ISBN: 978-3-95450-248-6 ISSN: 2673-5490 doi: 10.18429/JACoW-IPAC2025-TUPB047

CERN-MEDICIS: A UNIQUE FACILITY FOR THE PRODUCTION OF RADIONUCLIDES FOR MEDICAL RESEARCH

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Abstract

The MEDICIS facility is a unique facility located at CERN, dedicated to the production of non-conventional radionuclides for research and development in imaging, diagnostics and radiation therapy, and based on offline mass separation. It exploits a classified area for handling of highly radioactive open sources, a dedicated isotope separator beam line, a target irradiation station at the 1.4 GeV Proton Synchroton Booster (PSB) and receives activated targets from external institutes during CERN Long Shut-Downs. After collection, the batch is prepared to be dispatched to a research center. Since its commissioning in December 2017, the facility has provided novel radionuclides such as Ba-128, Tb-155, Sm-153, Tm-165 Ra-224/Pb-212 and Ra-225/Ac-225 with high specific activity, some for the first time, to research institutes part of the collaboration. CERN-MEDICIS has advanced significantly to reach mature processes to translate into clinical application for the most promising radionuclides. The following gives a review of MEDICIS operation and highlights since 2023.

INTRODUCTION

The CERN-MEDICIS facility provides high-purity radionuclides for medical research, by mass separation of isotopes produced from irradiation of thick targets with 1.4GeV protons from CERN's Proton Synchrotron Booster, or externally irradiated sources. Since its first beam commissioning in December 2017, some highlights and achievements of the facility have been reported in [1] and [2]. Both references showcase the growing activity deliveries, efficiencies obtained and number of batches delivered throughout the years, known as Key Performance Indicators (KPI) and further detailed in [3]. The facility has achieved its nominal operational and technical performance targets, enabling a mature and reproducible process. This review aims at giving an update on the facility's performances since 2023, summarized in Table 1. It gives insights for 2025, 8 years after producing its first radioactive ion beam in December 2017.

FACILITY OUTPUTS

In 2023 and 2024, CERN-MEDICIS entered into its respective fifth and sixth year of operation with a high demand from the external partners and collaborating institutes across Europe and Asia. During that time, the facility was operated with the mindset of re-using target units and target material in view of optimizing their use and minimizing the radioactive waste produced.

A record total activity of 3.8 GBq was collected and delivered for the biomedical program in 2023 and 2 GBq in 2024, reflecting on the progress of KPI #1 linked to the collection activity and efficiency. During the past two years, MEDICIS has been strongly solicited by its biomedical partner institutes in the production of alpha emitters such as Ac-225. Ac-225 is produced at MEDICIS either directly or collected via the decay of its parent radionuclide, Ra-225 [4]. A record collection efficiency of 72 % has been obtained in 2024 for Ra-225. This result is higher than the historical collection efficiency of Ra-225 at ISOLDE (63 %) [5], and more recent molecular developments [6]. The collection efficiency expresses the ratio between the activity obtained at the end of the collection over the activity available at start, produced inside the target material and estimated using FLUKA [7]. Figure 1 shows the efficiencies obtained in 2023 and 2024 from 4 different targets, with a visible effect of the multiple irradiation on the efficiency performances. The figure shows an average efficiency of 40 % ± 30 % can be obtained. The decreased efficiency can be explained by the sintering of the target material over multiple heating/cooling cycles, or ion source decreased performances [8].

In order to support the increasing demands on medically relevant radium isotopes, laser ion source developments have been initiated and the double collection possibility was implemented, and successfully used to simultaneously collect the two neighboring mass nuclides Ra-224 and Ra-225 on two different collection foils [2]. This has been combined with radiochemistry developments at MEDICIS and in collaboration with Hevesy Lab in DTU in Denmark [9]. A Ra-224/Pb-212 generator has been further developed.

Two other radionuclides have been collected in parallel: Tm-165 and Tm-167. Tm-165 is a generator for the pure auger emitter Er-165. It has been shipped to Hevesy Lab in the framework of PRISMAP [10], by means of a dedicated plane that delivered this 30-hour-half-life radionuclide within 4 hours door-to-door, limiting the decay of the product upon arrival. At the same time, Tm-167 was delivered to two others partners institutes, notably the Paul Scherrer Institute (PSI) [11, 12] in Switzerland and to the National Physics Laboratory (NPL) [13, 14] in the United-Kingdom, maximizing the output of the facility (KPI #3 and #4).

