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Céleste Souche, Juliette Fouillet, Charlotte Donzé, Emmanuel Deshayes, Léa Rubira, et al.. In-depth study of the  $^{68}\text{Ga}$  radiolabeling conditions of a bisphosphonate monoamide analog of DOTA for bone imaging. 11èmes Journées Méditerranéennes des Jeunes Chercheurs, Nov 2023, Montpellier, France. hal-04803888

**HAL Id: hal-04803888**

**<https://hal.science/hal-04803888v1>**

Submitted on 26 Nov 2024

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# In-depth study of the <sup>68</sup>Ga radiolabeling conditions of a bisphosphonate monoamide analog of DOTA for bone imaging

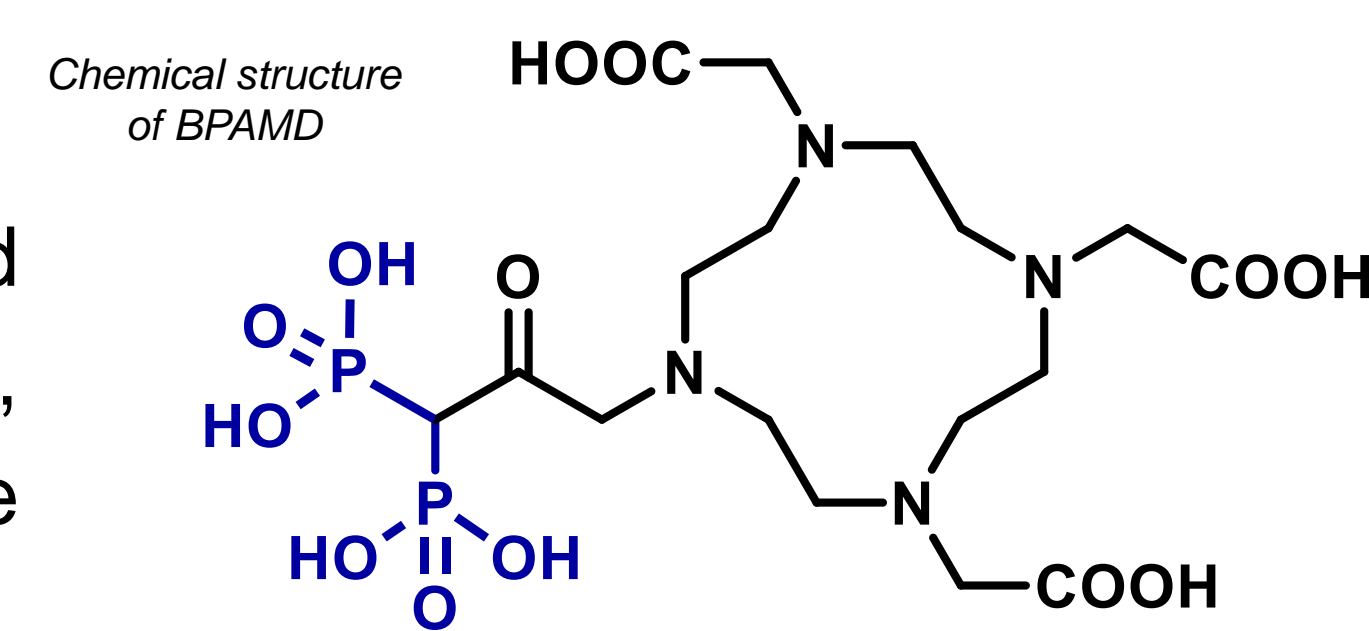
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## INTRODUCTION

Bone is one of the most common sites of metastasis, particularly for prostate, breast and lung cancers [1]. Consequently, early and accurate non-invasive diagnosis of bone metastases is essential in the management of these diseases. To this end, bisphosphonates can be used as imaging agents with bone tropism [2]. In particular, the DOTA-functionalized bisphosphonate BPAMD is currently used for preclinical and human indications, especially for <sup>68</sup>Ga PET imaging [3].

