Enhancing Capacity and Synthesis of 68-Ga-PSMA with lyophilized ready to use Kit for Nuclear Pharmacy Applications

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Introduction:

The 68Ge/68Ga generator has the potential to greatly expand positron emission tomography (PET) imaging to benefit more patients, by allowing many PET applications in hospitals that don't have immediate access to cyclotrons and costly radiochemistry facilities.
It is often suggested that ^{68}Ga is the new ^{99m}Tc, drawing parallels with conventional radiopharmacy practice where radiopharmaceuticals are prepared with little more complex equipment than a syringe and a vial.
However, there are further barriers to overcome in order to realize ^{68}Ga potential, and making current ^{68}Ga labeling methods more like those associated ^{99m}Tc than with ^{18}F.

Isotopia Molecular Imaging Ltd. (ISOTOPIA) is a major nuclear pharmacy providing SPECT and PET radio-pharmaceuticals to the growing field of nuclear medicine in Israel.
When imaging prostate cancer with 68-Ga-PSMA was first introduced in November 2014, it was available only as a manual pharmacy synthesis.
In order to enhance availability and precise production of 68-Ga-PSMA "ISOTOPIA" introduced a kit for fast and easy labeling of PSMA at the end of 2016 that has been used for the last 2 years.
In this paper we describe our experience in using the kit and provide comparison of production parameters in comparison with the old labeling method.

Objectives

68-Ga-PSMA-11 is widely used for PET imaging of the prostate-specific membrane antigen (PSMA), which is a valuable tool for the detection of prostate cancer lesions.
Herein we compare the production parameters of 68-Ga-PSMA-11 by a synthesizer method that took place during the second half of 2015 and 2016 with a room temperature cold kit methodology that was practiced during 2017 and 2018.

Methods:

68-Ga-PSMA-11 was prepared either by using a Modular-Lab module of (EZAG, Berlin, Germany or IBA RadioPharma Solutions) or using a lyophilized cold kit (isoPROtrace-11, ISOTOPIA Israel) with a commercially produced 68Ge/68Ga generator (50 mCi) and a fractionated elution (2.5 ml of 0.1 M HCl).

For the synthesizer based standard radiolabeling, 10 µg PSMA-11 precursor (10.5 nmol) in 20 µL and 0.3 to 0.35 mL sodium formate (1.5M) were transferred into the destined glass vial following by fractionated elution (2.5 ml of 0.1 M HCl) of the 68Ge/68Ga generator, followed by heating at pH 4.0-5.0 for 5 minutes at 95 °C.

After cooling to ambient temperature (5 minutes) the reaction mixture was passed to preconditioned C-18 cartridge (Sepak® Waters) to remove non-incorporated free Ga-68 from the final product. The overall process takes about 25 minutes.

For labeling with the lyophilized cold kit isoPROtrace-11, 2.5 ml 0.1 M HCl of the middle 68-Ga elution fraction were added to the kit, shook for dissolving the vial's contents and kept for 5 minutes at room temperature.

Chemical and radiochemical purity were assessed with TLC.

Schematic presentations of the labeling processes are summarized in Figure 1, 2 and 3.

Figure 1 – Schematic flow sheet for the manufacturing process of ^{68}Ga-PSMA (11 or 617) Produced with an EZAG automatic synthesis module

