PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

# A novel method for multi-component continuous real-time aerosol monitoring using Fourier Transformed Infrared (FTIR) spectroscopy for *in vivo* studies

*September 2-7, 2018*
*10th International Aerosol Conference*
*Saint Louis, Missouri, USA*

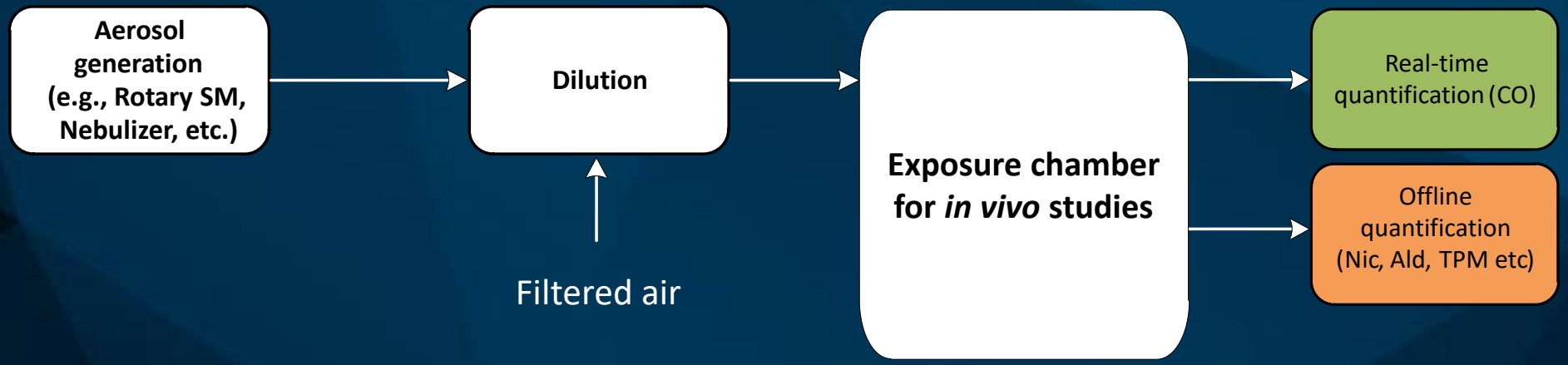
*Tan Wei Teck, Subash Krishnan, Patrick Vanscheeuwijck*
*Philip Morris International R&D*

# Outline

- Introduction
  - Background
  - Motivation & target
- Experimental setup
- Results: Real-time results of multiple components from FTIR vs. results from offline method
- Case studies: Application of FTIR for aerosol optimization and characterization
- Summary

# Background

- *In vivo* studies carried out to assess the aerosol toxicity require proper characterization in order to demonstrate appropriate exposure.
- Aerosols in scope for this presentation are smoke generated from combustible cigarettes as well as aerosols from Reduced-Risk Products (RRP[1]), such as the Tobacco Heating System (THS) and e-cigarettes (e-cig).
- Carbon monoxide (CO), monitored in real time for cigarette smoke, is not present in some RRPs (e.g., e-cig).
- Nicotine concentration is typically the dosing parameter for RRP *in vivo* studies, but only offline methods are available.




[1]Reduced-Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. We have a range of RRPs in various stages of development, scientific assessment, and commercialization. Because our RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful constituents than found in cigarette smoke.

# Motivation and target

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

- Motivation:
  - Offline quantification of nicotine has a long lead time due to the time required for sampling and processing.
  - Enhance adherence to test guidelines.
    - *"The exposure atmosphere should be held as constant as practicable. A real-time monitoring device, such as an aerosol photometer for aerosols or a total hydrocarbon analyzer for vapors, may be used to demonstrate the stability of the exposure conditions."*
    - *"Time to attain chamber equilibration (t95) should be calculated and reported."*

    *OECD Test guideline 413, Paragraph 27*
  - Offline quantification of nicotine is resource intensive and, as such, susceptible to human error at various stages of the process.

