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Comparison of Two Synthesis Methods for ^{68}Ga -PSMA-11

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Greg Walker¹, Karen Allen¹

Background

Illuccix® (Kit for Preparation of ^{68}Ga Glu-urea-Lys(ahx)-hbed-CC Injection; also known as gozetotide) is approved for use in Australia as well as the US, Canada, Brazil, and select European countries, as a radioactive diagnostic agent indicated for use with positron emission tomography (PET) imaging combined with computerised tomography (CT) in patients with prostate cancer who are at risk of metastasis and who are suitable for initial definitive therapy, who have suspected recurrence based on elevated serum prostate specific antigen (PSA) level, and for the selection of patients with metastatic prostate cancer in whom lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated.¹ ^{68}Ga -PSMA-11 targets prostate-specific membrane antigen (PSMA), a cell membrane protein expressed on >90% of prostate cancer cells.²

Illuccix is supplied to allow for direct preparation with eluate from any appropriate ^{68}Ga source. Two kits are available (Configuration A and Configuration B), which are recommended for use with Good Manufacturing Practice (GMP) grade Eckert & Ziegler Gallia-Pharm® (“E&Z”) and IRE EliT Galli Eo™ (“IRE”) $^{68}\text{Ge}/^{68}\text{Ga}$ generators, respectively.

Configuration A can also be used with cyclotron-produced ^{68}Ga -Chloride₃ ($^{68}\text{GaCl}_3$).

^{68}Ga -PSMA-11 may also be prepared using various proprietary synthesis systems (Modular-Lab eazy, Eckert & Ziegler GmbH, Berlin), which require a protracted multi-step setup process, along with the fractionation and freeze storage of the associated peptide. The requirements for quality control of cold fractionated batches and individual synthesis runs include High Performance Liquid Chromatography (HPLC) in addition to Thin Layer Chromatography (TLC). Only TLC is required for Illuccix preparation.

In all cases, between 1 and 4 patient doses are produced per synthesis run, and this is dependent on the age of the Germanium-Gallium generator, normally up to 12 months from the date of manufacture. ^{68}Ge , the parent isotope, decays with a half-life of 271 days, and ^{68}Ga , 67.6 minutes.

In Australia, the Eckert & Ziegler IGG100 generator and multi-elution tool is commonly available. Demonstrating that the IGG100 generator can also be used with Illuccix kits successfully may support implementation of Illuccix into established routine without requiring a new ^{68}Ga source. Accordingly, we present results from a study to demonstrate feasibility of ^{68}Ga -PSMA-11 production using Eckert & Ziegler IGG100 generators.

We present comparisons of Illuccix and Modular-Lab eazy preparation methods for Australian sites using these 2 methods, with particular attention to preparation time, overall procedure time, operator radiation dose and general utility.

Methods

For each of 4 synthesis runs of both Illuccix (Telix Pharmaceuticals) and Modular-Lab eazy (Eckert & Ziegler Medical, Bayer) systems, the following parameters were recorded:

- Time elapsed using a stopwatch for seven protocol steps: preparation, generator elution, labelling / synthesis, calibration, quality control, results processing, documentation and shutdown
- Total time for all additional steps required to order, prepare, store and manage product batches prior to synthesis and use
- Whole body radiation dose, measured at the operator's chest level, using a personal SiPM radiation monitor (Radacode 102, Cyprus, 2024)

Whole-body radiation dose measurements were recorded in microSievert (mSv) units and included background radiation exposure. The radiation monitor was recently check-calibrated against an OSL dosimeter standard (Landauer