Automating the radiolabeling of DOTA-bisphosphonates with <sup>68</sup>Ga was readily identified as a challenge [4] and no relevant protocol has yet been detailed in the literature. Consequently, the influence of the different parameters involved in automated radiolabeling has not been studied, as reported for other <sup>68</sup>Ga radiopharmaceuticals [5]



## METHODS

Two automated synthesis sequences were set up on a GAIA®/LUNA® module (Elysia Raytest) for the <sup>68</sup>Ga radiolabeling of BPAMD. Then, the influence of the reaction buffer, anti-radiolysis compound, and amount of vector on the radiolabeling process was studied. [<sup>68</sup>Ga]GaCl<sub>3</sub> (t<sub>1/2</sub> = 68 min) was eluted from a <sup>68</sup>Ge/<sup>68</sup>Ga radionuclide generator (GalliAD®, IRE Elit). All assays were done in triplicate. Radiochemical purity (RCP) of the resulting [<sup>68</sup>Ga]Ga-BPAMD was checked by radio-TLC and radio-HPLC.

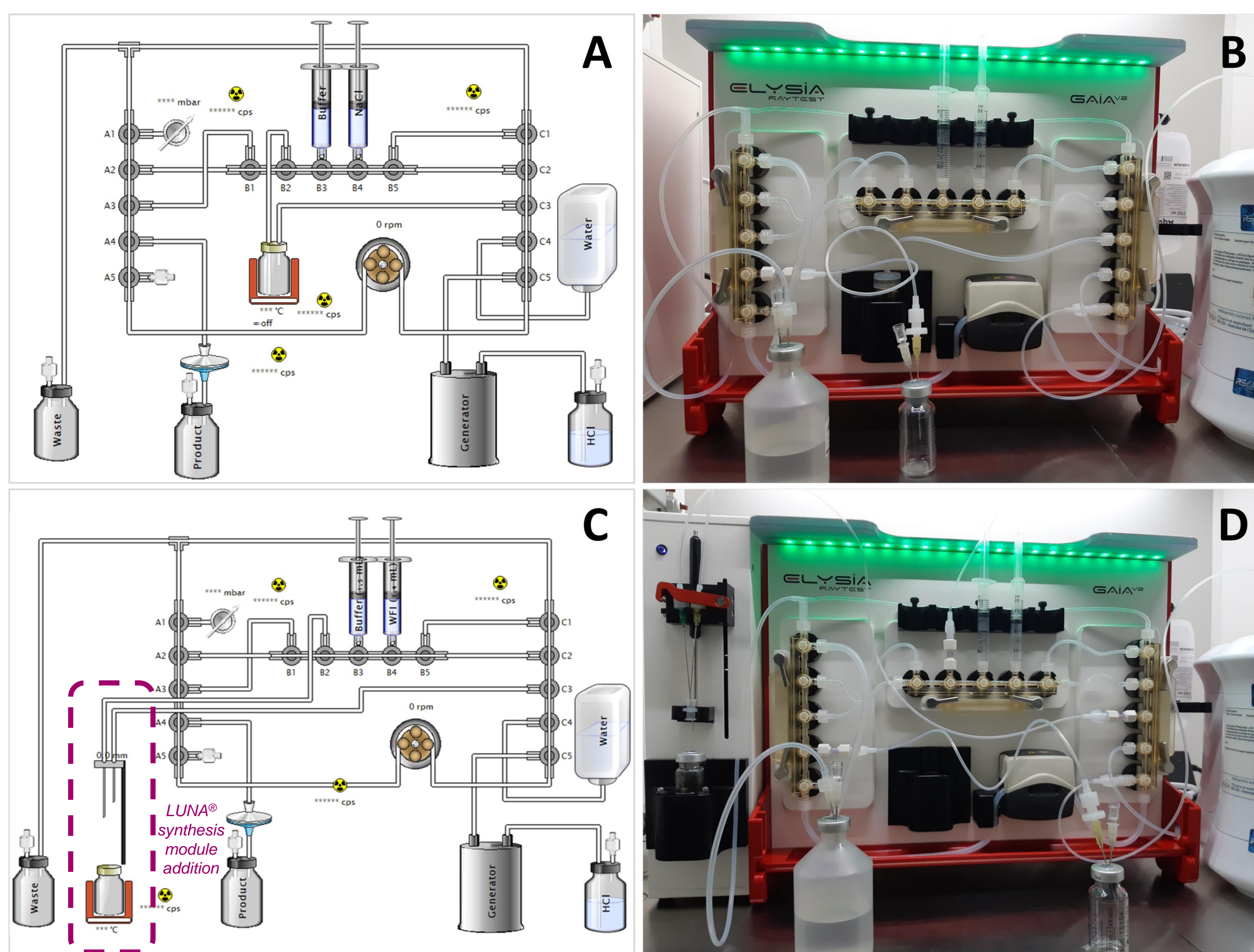
## RESULTS

A first automated synthesis sequence was set up on the GAIA® module only and involved a single-use 3-ramp tubing set with a captive vial (A, B).

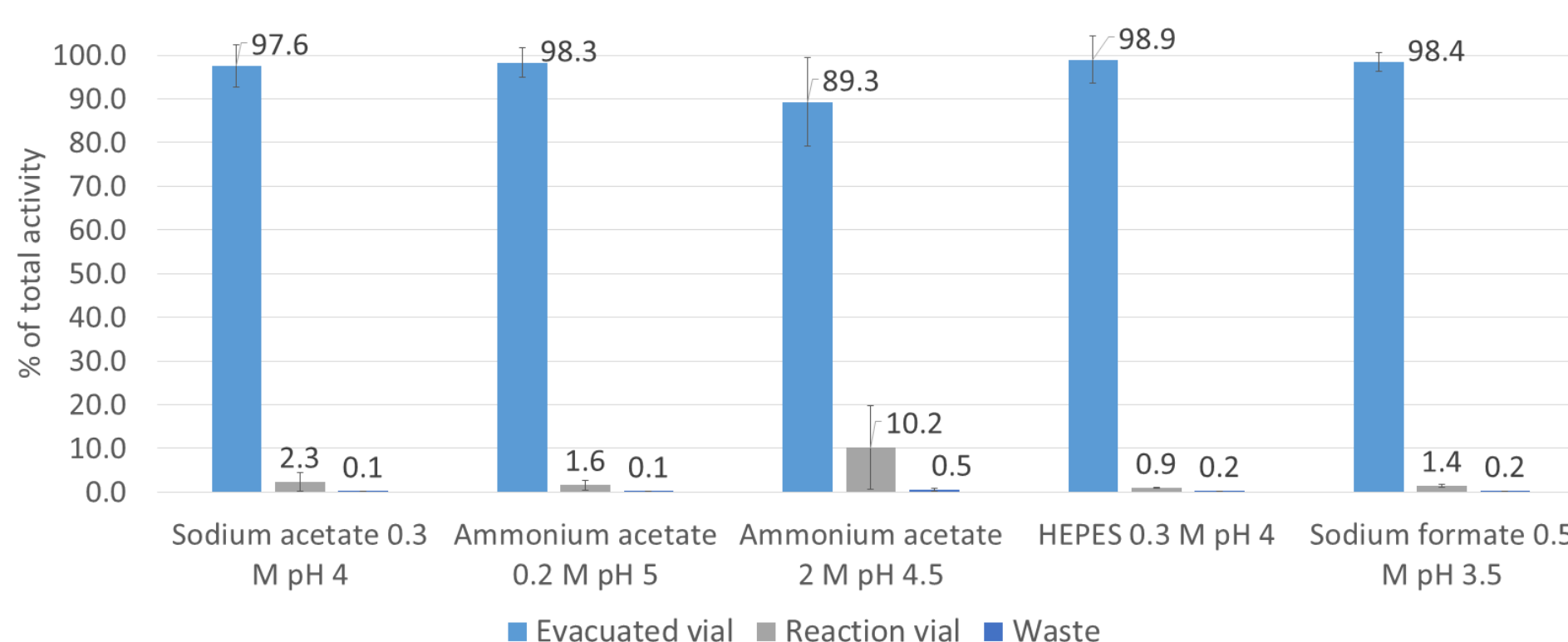
A second automated synthesis sequence was set up on the dual GAIA®/LUNA® modules to allow the use of various reaction vial models (C, D).