# Motivation and target

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

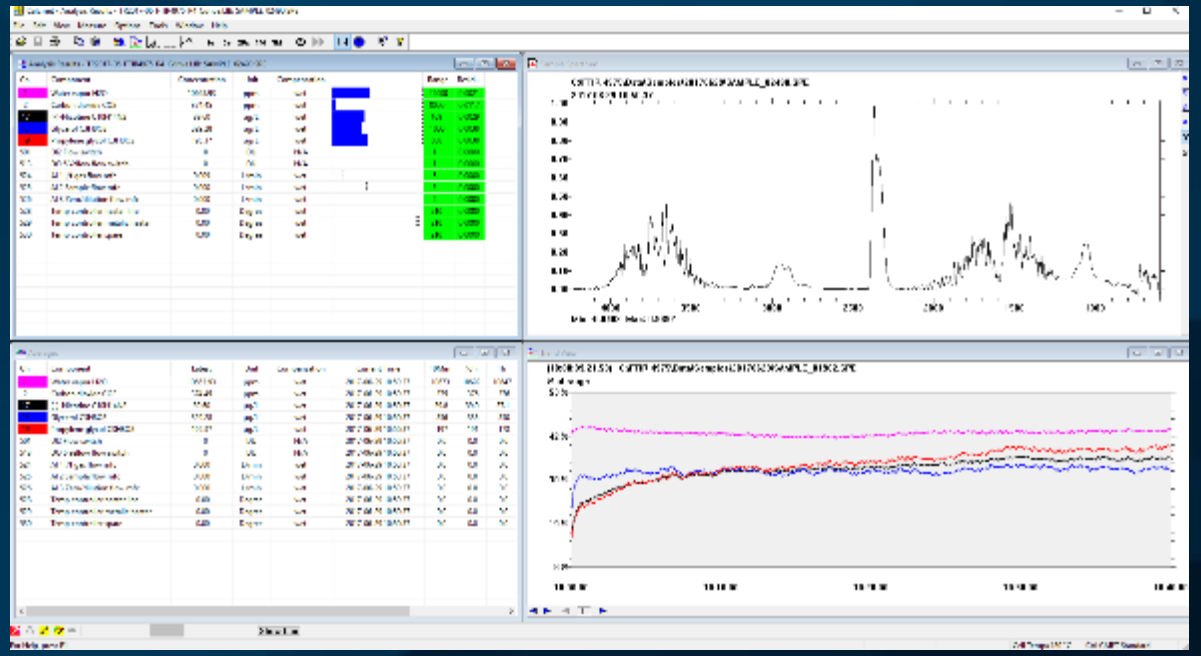
- Target:
  - Quantify, in real time, concentration of nicotine and other aerosol constituents (e.g., propylene glycol and glycerin) in RRP aerosol for *in vivo* studies.

# Selected FTIR system

- Gasmet™ CX4000 FTIR Gas analyzer
- PC with Calcmet™ software

# Principle of operation

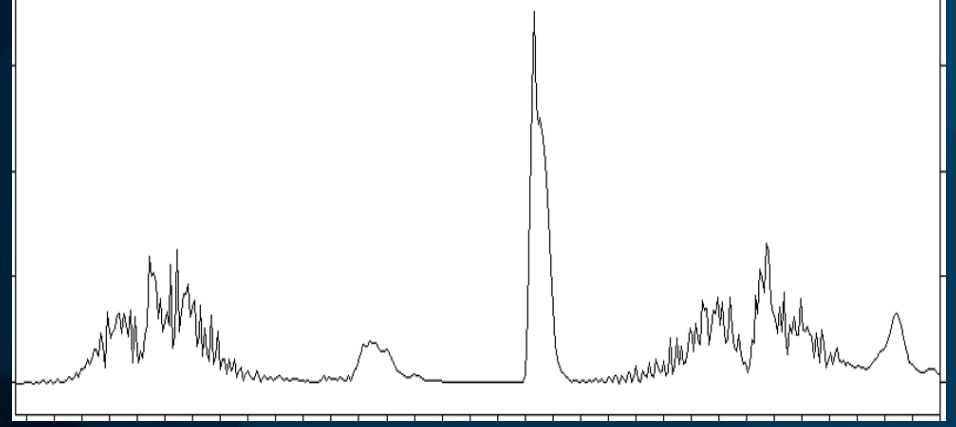
- Michelson Interferometer performs Fourier transformation on infrared (IR) beam passing through the sample chamber.
- Calcmet™ software calculates factors for ref. spectra of selected gaseous compounds.



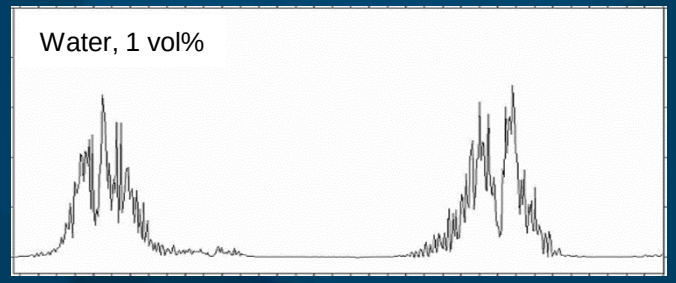
# Analysis of FTIR spectra

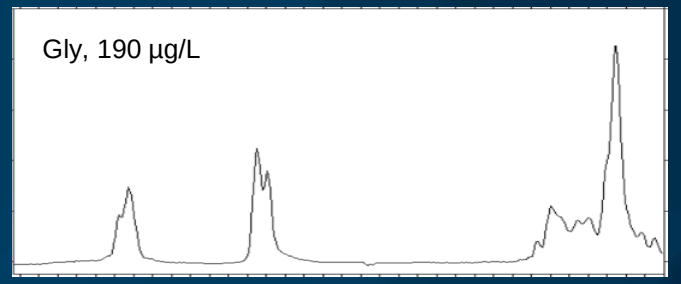
Quantification based on IR absorption (wave number 900 cm-1 to 4200cm-1)