The Lausanne University Hospital (CHUV) [15] in Switzerland is assessing the possibility to use the in-vivo

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Table 1: Summary of Radionuclide Production at MEDICIS Since 2023

Year	Produced Isotopes	Total collected activity (MBq)	Maximum efficiency (%)	Number of batches
2023	Sc-43,44g/m,46,47; Ba-128; Cs-129; Tb-149,155; Sm-153; Tm-165,167; Ra-224,225/Ac-225	3.8 GBq	41 % (Ra-225)	25
2024	K-43; Sc-43,44g/m,47; Cu-67; Tb-149,155; Tm-165; Ra-224,225/Ac-225	2.0 GBq	72 % (Ra-225)	18

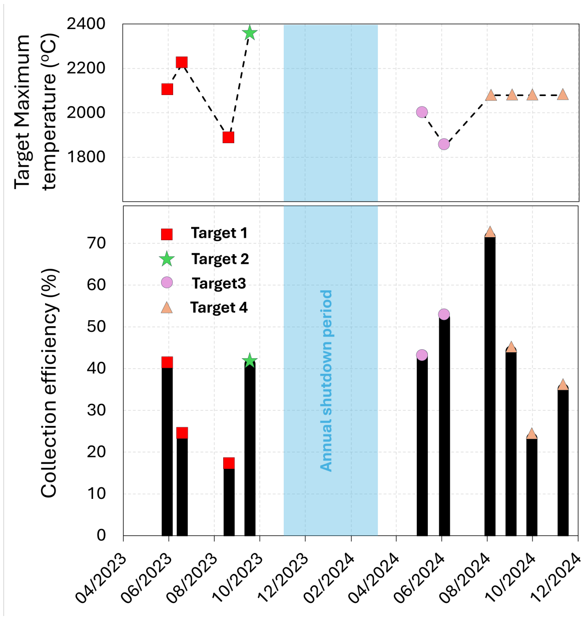

Figure 1: Ra-225 collection efficiency evolution since 2023. The maximum target temperature reached during the collection is given by the upper graph.

generator Ba-128/Cs-128 as a new calcium surrogate for the treatment of osteosarcoma. Several batches have been delivered to CHUV since the project was accepted by the collaboration in 2021. It has been shown that Ba-128/Cs-128 accumulates in the bone but also significantly and undesirably in the kidneys. In order to assess if this accumulation is coming from Ba-128 itself, or from its decay product Cs-128, MEDICIS provided Cs-129 to show that the strong uptake in the kidneys is due to direct Cs. MEDICIS collected a record activity of 1.3 GBq of Ba-128 and Cs-129 in 2023 in a single batch, largely fulfilling the activity needed by CHUV to complete the first part of this study. The study will be completed with additional batches of Ba-128 that will be provided in the coming years.

Others radionuclides such as K-43, Sc-43/44, Eu-145, Gd-149, Tb-155 and Tm-165 have been provided with an activity per batch up to 100 MBq to our external partner institutes and PRISMAP users, used for research and preclinical biomedical projects.

RECENT DEVELOPMENTS

Campaigns of release studies are conducted since 2023 at CERN-MEDICIS to investigate the thermal release of refractory elements such as Scandium (Sc) and Terbium (Tb). It is performed by mean of a dedicated set-up where an irradiated sampled is placed in a target and ion source system (TISS), itself coupled to a dedicated pumpstand, as shown in Fig. 2. The target is heated up to reproduce the conditions of a real MEDICIS collection. A high-purity germanium (HPGe) gamma-spectrometer is used for the assessment of the remaining activity in the target, at different temperatures of the unit. The recent data provide valuable insights for ISOL facilities, radiation protection matters in fire risk assessments, and theoretical model development [16].

CERN-MEDICIS has the capacity to provide radiochemistry processing on the collected samples. Recently, for the production of the new therapeutic agent Pb-212 for targeted alpha therapy, two different types of Ra-224/Pb-212 generators were developed based on several collections of Ra-224 performed at MEDICIS. Ra-224/Pb-212 generators were based on i) collection of emanated Rn gas from a radium source and ii) chromatographic separation of Ra & Pb. The first type of generator was successfully tested for high purity elutions with starting activity up to 80 MBq. The average efficiency of the generator was found to be 37 %. A similar generator was dispatched to Hevesy Lab, for further studies including radiolabelling and complex stability in mouse serum.

Molecular ion beam and target material developments for medical Sc radionuclide mass separation led to successful extraction and collection of Sc-44m/g, Sc-46 and Sc-47 with high radiochemical purities from a ^{nat}TiC (average grain size of 1-2 μm) target. The Sc radionuclides were extracted and mass separated as molecular difluoride and monofluoride ion beams with collection efficiency of more than 1 %. A two-step laser resonance ionization scheme was used at the dedicated laser laboratory MELISSA [17] to obtain $^{45}Sc^+$, $^{46}Sc^+$ and $^{47}Sc^+$ ion beams from ^{nat}V foil target for the first time at MEDICIS [18].

As the collection efficiencies and collected activities per batch at CERN-MEDICIS are significantly increasing (KPI # 1), the post-collection radiochemistry procedures also require development. The mass-separated radionuclides are collected on Zn-, Cu- or Al-covered gold foils or on salt-covered Al foils. The automation of radiochemical separation procedures from collection materials and isobaric contaminants helps to reduce the ionizing radiation exposure to the operators and improve reproducibility and sepa-

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ration efficiency. Additionally, it reduces radioactive waste and contamination risks and is a step towards its use for chemical research. A particular interest was shown for Sc radionuclides, where implantation of $^{47}ScF_2^+$ molecular beam was accompanied by isobaric Ti isotopes with a ratio of 1 to 6000 atoms/s respectively [19]. Collaborating with the University of Latvia, an in-house, semi-automated extraction chromatography setup with N,N,N',N'-tetrakis-2-ethylhexyldiglycolamide (DGA Resin, Branched, TrisKem International) was established [18]. The simplified procedure only requires the operator to place the collection foil with the sample in the system, and supervise the separation. The radioactive sample in liquid form, ready for radiolabeling tests, could be obtained within 2.5–3.0 mL solution. To remove high quantity metallic isobaric contaminants, a prototype electrochemical separation method from a dissolved sample was also developed, depositing contaminant ions such as V^{2+}, Ti^{3+} on the electrode and leaving Sc^{3+} ions in the solution for subsequent extraction chromatography [20].