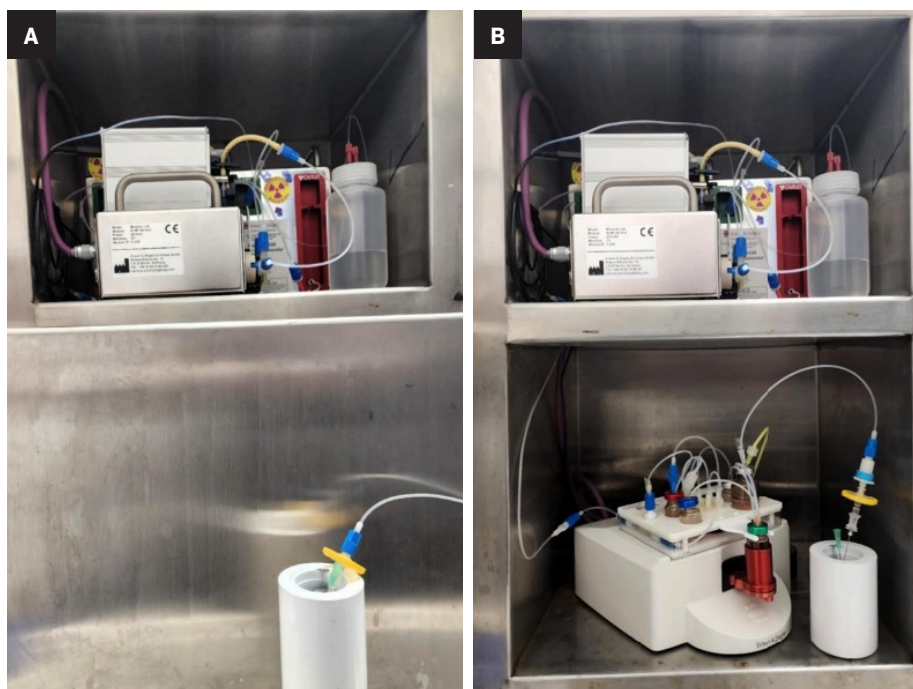


Figure 1. Generator housing configured for Modular-Lab easy (A), and Illucix (B). Upper chamber contains generators with pump and eluant reservoir. Lower section, synthesis unit and assembled cassette, and shielded ^{68}Ga -PSMA-11 vial containing peptide and buffer with direct connection to the generator

Inc., Glenwood IL, NVLAP accredited). Estimated annual radiation exposure was extrapolated, allowing for varying generator activity and yield. All recommended quality control procedures were followed, in accordance with the respective manufacturers' protocols. All synthesis runs were performed with consistent technique by a single, experienced operator to obviate inter-operator variability. The laboratory setup is depicted in Figure 1.

Modular-Lab easy procedure

The synthesis consumables were contained in the form of a partially assembled, sterilized plastic cassette containing various vials and interconnecting tubing, along with a separate reagent kit containing buffer, diluents, syringes, needles, vents, spikes and filters.

After the components were unpacked, a 60-step procedure followed to prepare the cassette for synthesis. A vial of pre-fractionated PSMA peptide was thawed from very deep freeze and added to the reaction vial in the cassette during the final stages.

The cassette was mounted on the synthesis unit, which controls the flow of generator eluate and reagents through the process, then the synthesis process initiated by software to control the generator peristaltic pump, sending Gallium-68 eluant to the cassette, and all of the subsequent transfers of reagents through the cassette.

Including the period of labelling in the heated reaction vial, and all associated reactions, transfers and filtering, the process lasted approximately 14 minutes.

On completion of the synthesis, the final product was measured for radioactive yield in a dose calibrator (CRC 55t-PET, Capintec Corporation, New Jersey), and samples prepared for both TLC and HPLC. There was some time overlap with these procedures; however, intravenous administration of the product to the patient could not occur until both were complete and the results deemed acceptable.

Illucix procedure

The 3 component vials of the Illucix Part A kit were stored at 4-8°C and prepared with aseptic technique, with the vial closures swabbed with alcohol.

Using sterile disposable syringe and non-metallic drawing spike, 5 mL of buffer solution was transferred to the vial containing lyophilized peptide, which was then connected directly to the generator pump line via a sterile 0.22 micron filter. An air vent was placed to equalize pressure during elution.

Generator elution was initiated via software controlling the peristaltic pump, to deliver 5 mL of eluant directly into the peptide / buffer vial within 3 minutes.

Radiolabelling was allowed to complete for 5-6 minutes, and then the product vial was removed for measurement, as described above, and a sample prepared for TLC.

Individual doses were then dispensed and administered intravenously to waiting patients in preparation for their PET/CT scan 60 minutes later.

Results

Illucix was found to be superior in terms of speed, ease of use and lower radiation dose to the operator, with higher product yield available for patient injection.

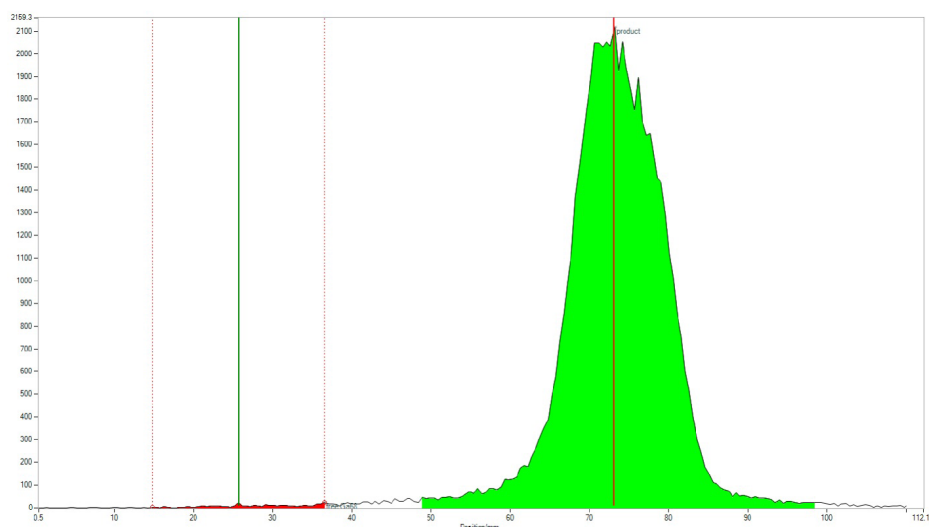


Figure 2. Results of typical Thin Layer Chromatography quality control, showing greater than 97% labelling efficiency for Illucix. Similar results were achieved with the Modular-Lab easy method.