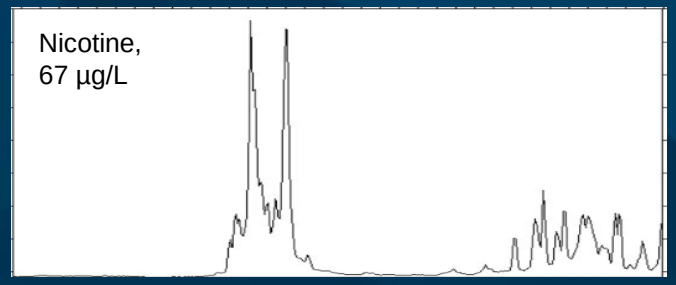
Sample spectrum from e-cig aerosol

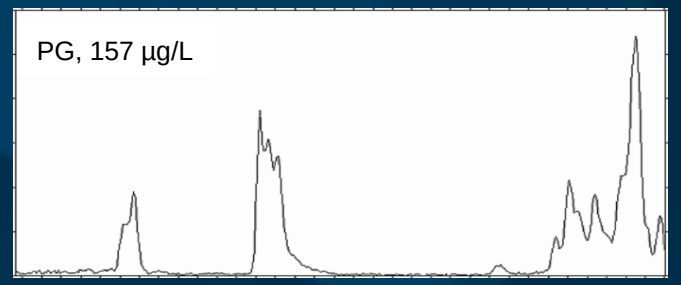


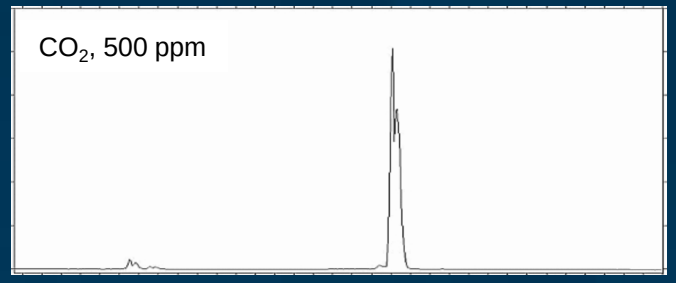
Reference spectra (not to same scale)