Total synthesis time for both methods was ~23 min.

Reaction conditions study assays were conducted with method A, without initial purification of the <sup>68</sup>Ga eluate on strong cation exchange (SCX) cartridge.



### 1) Nature and molarity of the buffer solution



#### AcONH<sub>4</sub> 0.2 M:

- Good RCP
- Moderate, non-reproducible radiochemical yields (RCY)

#### AcONH<sub>4</sub> 2 M, HCOONa 0.5 M:

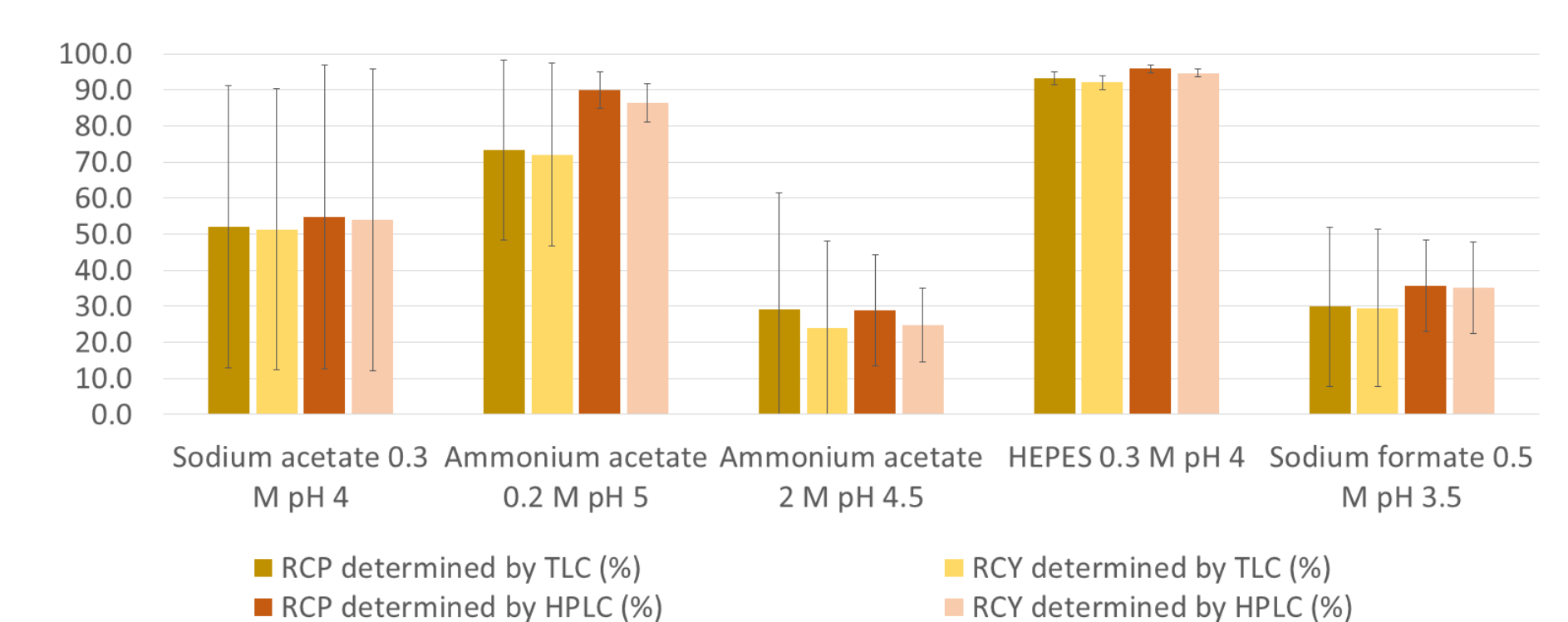
- Low RCP and RCY despite good pH control