Radiopharmaceutical quality

There was no discernible difference between methods in radiochemical purity of the end product (Figure 2). However, the more complex Modular-Lab easy procedure is subject to occasional failure to label, usually due to inconsistent setup or other untraceable problems.

Bulk batch preparation time

For Illucix, preparation involves ordering, receipt of shipments and basic stock control, with storage under normal refrigeration. Time taken in the aggregate to manage a batch of kits to service 60 patients is approximately 10 minutes.

In addition to the tasks required to manage described above, the Modular-Lab easy system requires a separate bulk peptide, which is stored under very deep freeze conditions. This is fractionated into multiple liquid aliquots ahead of use, with HPLC quality control performed on a sample of the “cold” peptide. The individual peptide doses are then refrozen until use, and expiry times monitored. For a batch of peptide to ultimately produce 60 patient doses, the preparation time totals 40 minutes. Time difference between systems: 30 minutes per batch.

Individual synthesis run time

The comparative durations for each component step are shown below. Illucix preparation is faster by an average of 25 minutes, with a time advantage in every step (Figure 3).

Decay losses

Radioactive decay of the final product can be considered to begin at the end point of the elution process, and for the purposes of measuring wastage of the available dose for patients, to end when the final QC step is complete. For the Modular-Lab easy cassette process, this time amounts to 30.5 minutes, and Illucix, 12.4 minutes. This time differential of 18 minutes results in a further 17% loss of final product activity, which in some scenarios could amount to an entire patient dose lost to decay.

Radiation

An increase in operator radiation dose measured at chest level of 1.9 mSv was observed as an average over four runs, with the Modular-Lab easy system giving the higher dose (Figure 3B). This is thought to be mainly due to the increased time handling QC samples, and the increased time spent exposed to background radiation in the laboratory.

An annualized dose estimation, as an example, for a single operator performing 5 runs per week over a 47-week working year might accumulate an additional dose of 450 mSv based on figures from the current study but rising to 800 or more if the initial higher activity of the generator at the beginning of its life is accounted for. The Eckert & Zeigler IGG100 generator used in this study contained 1850 MBq of ^{68}Ge at calibration, and only 570 at the time of the study. The eluate and product activities would have been proportionately higher earlier in the generator's life, resulting in the higher operator doses over a 12-month period.

Discussion

To our knowledge, this is the first study to assess feasibility of ^{68}Ga -PSMA-11 production using Eckert & Zeigler IGG100 generators with Illucix and Modular-Lab easy preparation methods for Australian sites. With workflow data, including preparation time, overall procedure time, operator radiation dose and general utility of both methods, we aim to provide Australian sites with data to choose ^{68}Ga -PSMA-11 preparation methods that best suit their needs.

The benefit in reduced operator time with Illucix demonstrated in this study is cumulative, and measurable, resulting in significant workflow efficiencies over periods of months and years. Training time will also be reduced, with only basic laboratory techniques required. Shorter time frames for the synthesis process will also mean increased product yield and the capacity for greater patient throughput.

The capital cost of the extra equipment required for the Modular-Lab easy method may also be an important consideration. This would include a deep freezer and HPLC unit. There are also many laboratory consumables involved: HPLC reagents, purified water, peptide vials, laboratory balance, pipettes, as well as maintenance and training costs.

Our study is in line with previous reports on cost savings seen in cold kits.^{3,4}