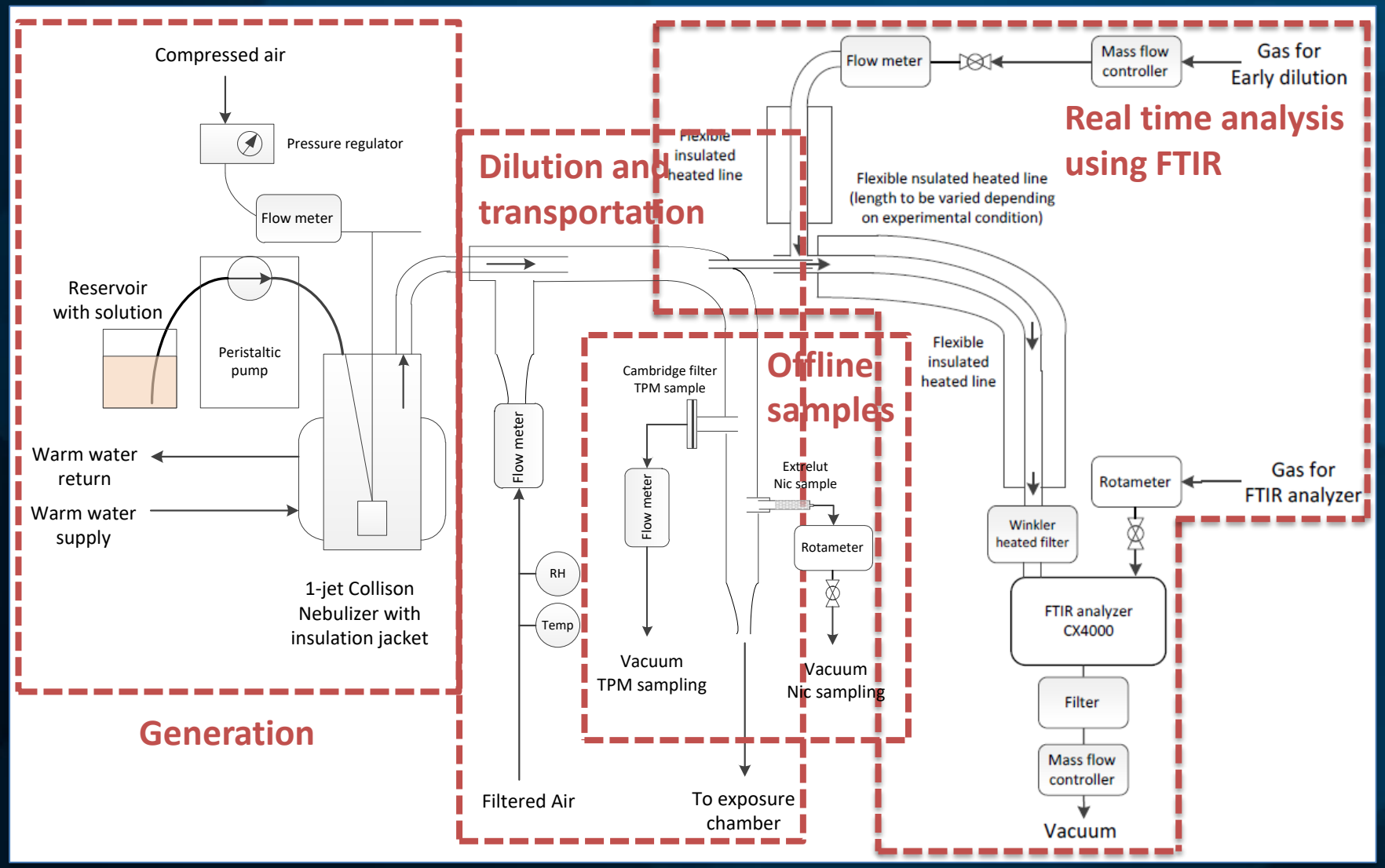




Analysis:

| | |
|---|---|
| 0.925 * Water 1 vol-% | = **0.925 vol% Water** |
| 0.762 * Nicotine 67 µg/L | = **51.10 µg/L Nicotine** |
| 0.809 * Gly 190 µg/L | = **153.8 µg/L Gly** |
| 1.791 * PG 157 µg/L | = **281.6 µg/L PG** |
| 0.765 * $CO_2$ 500 ppm | = **382.7 ppm $CO_2$** |

