Cyclotron project of the Institute for Nuclear Research and Nuclear Energy

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Abstract. We present the cyclotron project of the Institute for Nuclear Research and Nuclear Energy which aims to centralize national the production of radioisotopes and radiopharmaceuticals and to provide opportunities for interdisciplinary research and education in the fields of Physics, Chemistry, Biology and Nuclear Energy. The human resources needed for the successful operation of the production program of the centre are also described in this article. An account of the ongoing research related to the radiation protection and radiation shielding of the cyclotron is made.

1. Introduction

Each country with ambitions to develop and sustain nuclear physics and nuclear energy shall establish its own national nuclear research facilities for basic training and education of the new generations of researches and engineers needed for the successful development of science and industry. In the last two decades many countries have decided to established nuclear physics centres based on a cyclotron accelerator. Such centres have been constructed at: the Laboratori Nazionali di Legnaro, INFN, Italy [1]; CYclotron pour la ReCherche et IEnseignement of the Institut Pluridisciplinaire Hubert Curien in Strasbourg, France [2]; Institute of Radiopharmaceutical Cancer Research of Helmholtz-Zentrum Dresden Rossendorf, Germany [3]; iTemba lab, South Africa [4]; TRIUMF Canada [5]; China Institute of Atomic Energy [6] etc. The programs of many of the new centres combine nuclear physics and applied research with production of radioisotopes and radiopharmaceuticals for the nuclear medicine. The development of new radiopharmaceuticals and their use in preclinical imaging is one of the major activities of the new centres. Depending on the characteristics of the radioisotopes used, the radiopharmaceuticals can be applied for diagnostics, therapy and theranostics. The role of the radiopharmaceuticals for targeted therapy and their market share are expected to rise significantly within the next ten years.
The history of radioisotopes and pharmaceuticals production in Bulgaria is related to the history of the research reactor IRT 2000. IRT 2000 is the first and still the only Bulgarian research nuclear facility. The reactor worked for decades under the operation of INRNE-BAS. Unfortunately it was stopped in 1989 and since then there is no operational nuclear research facility in Bulgaria, neither a nuclear reactor, nor an accelerator facility. Most of the colleagues which used to work at the Research reactor are retired and Bulgaria is going to lose the knowledge in this field.

When the research reactor was working, different types of radioisotopes were produced for nuclear medicine for all oncological centers in the country and for the industry. Moreover, eight different types of cold technetium kits were developed, licensed for medical use, produced at INRNE-BAS and supplied to the hospitals in Bulgaria: DTPA and DMSA - for kidney diagnosis (to identify various kidney diseases such as renal stones, cysts, tumors, etc.); Glucoheptonat – for visualization and evaluation of renal perfusion; MDP and HEDP - to follow the progression of some bone changes, trauma recovery, etc.; Phytat – to detect cutaneous malignant melanoma and often associated with it thyroid cancer; MDP-RBC - angiographic examinations; DMSA – V- for detection of primary and metastatic prostate, breast, lung and bone cancer.

An illustration of the usage of HEPD, produced at INRNE-BAS for the purpose of bone scintigraphy is shown in Figure 1.

![Bone scintigraphy by Tc99m – HEDP. A front image of the patient is shown on the left side of the picture. A back image of the patient is shown on the right side of the picture. Dark spots indicate malignant cancer metastases.](image)

**Figure 1.** Bone scintigraphy by Tc99m – HEDP. A front image of the patient is shown on the left side of the picture. A back image of the patient is shown on the right side of the picture. Dark spots indicate malignant cancer metastases.

The Cyclotron project at INRNE-BAS started in 2012 as an initiative of the Council of Ministers of the Republic of Bulgaria. Since 2014 the project is a part of the updated "Bulgarian National Roadmap for Research Infrastructure”. The project envisions a new cyclotron laboratory as a part of INRNE-BAS consisting of: a sector for the production of $^{18}$F-FDG, called Fluorodeoxyglucose, and in future, of other radiopharmaceuticals that meets the regulatory requirements in the field of radiation safety and GMP (good manufacturing practices) in the pharmaceutical industry; a bunker with a TR-24 cyclotron; a sector for
applied research and development in radiopharmacy; a sector for small animals imaging; a vivarium for housing the small animals; service and office areas; conference room etc..

The cyclotron laboratory of INRNE-BAS is the only planned for construction nuclear research infrastructure in the country. With the new facility we will restart our experimental research program not only in the field of nuclear physics, but also in many interdisciplinary fields related to nuclear physics and nuclear medicine [7,8].

In the next twenty years, with the TR24 cyclotron [8], INRNE-BAS will be able to produce a wide range of radioisotopes with applications in medicine with a relatively low initial investment and moderate maintenance costs.