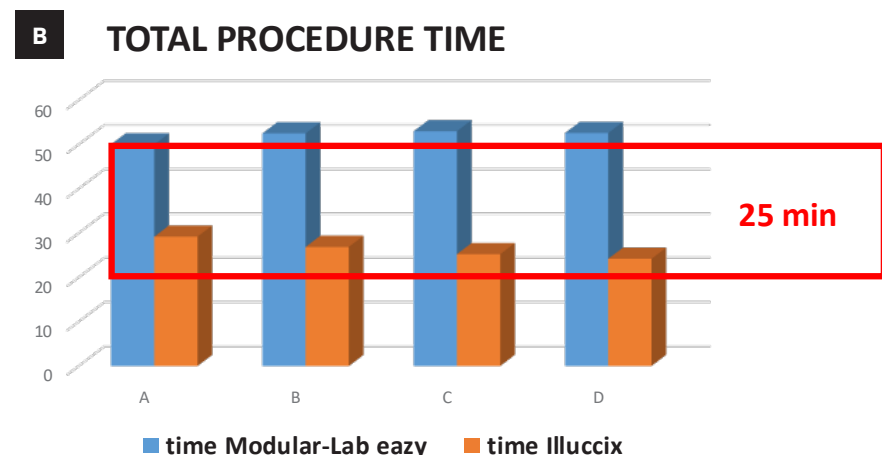
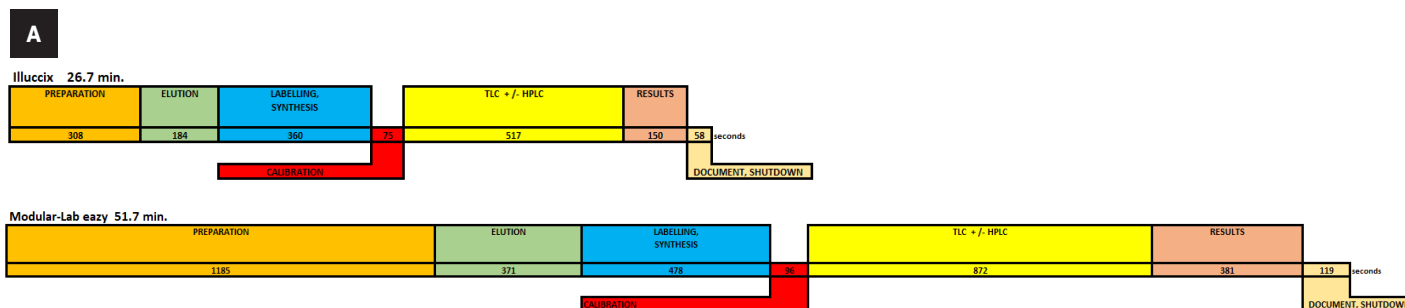


Figure 3. (A) Summary of differences in duration of labelling procedure. (B) Comparison of procedural timings for Illuccix, top, and Modular-Lab easy process, bottom, showing the longer duration for all steps in the Modular-Lab easy process.

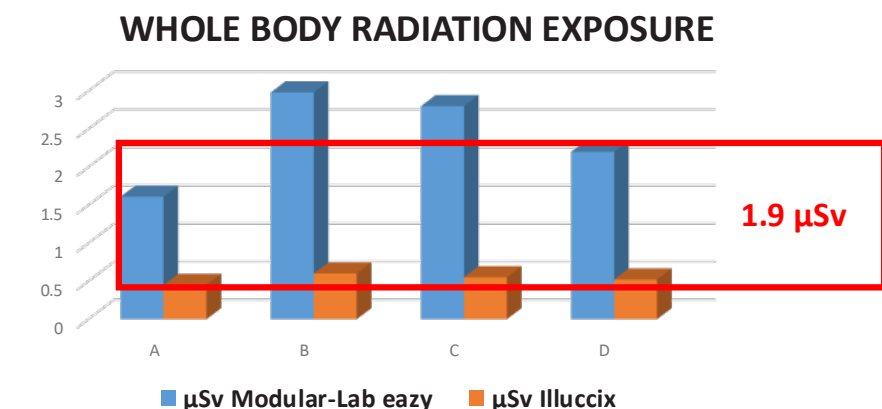


Figure 4. Summary of differences in whole-body radiation exposure over four runs.

One study found reduced sources of error, shorter synthesis time, cost savings in sense of avoiding need of expensive hardware (up to 70%), higher radiochemical yield, and purities >98% with cold kits.³ These studies point out that cold kits do not require any additional investment like hot cells, automated synthesis module, disposable cassettes, reagent kits, or heavy, time-consuming

quality control methods.^{3,4} We found similar labelling efficiency during quality control between Illuccix and Modular-Lab easy methods, despite Illuccix preparation time being much shorter. Thus, kits like Illuccix are more cost effective in terms of equipment investment and time.

Our study suggests, in certain scenarios, an increased radiation dose of

up to 800 mSv, or 4% of the maximum permissible dose using the Modular-Lab easy synthesis system. In the context of a considered application of the ALARA radiation principle for occupational radiation exposure, this is a significant radiation “cost” and might amount to around a 12-14% contribution to annual personnel dose if a local dose constraint of 5 mSv were in effect.

Bringing the highest quality of care to Australian patients with prostate cancer requires constant refinement of diagnostic products and service delivery, and any possible efficiencies need to be evaluated and implemented effectively. By validating the combination of a commonly used and available Gallium-68 generator with a user-friendly and faster synthesis kit, with superior product yield, it is expected that imaging providers and patients will benefit substantially.

Disclaimer

Telix Pharmaceuticals provided Illuccix kits. Medical editing support provided by Jess Roetman, (Telix Pharmaceuticals).

References

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