# Experimental setup



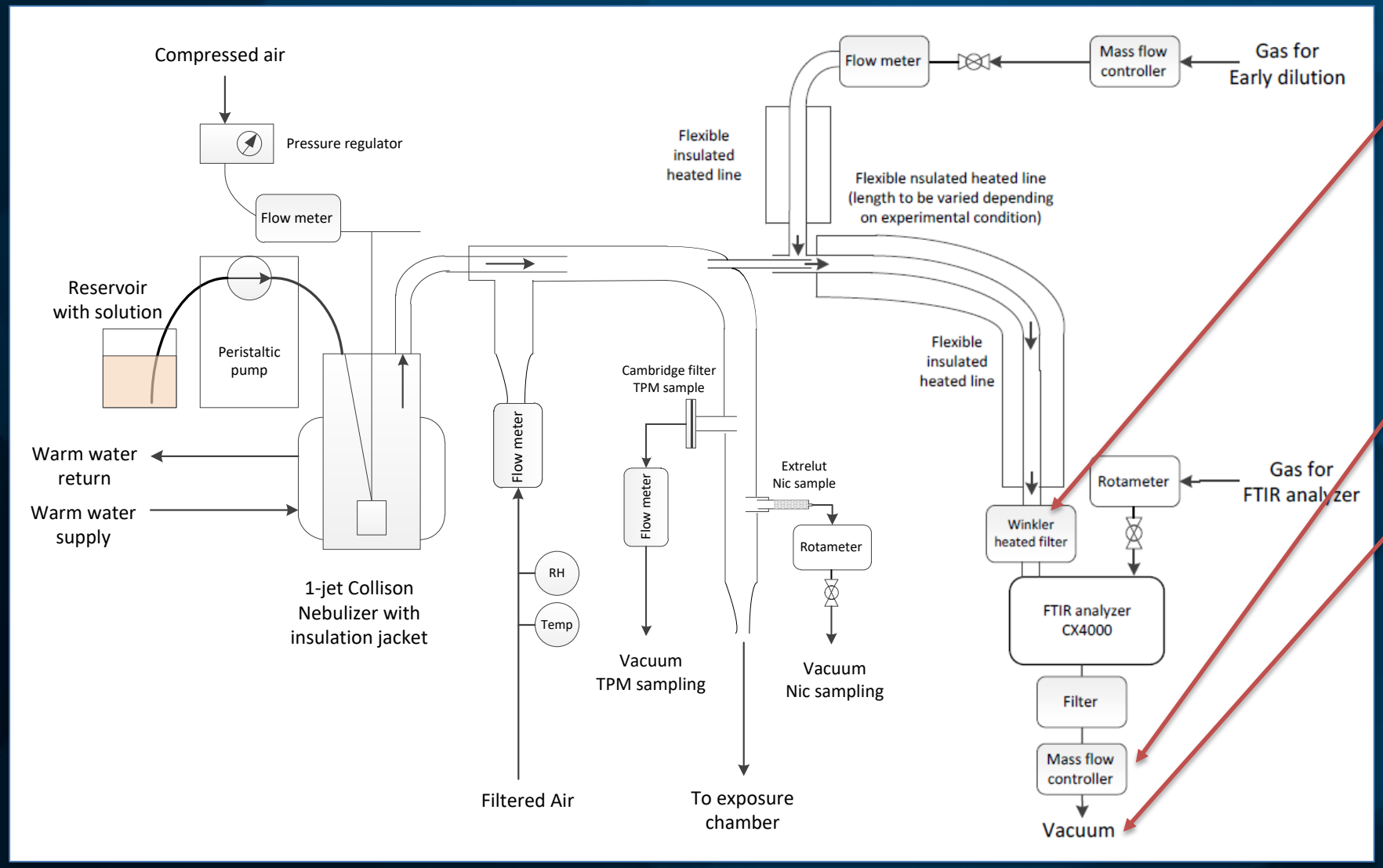

- Offline samples:
  - Nicotine:

    Trapped using $H_2SO_4$-impregnated Extrelut® NT3 sorbent tube and analyzed using gas chromatography with flame ionization detector (GC FID).
  - Gly, PG:

    Trapped on 44 mm glass fiber filter and analyzed using GC FID.