#### AcONa 0.3 M:

- Moderate, non-reproducible RCP and RCY

#### HEPES 0.3 M pH 4:

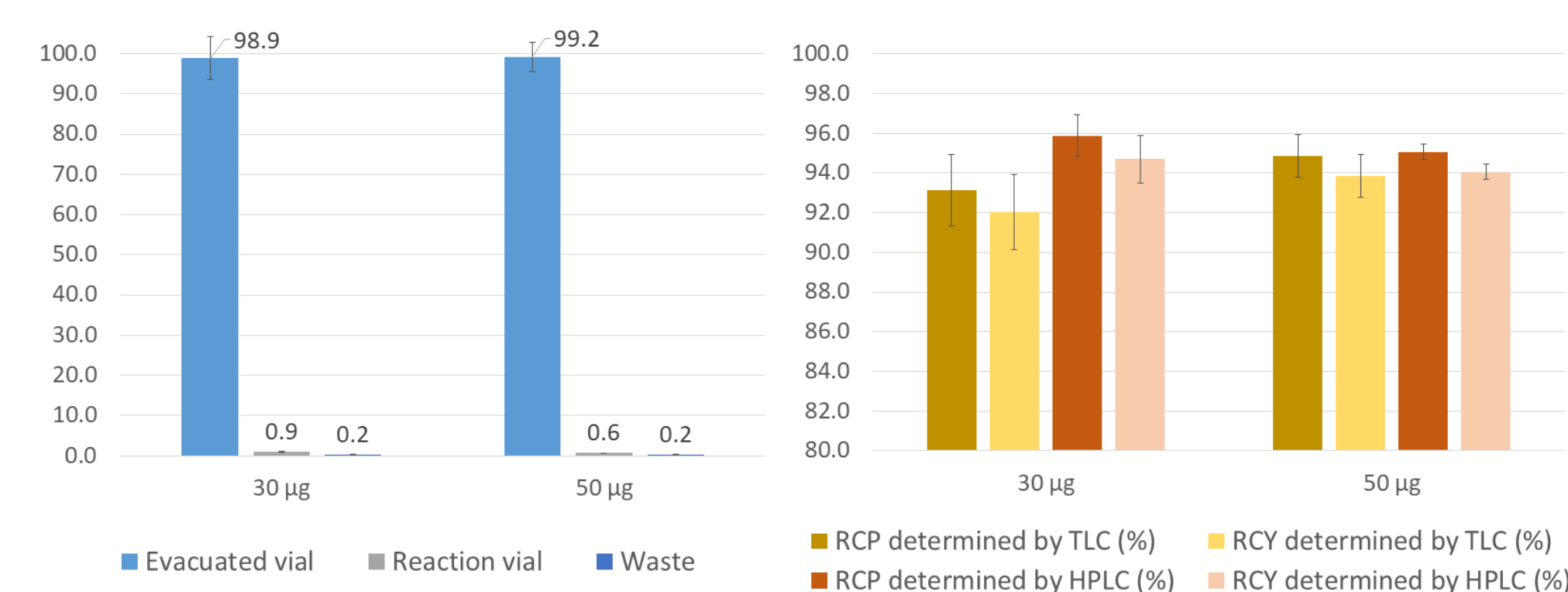
- High RCP and RCY