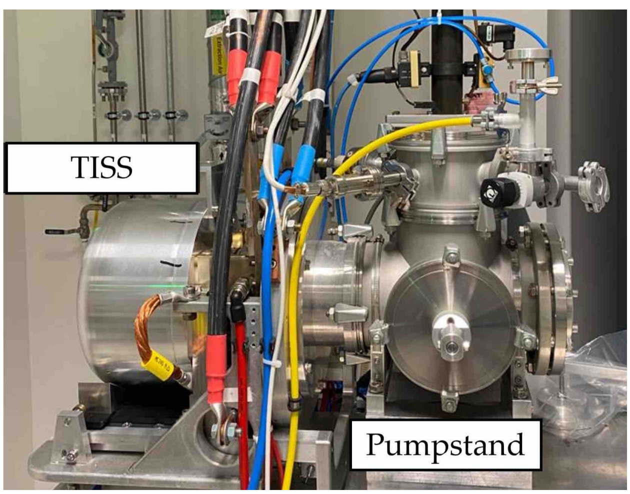

Figure 2: Picture of the setup used for the release studies of Sc and Tb in real MEDICIS operation conditions [19].

During the years 2023 and 2024, new developments have been performed in the MELISSA laser laboratory [17]. In particular, the development of an innovative laser source, based on the stimulated Raman scattering process [21], has been ongoing, in order to extend the accessible wavelength range of the laser system. A z-fold cavity based on a diamond crystal as the Raman medium has been designed and tested for the first time during a collection of Ra-225. The first step of the Ra-225 laser ionization scheme used requires a wavelength of 482.72 nm [22]. This wavelength is beyond the range of the intra-cavity doubled Ti:Sa lasers used in the MELISSA laboratory and therefore required an alternative generation route. The new Raman laser design was therefore tested with a pump from the Ti:Sa laser at 427.70 nm, leading to a second order stoke shift to 482.72 nm (first Stokes = 453.55 nm). The proof of principle during a collection of Ra-225 demonstrated an improvement of +16 % of instantaneous ionization efficiency with low power of 1 mW. The final design of the diamond-based Raman laser is currently assembled and will be implemented during the second semester of 2025, in order to improve the efficiency of the collections of Ra-225 reported in Fig. 1. In parallel, a new laser scheme has been developed for the ionization of Eu, recently added to the MEDICIS portfolio, with the collection of Eu-145. An new laser scheme was found using only solid-state Ti:Sa lasers and subsequent second harmonic generation, as only these lasers are available at MELISSA. Multiple auto-ionizing states were found in the frequency-doubled-Ti:Sa range, and the best scheme was used during a collection in 2024, with a final total efficiency (including diffusion, effusion, ionization and transport efficiencies) of 1.85 % for Eu-145. Further analysis and tests are ongoing to optimize the collection of Eu in the coming years.

PERSPECTIVES FOR 2025 AND BEYOND

After a few months of maintenance and upgrades, MEDICIS restarted operation in March 2025 with a rich scientific program. Ra-224 and Ra-225 are still highly requested with the addition of Ra-223. Additional requests for the newly developed Eu-145 beam are also amongst the list following the successful first collection supported by MELISSA, triggering a new assessment of nuclear data of high interest at NPL in London. A newly approved MEDICIS project, notably including Ac-226, will be a new addition to the radionuclides to be collected this year with proton irradiation at CERN. External sources of Sm-153 are foreseen for mass separation from their enriched Sm-152 target material for medical applications, and approved by the CERN Council for first clinical trials of MEDICIS' radionuclides at the hospital of Heidelberg, in Germany. Machine development will be conducted around Sc and Tb production optimization and Cu-67 production development, as well as in the investigation of nanostructured target materials, for better release of refractory elements. The release studies recently initiated are providing new data on the behavior of radionuclides under extreme temperature conditions and will continue to be further conducted as part of MEDICIS' experimental research and development program.

ACKNOWLEDGMENTS

The authors would like to thank the collaborators, partners and the groups involved in the safety, the development and the operation of the facility such as BE-CEM, BE-OP, EN-CV, EN-DHO, EN-HE, EN-MME, HSE-RP, SY-BI, SY-EPC, SY-STI, TE-VSC. We wish to thank all the members of the CERN-MEDICIS collaboration for their continuous support, advice and commitment.

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No.101008571 (PRISMAP), No. 861198 (MSCA ITN LISA) and the CERN Knowledge Transfer fund, Switzerland.

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