    versus
- Real-time analysis using FTIR

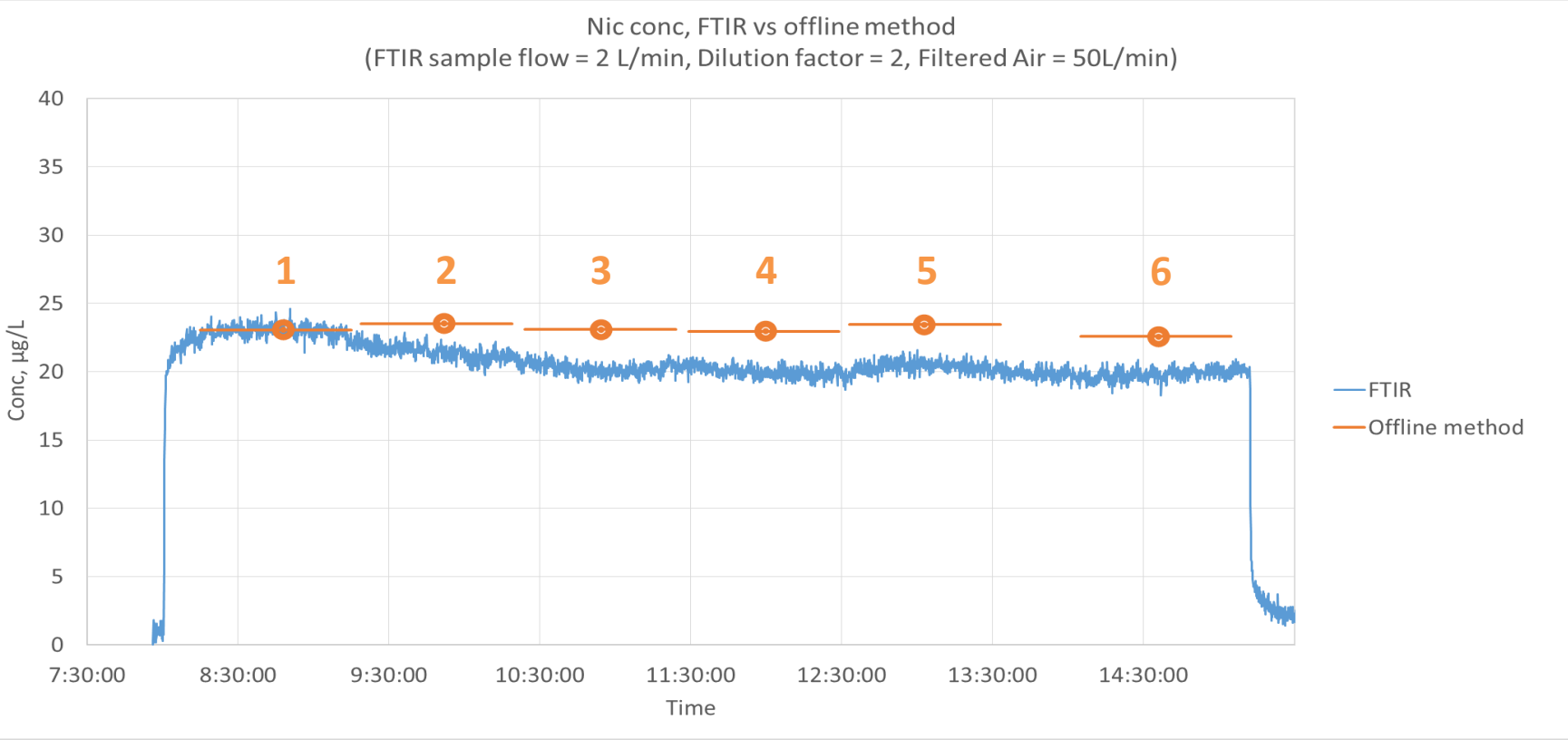
# Experimental setup




- Heated filter at 200˚C, with 2 µm stainless steel filter element, installed before FTIR.

- Sampling flow rate controlled using mass flow controller.
- Sample drawn into FTIR using house vacuum.

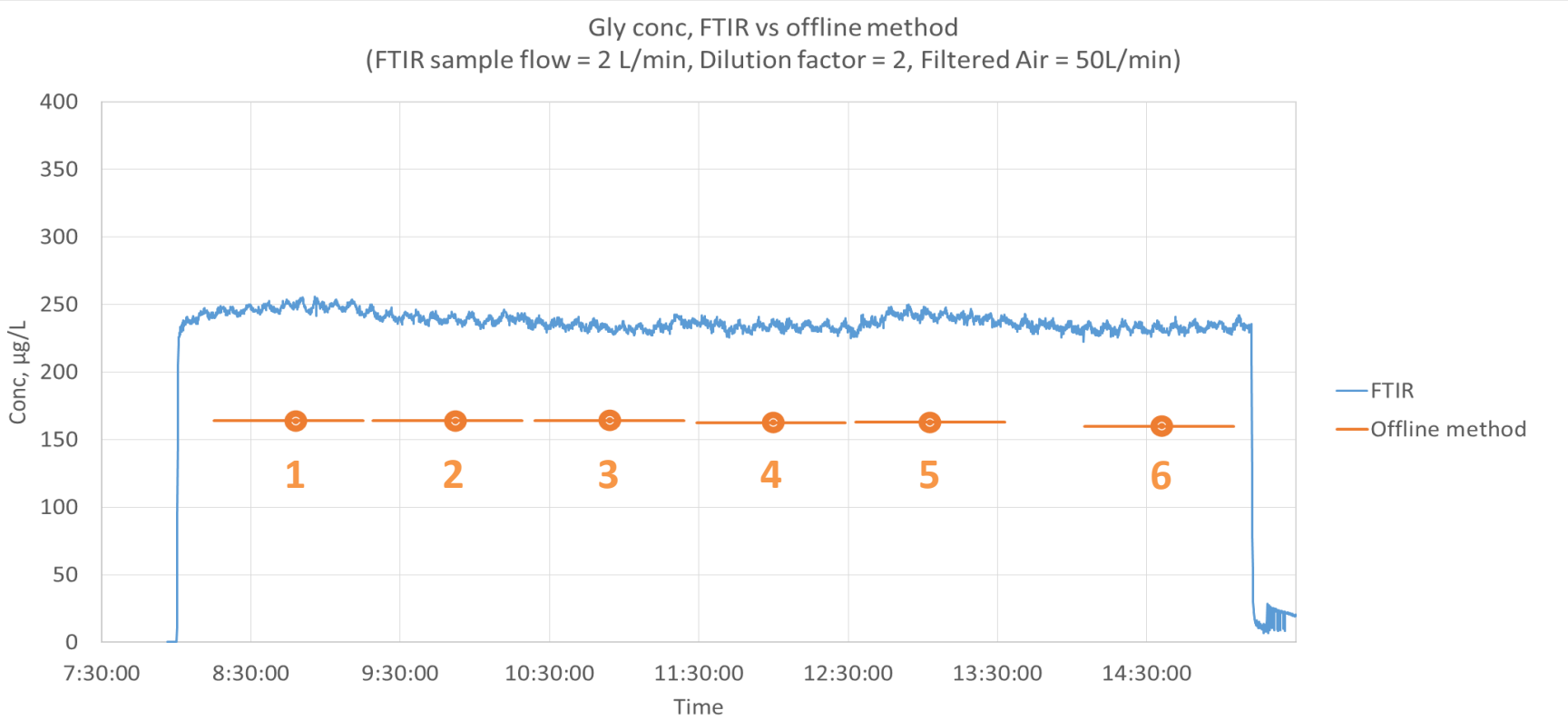
# Results from modified setup - nicotine