### 3) Amount of BPAMD

+ 66% of vector amount engaged in the reaction =

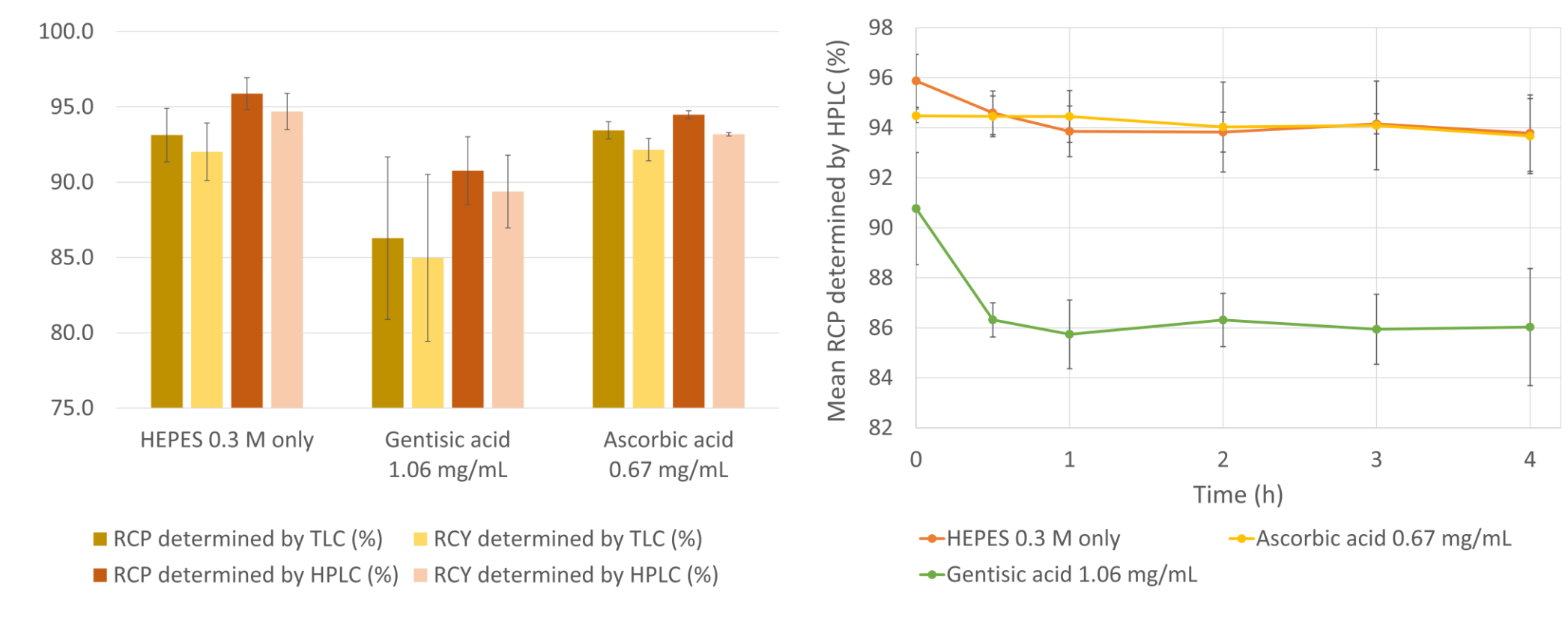
- Comparable RCP
- Slightly better RCY
- More reproducible results