2. Human resources

The successful production of radioisotopes and radiopharmaceuticals depends on the staff involved. Therefore, sufficient and qualified personnel are needed. In accordance with the Rules on Medicinal Products in the European Union, and in particular in Volume IV of the European Guidelines for Good Manufacturing Practice – Medicinal Products for Human and Veterinary Use, it is stated that management must define an organizational structure and present it in an organigram. The organigram must clearly show the management hierarchy and the links between the heads of production departments, quality control departments and the position of the qualified person. Figure 2 shows the organizational structure of a radiopharmaceutical production company.

![Organizational structure of a radiopharmaceutical production company](image.png)

Figure 2. Organizational structure of a radiopharmaceutical production company

For the purposes of this paper, only the specific personnel needed to support the GMP production of radiopharmaceuticals at the National Cyclotron Center at INRNE-BAS will be considered. In order for such a facility to be established and successfully operated a team of mechanical engineers, electrical engineers, physicists and technicians is also required to ensure the safe operation of the cyclotron and its maintenance. Furthermore, a team of logistics and sales specialists to analyze the market, develop and implement marketing and advertising policies to promote the products and services offered by the company, as well as to conduct trading activities is also needed. However, it is essential to determine key
management personnel, including the head of the production department, the head of the quality control department and one or more qualified persons. The legislation explicitly states the obligations and requirements for occupying these positions.

The role of the qualified person is most crucial. This position must be taken by a full-time worker who meets the following requirements: to be a Master of Medicine, Pharmacy, Chemistry, Biotechnology or Biology and to have at least two years of practical experience in pharmaceutical manufacturing and/or in the qualitative and quantitative analysis of medicinal products and active substances.

The educational course must include the following subjects: physics; general and inorganic chemistry; organic chemistry; analytical chemistry; pharmaceutical chemistry and analysis; general and applied biochemistry; physiology; microbiology; pharmacology; pharmaceutical technology; pharmacognosy; toxicology.

The next key position is the head of production. His/her main responsibilities include: approving instructions relating to manufacturing activities and ensuring their strict application; ensuring the conditions for production and storage of products in accordance with the approved documentation (technological regulation, written procedures and specifications); coordination and control of the evaluation and signing of the technological documentation by an authorized person; control of the adequacy of the technical support and maintenance of the premises and equipment and ensuring that the necessary validation is carried out; providing the necessary initial and subsequent theoretical and practical training for the department's employees.

In order to be able to fulfill his duties, the head of production must have: a Master's degree in Pharmacy, Chemistry or Biology; additionally recognized specialization in Radiobiology or Radiochemistry (for radiopharmaceuticals or for medicinal products subject to ionizing radiation); at least two years of practical experience in pharmaceutical manufacturing and qualification to work in environment with ionizing radiation.

The operational production of radiopharmaceuticals must be carried out in accordance with the regulatory requirements and rules for good manufacturing practice. Therefore, operators in the production department must have a university degree in Chemistry, Radiochemistry, Biology, Radiobiology or Pharmacy; practical experience in pharmaceutical manufacturing; hands-on experience in working with linear particle accelerators and qualification to work in environment with ionizing radiation.

The head of the quality control department also plays a key role in the organizational structure of the National Cyclotron Center at INRNE-BAS. The holder of this position must be a person with a Master's degree in Pharmacy, Chemistry or Biology and at least two years of practical experience in pharmaceutical production, as well as an additional recognized specialization in Radiobiology or Radiochemistry.

The main responsibilities of the head of the quality control department are related to the commitment to approve or reject the starting materials, packaging materials and intermediate, bulk and final products; to ensure that all necessary tests are carried out and batch documentation is evaluated; to verify and approve specifications, sampling instructions, test methods and other quality control procedures; to ensure validation of the analysis procedures and methodologies used; to provide the necessary initial and subsequent theoretical and practical training to the employees of the department.

The heads of the production department and the quality control department have some common responsibilities related to the design, implementation, monitoring and maintenance of the quality management system. These include the responsibility to approve
written procedures, technical documentation and amendments; to control production conditions; to maintain the necessary hygiene standards in the production and control rooms; to train staff; to approve and control suppliers of starting and packaging materials; to approve and control the manufacturers contracted for production and/or analysis; to control the storage conditions of starting and packaging materials and final products; to store batch documentation; to monitor compliance with the requirements for good manufacturing practice; to carry out periodic inspections and sampling to control factors affecting the quality of medicinal products.

According to the regulatory requirements, each undertaking that operates a nuclear facility is required to designate a radiation protection officer who shall be entrusted to undertake functions and obligations in respect of radiation protection supervision and to perform relevant radiation protection tasks.

3. Present activities

One of the ongoing activities related to the National Cyclotron Centre is conducting Monte Carlo simulations. The aim is to optimize and analyze the site’s radiation protection, i.e. the cyclotron bunker and the local target shielding. For the purpose, we chose to employ the FLUKA code [9, 10] since it is known to be reliable for radiation shielding analysis of low and high energy accelerators [11-13]. In this task, many factors have to be considered, as the cyclotron workload, target, concrete for the bunker walls and the material of the local target shielding.