| Sample no. | Offline method, µg/L | FTIR, µg/L | Ratio FTIR : Offline method |
|---|---|---|---|
| 1 | 23.06 | 22.99 | 1.00 |
| 2 | 23.52 | 21.42 | 0.91 |
| 3 | 23.07 | 20.25 | 0.88 |
| 4 | 22.94 | 20.01 | 0.87 |
| 5 | 23.43 | 20.37 | 0.87 |
| 6 | 22.57 | 19.77 | 0.88 |

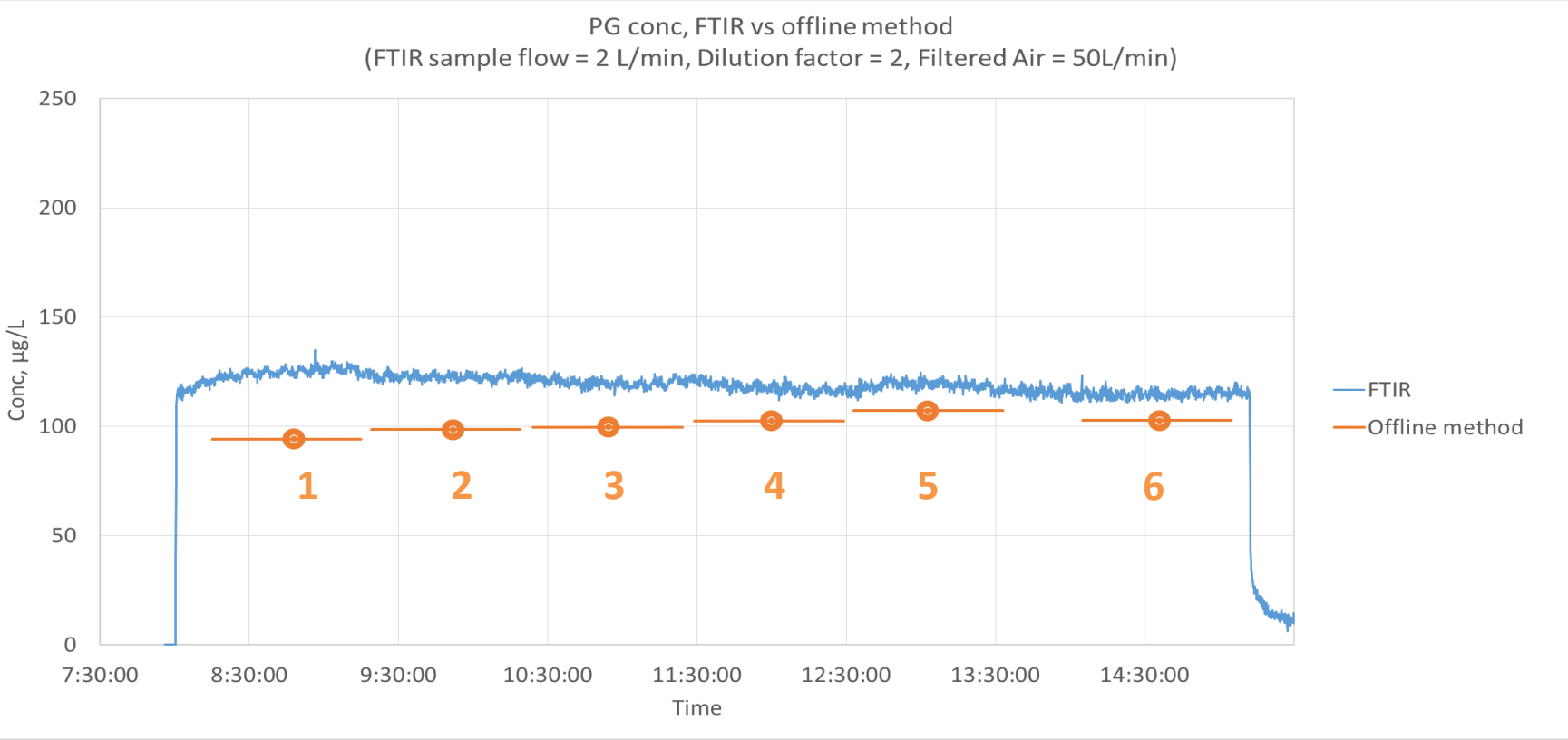
- Concentration spikes not observed.
- Nic results from FTIR on average 10% lower than offline method.