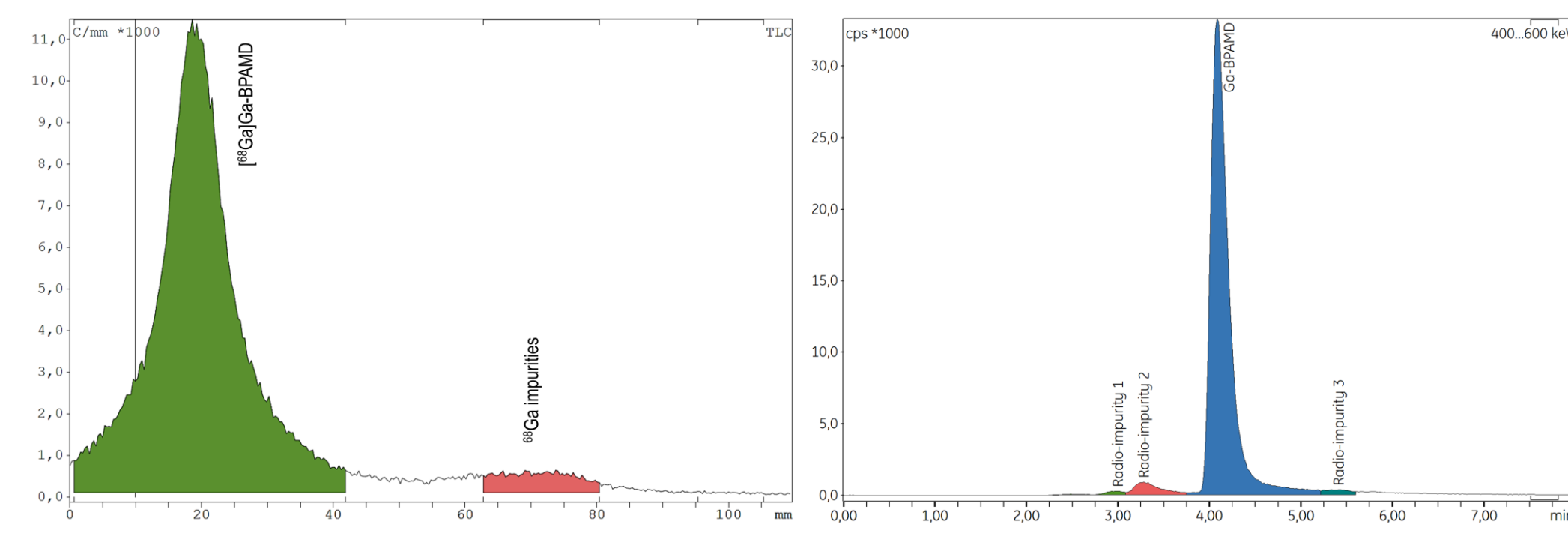
### 2) Presence of an anti-radiolytic compound

As the preparation appeared originally stable over time, gentisic acid did not show any enhancement and even tended to decrease RCP.

Ascorbic acid 0.67 mg/mL did not show significant benefit of RCP values but slightly improved the overall outcome of the radiolabeling reaction

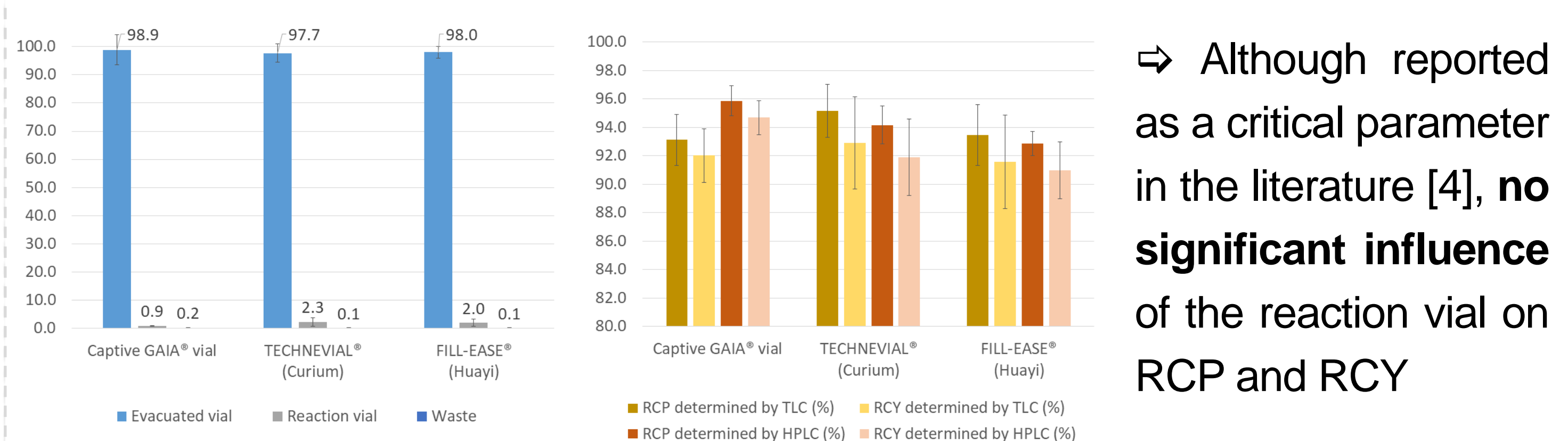


Cleaner chromatography profiles



### 4) Type of reaction vial

⇒ Although reported as a critical parameter in the literature [4], no significant influence of the reaction vial on RCP and RCY