The first objective of the future cyclotron centre is the production of $^{18}$F since, in Bulgaria, the number of nuclear imaging procedures in oncology using fluorodeoxyglucose ($^{18}$F-FDG) keeps increasing over the last 10 years [14]. The radionuclide $^{18}$F is the product of (p, n) reaction on an $^{18}$O enriched H$_2$O target. The irradiation of the target produces secondary particles (neutrons and g-rays) which in turn activate the construction materials of the bunker walls. Some of the products of this activation are long-lived radioactive nuclides which have to be taken into account when managing the radioactive waste generated as a result of the cyclotron operation. In our previous studies [15] we have explored the possibility of using local shielding around the target for production of $^{18}$F. Our first results [15] have shown that a local target shielding can be useful in limiting the spatial distribution of the secondary particles, which in turn leads to lower activation of the bunker walls. Hence, we decided to extend our studies in two directions - optimization of the local target shielding and radiation protection analysis of the cyclotron bunker. For our simulations we use two different model systems – a simplified spherical geometry and a full-scale bunker (Figure 3).

![Figure 3](image-url)
The simplified spherical geometry is useful when a simple physical picture is needed. We employ the spherical geometry in our studies for the activation of the concrete walls and for optimization of the local target shielding. This geometry has three main parts. The first part is an air-filled sphere. A source of secondary neutrons is positioned in its centre. The other two parts are concentric spherical shells representing, respectively, the local target shielding and the concrete bunker wall. Our neutron source replicates the secondary neutrons emitted during irradiation of a target for production of $^{18}$F. Using such a source we improve substantially the statistical error of our results for the activation of the bunker walls and the local shielding. Our preliminary results for local target shielding made of borated polyethylene with a thickness of 5 cm [16], 10 cm and 20 cm [17] are for the activation of the spherical concrete shell and for the distribution of the secondary neutrons in the geometry studied [16,17]. Overall, our results in this geometry show that 20 cm of borated polyethylene reduces considerably the neutron fluence in the bunker walls and the activity of the generated radionuclides. In our preliminary studies, we did not consider impurities in the concrete like Eu, Cs, Co, Sc, Ta which have very low concentration, of the order of particles per million, but upon neutron irradiation generate long-lived radionuclides increasing substantially the activity and volume of the radioactive waste that will be produced upon decommissioning. For our most recent simulations in the spherical geometry, we took into account these impurities in two types of concrete - ordinary concrete with Portland cement (CPC) and low activation concrete (LAC) with limestone, and explored the effect of 5 local shielding materials. First, we chose classical radiation shielding materials as paraffin and borated polyethylene. We also considered shielding materials containing high Z elements as Fe and Mn. These materials are mixtures of paraffin and ferro-boron (M1), paraffin and carbon steel (M2), and a sandwich structure comprising of a layer of paraffin and a layer of the mixture M1. They were found to be ineffective since they become activated, which increases the ambient dose equivalent rates for the personnel working around the target. Another issue is that the shielding itself becomes an additional radioactive waste. The classical shielding materials as paraffin and borated polyethylene are a better good choice for local shielding since their activation is much lower than the high Z materials. The gamma ambient dose equivalent inside the bunker, after 20 years of cyclotron operation, is lowered 10 to 15 times when local target shielding of paraffin or borated polyethylene is applied. Our studies on the effect of changing CPC with LAC show that this leads to an additional 10 times decrease of the gamma ambient dose equivalent inside the bunker.

In the full-scale bunker model, we studied the distribution of the neutron and the gamma-ray ambient equivalent dose rates inside the bunker and the respective attenuation profiles inside the walls. Our results show that a 250 cm thick outer wall is enough to provide radiation protection fulfilling the legal radiation safety requirements. The values of the gamma and the neutron ambient equivalent dose rates outside the bunker are equal or lower compared to the value of the local (Sofia, Bulgaria) background radiation dose rate – 0.1 to 0.2 μSv/h.

With time, the cyclotron centre in Sofia will develop a fundamental research program in the fields of phase transitions in nuclear physics [18], chirality in nuclei [19,20] and nuclear structure of light nuclei [21].

4. Conclusions
Initially, the main activities of the centre will be in the field of radiopharmacy, radiobiology, radiochemistry, radiation protection and dosimetry. The education and training of physicists,
chemists, pharmacists and biologists for radioisotopes production, radiochemistry, quality control of radiopharmaceuticals and their uses in medical imaging, as well as training of specialist for the nuclear energy industry will have a central role in the development of the centre. Most of the training and education activities will be carried out by involving the students in the ongoing research projects of the centre.

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