters for the synthesis of the DOTAELA as ligand and the ^{177}Lu-DOTAELA chelate complex have been developed;

3) Methods of analytical control over the progress of the obtaining process and the quality of the ^{177}Lu-DOTAELA radiopharmaceutical have been developed;

4) A technological scheme for obtaining a radiopharmaceutical ^{177}Lu-DOTAELA with a radiochemical purity of more than 95% has been developed;

5) A draft Specification for a novel radiopharmaceutical 177Lu-DOTAELA has been elaborated.

Presented in the Thesis Research Gurin A.N. the results are **reliable**, since they were obtained using modern equipment. The scientific results obtained by the applicant were obtained by summarizing a large number of their own experimental and available literature data. The conclusions formulated in the Thesis are substantiated, correct and logically follow from the content of the Research.

Result 1 is novel, since the activation of ^{176}Lu by neutrons with obtaining ^{177}Lu with high and proper specific activity was carried out at the Institute of Nuclear Physics of the Ministry of Education and Science of the Republic of Kazakhstan, Almaty, and the parameters of the technological stages of obtaining ^{177}Lu for medical purposes were determined;

Result 2 is novel, since the author uses a wide range of modern physical methods of analysis to select the optimal technological parameters for the synthesis of the DOTAELA ligand and the ^{177}Lu-DOTAELA chelate complex;

Result 3 is novel, since the author proposes optimal analytical methods with a detailed description of the methods to control the progress of the production process and the quality of the ^{177}Lu-DOTAELA radiopharmaceutical;

Result 4 is novel, since the author has obtained a radiopharmaceutical 177Lu-DOTAELA with a chemical purity of more than 95%, suitable for biotesting as a diagnostic and antitumor drug for triple negative breast cancer. A technological scheme for obtaining a radiopharmaceutical ^{177}Lu-DOTAELA is proposed.

Result 5 is novel, since the author, based on the results obtained, has developed a draft Specification for a novel radiopharmaceutical ^{177}Lu-DOTAELA.

The scientific results are characterized by high internal unity, since they were obtained when the main goal of the study was achieved, followed by the development of a potential radiopharmaceutical for the diagnosis and treatment of triple negative hormone-sensitive breast cancer with DOTAELA radiolabeling with the ^{177}Lu isotope, by consistently solving experimental technological problems, problems of drug quality control.

The results obtained by the applicant in the aggregate represent a scientific qualified work, in which scientifically grounded technical developments have been carried out, providing a solution to an important **urgent problem** of a novel radiopharmaceutical ^{177}Lu-DOTAELA creating for therapy and diagnosis of triple negative breast cancer.

The **results** obtained **should be used**:

- to carry out extended biological research developed by 177Lu-DOTAELA in order to create a drug for it for the diagnosis and treatment of triple-negative breast cancer;
- for the development of technological regulations for obtaining medicinal radio preparations and their temporary pharmacopoeial monographs;
- for textbooks on radiochemistry, pharmaceutical chemistry.

The **main provisions** of the Thesis Research are published in 5 scientific articles, 2 of which with an impact factor (Scopus) and 1 article in Medical Physics; abstracts of 5 reports at international conferences and 1 Patent PK for a utility model.

There are some **questions and remarks** to the author:

1. It is not clear from the text of the Thesis whether the DOTAELA ligand was obtained by the author for the first time, or was it provided by the University of Oslo? If NOVEL, why is there no evidence of its structure. If "no", why is there no link to the publication?
2. The author does not quite correctly use the term "radio purity" in the paper chromatography technique developed by the author.
3. Figure 27. The structural formula of the chelate complex is shown incorrectly.
4. Why did not the author protect the ^{177}Lu-DOTAELA preparation itself? The term of protection of the priority of the patent for a utility model "Method for radiochemical labeling of an organic compound with the lutetium-177 isotope" is almost expiring. Are patent protection proceedings carried out? If "yes", what is the "coverage" of the countries?
5. There are misprints and unsuccessful expressions in the text of the Thesis. Separate claims to the author for a huge number of NORMATIVE REFERENCES and DESIGNATIONS AND ABBREVIATIONS (some are used once in the text and are completely inappropriate as RK or USA). There is negligence in writing formulas, equations, etc.

However, the remarks made do not diminish the merits of the Thesis Research performed at a high professional level.

The Thesis Research "Development of a radiopharmaceutical based on Lu-177 labelled elagolix for therapy and diagnosis" in terms of relevance, scientific novelty, volume of results obtained, theoretical and practical significance **meets the requirements** of Sec. 2, 5, 6 of the "Rules for awarding scientific degrees" of the Committee for Control in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan for a comprehensive study of the process of

obtaining a radiopharmaceutical, starting the synthesis of the ^{177}Lu isotope and its purification, the DOTAELA ligand, labeling the latter with ^{177}Lu, and bringing the chelate complex ^{177}Lu-DOTAELA to a purity suitable for biological testing of the composition, as well as the development of a draft Specification for a novel radiopharmaceutical ^{177}Lu-DOTAELA - a candidate for a drug for diagnosing the treatment of triple-negative breast cancer, and its author, **Gurin Andrey Nikolaevich**, is worthy of being awarded a doctoral degree philosophy PhD in the specialty 6D060600 - "Chemistry".

Dr. Yu Valentina K.
Full Professor
Principal Scientist of Lab. Medicinal Synthetic and Natural Compounds Chemistry,
JSC "Institute of Chemical Sciences after named A.B.Bekturov"

November 23, 2020

I certify the signature of Full professor, Dr. Yu Valentina K.:

Scientific Secretary, candidate of Chem.Sci. Khakimbolatova K.Kh.