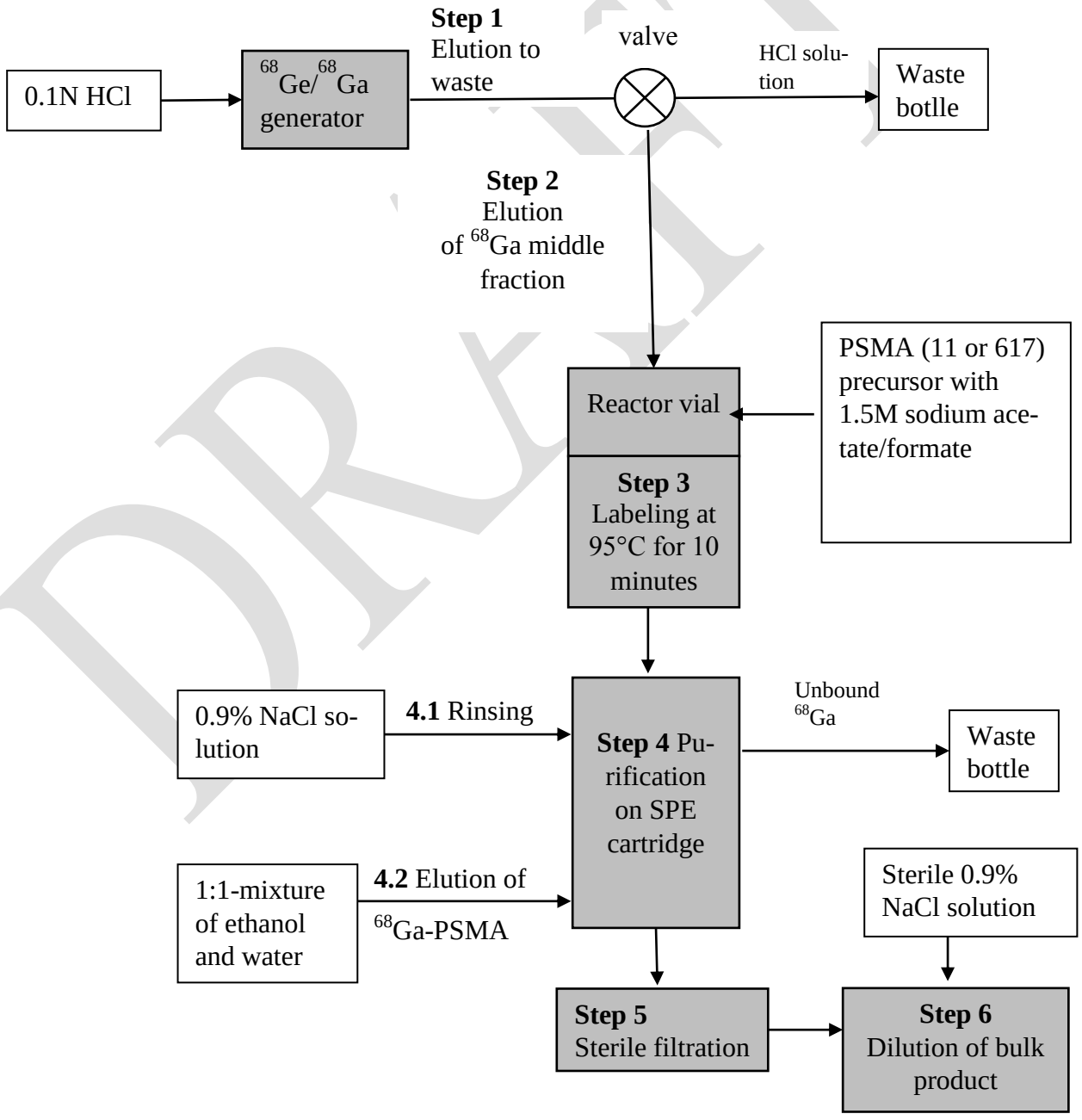
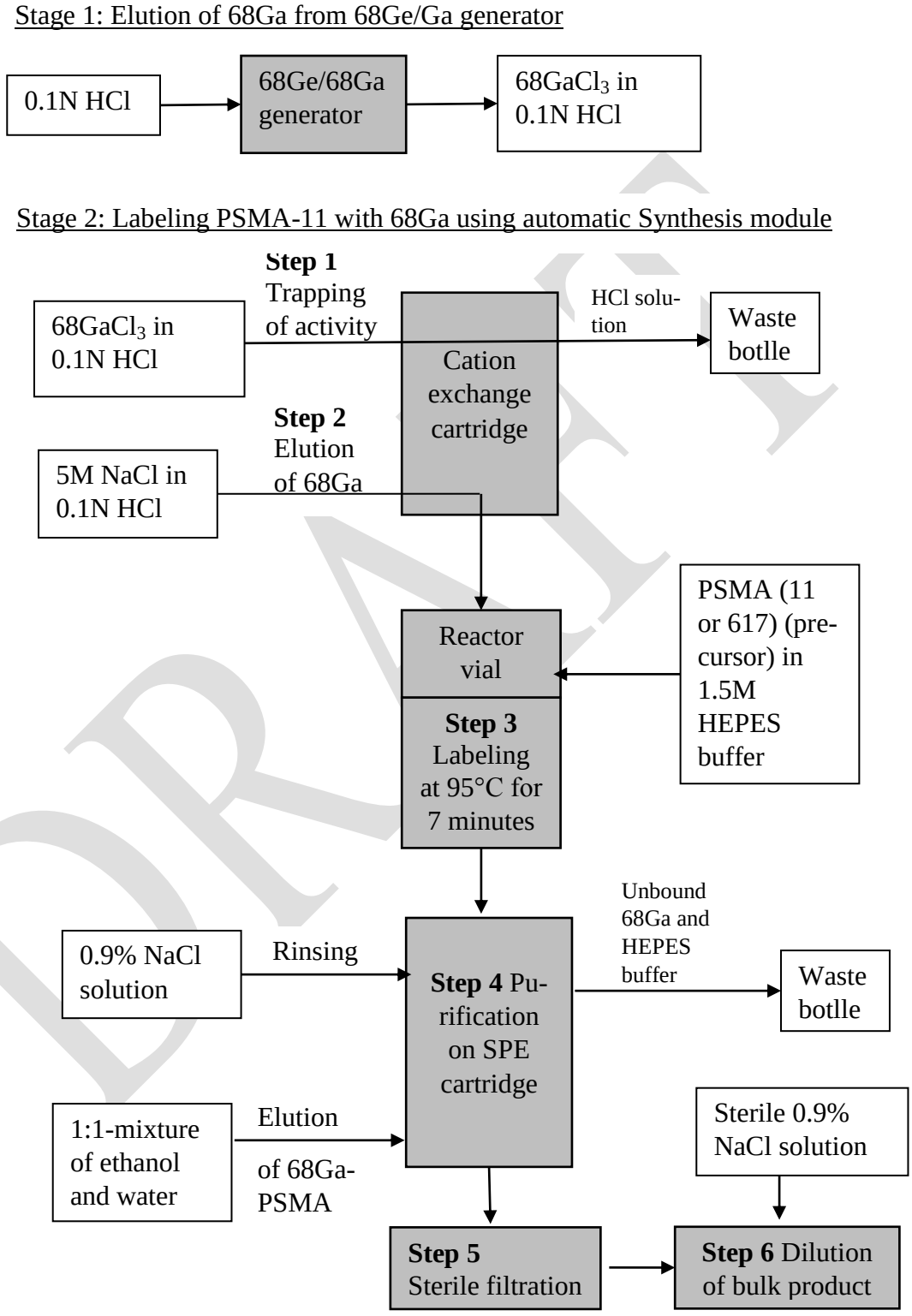