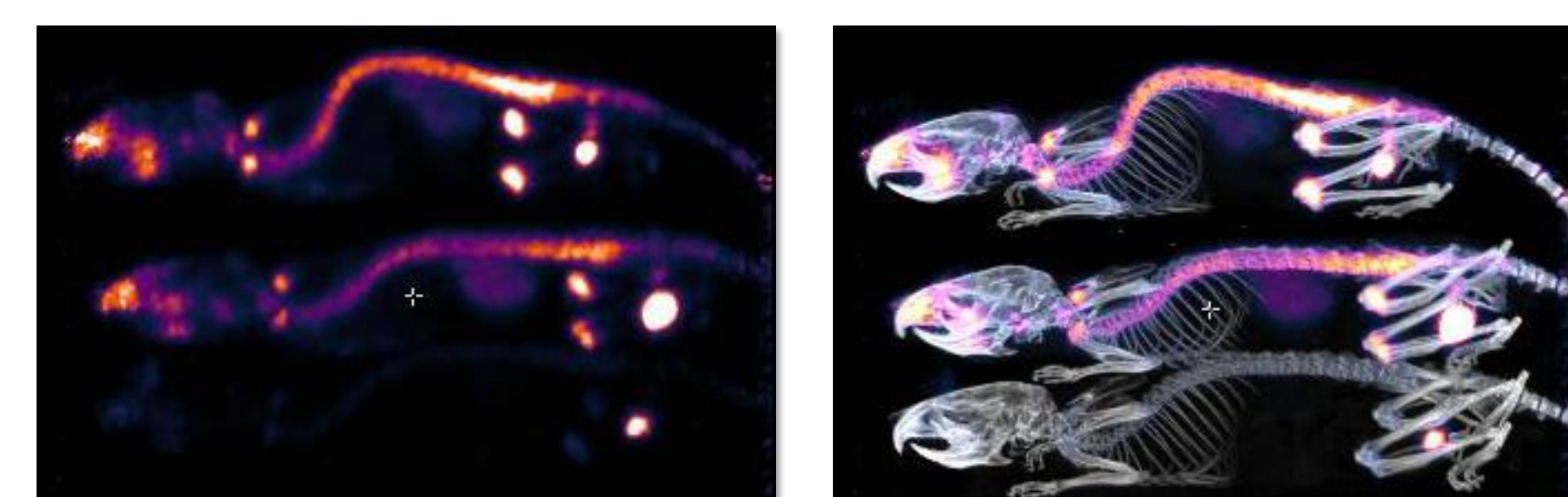
### 5) Final purification on SCX cartridge

Using a SCX cartridge to retain remaining <sup>68</sup>Ga<sup>3+</sup> after radiolabeling resulted in non-repeatable results (RCP: 74.4% ± 35.6%, RCY: 31.6% ± 29.9%) ⇒ Further investigations ongoing

## CONCLUSION

Optimized methods for automated production of [<sup>68</sup>Ga]Ga-BPAMD were developed through an in-depth study of the radiolabeling reaction parameters. [<sup>68</sup>Ga]Ga-BPAMD was obtained with >93% RCP and >91% RCY, in <25 min.

[<sup>68</sup>Ga]Ga-BPAMD obtained by automated synthesis was evaluated in vivo on healthy mice. Micro-PET imaging showed rapid, intense accumulation in the joints (shoulders and along the backbone), demonstrating bone tropism.



µPET (left) and µPET-CT (right) images: 2h post-injection of ~18 MBq [<sup>68</sup>Ga]Ga-BPAMD: IV tail vein (up) or IV retro-orbital (middle) injection.