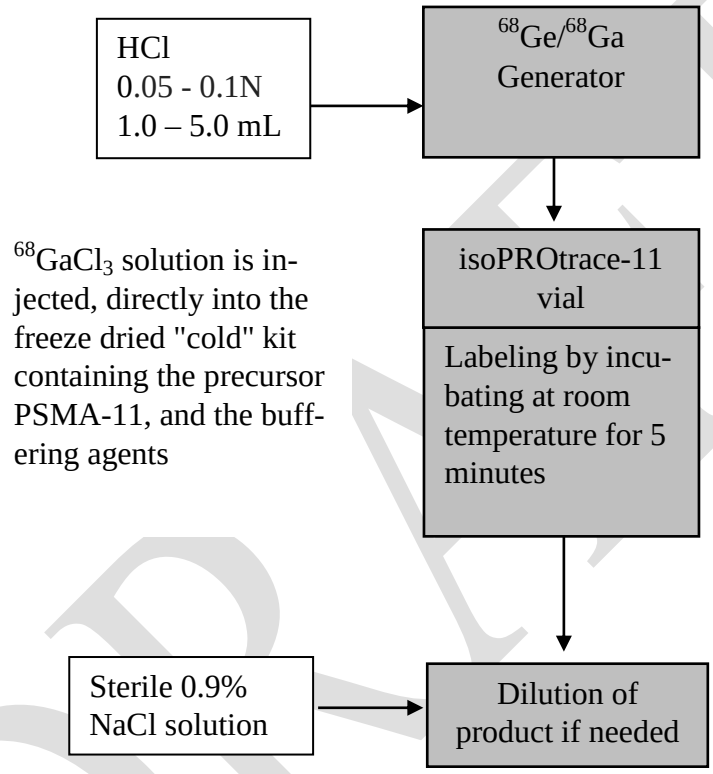
Figure 2 - Schematic flow sheet for the manufacturing process of ^{68}Ga-PSMA (11 or 617) Produced with an automatic synthesis IBA module[1]



[1] R. Martin, Fully automated synthesis of 68Ga-labelled peptides using the IBA Synthera® and Synthera® Extension modules, Abstract accepted for the 18th ESRR- European Symposium on Radiopharmacy and Radiopharmaceuticals conference (2016)

Figure 3 – **Schematic flow sheet of labeling isoPROtrace-11** ("cold" kit of PSMA-11) **with ^{68}Ga**

Step 1: Elution and adding the ^{68}Ga to the "cold kit" and labeling



Results

Automated synthesis of 68Ga-PSMA-11 resulted in radiochemical yields of 84.2 ± 6.3% and purities of > 95 % after 25 min.
The room temperature cold kit gave radiochemical yields of > 96 % and purities of >97 % after 5 min.

Results are summarized in Table 1.

Table 1

Parameter	2018 KIT Synthesis	2017 KIT Synthesis	2015 Module Synthesis
# of procedures	462	395	303
Mean time to final product ± SD (min)	6 ± 1.8	4.2 ± 1.3	15.7 ± 9
Yield (%)	96 ± 4	97 ± 6.2	84.2 ± 6.3
RCP (%)	97.4 ± 2.5	96 ± 16	95.2 ± 12.7

Discussion and conclusion

Using the kit method reduced the labeling time from 25 to 5 min allowing fast and easy labeling process that in addition saves also personnel time needed for reagents preparation, setting up the module and charging the module with the appropriate reagents.
Radiochemical purity was maintained above 95% and was even improved to the 97% range.
More important is the yield increase from 84% to 96% meaning that more labeled PSMA can be delivered for needing patients.
The kit method brings also increased production efficiency because less of the eluted 68-Ga is being wasted, leading to reduced 68-Ge/68-Ga generator expenses with income increase since more labeled PSMA is produced.
Moving to kit synthesis abolished the need for radiopharmaceuticals synthesis module and the need for "Shielded Hot Cell", this change by itself saves more than 150,000 € in infrastructure needed for module synthesis.