# Results from modified setup - glycerin




| Sample no. | Offline method, µg/L | FTIR, µg/L | Ratio FTIR : Offline method |
|---|---|---|---|
| 1 | 164 | 247 | 1.51 |
| 2 | 164 | 240 | 1.46 |
| 3 | 164 | 234 | 1.43 |
| 4 | 162 | 234 | 1.44 |
| 5 | 163 | 240 | 1.47 |
| 6 | 160 | 233 | 1.45 |

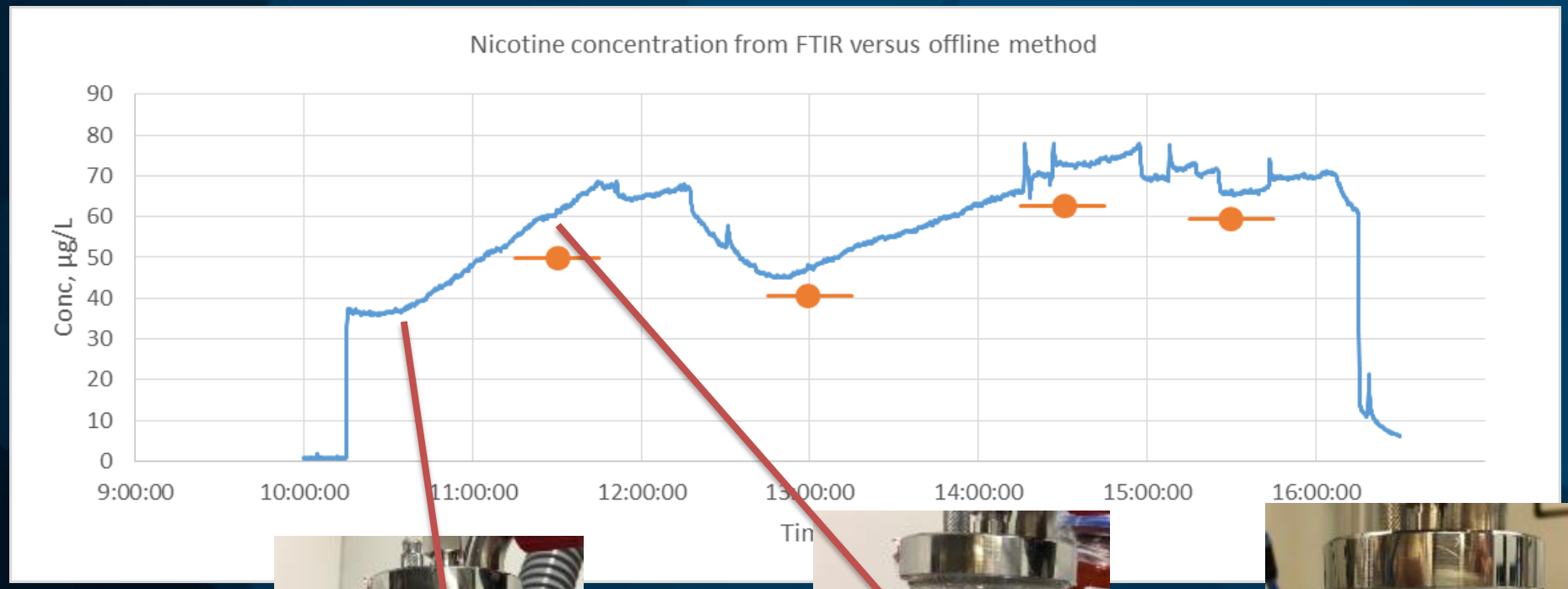
# Results from modified setup - propylene glycol

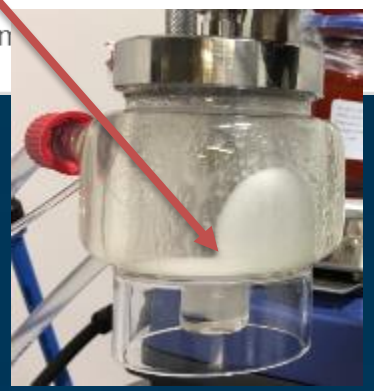



| Sample no. | Offline method, µg/L | FTIR, µg/L | Ratio FTIR : Offline method |
|---|---|---|---|
| 1 | 94 | 125 | 1.32 |
| 2 | 98 | 123 | 1.25 |
| 3 | 100 | 120 | 1.20 |
| 4 | 102 | 118 | 1.15 |
| 5 | 107 | 119 | 1.11 |
| 6 | 103 | 115 | 1.12 |

# Case study 1: Influence of nebulizer liquid level on nebulization efficiency

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

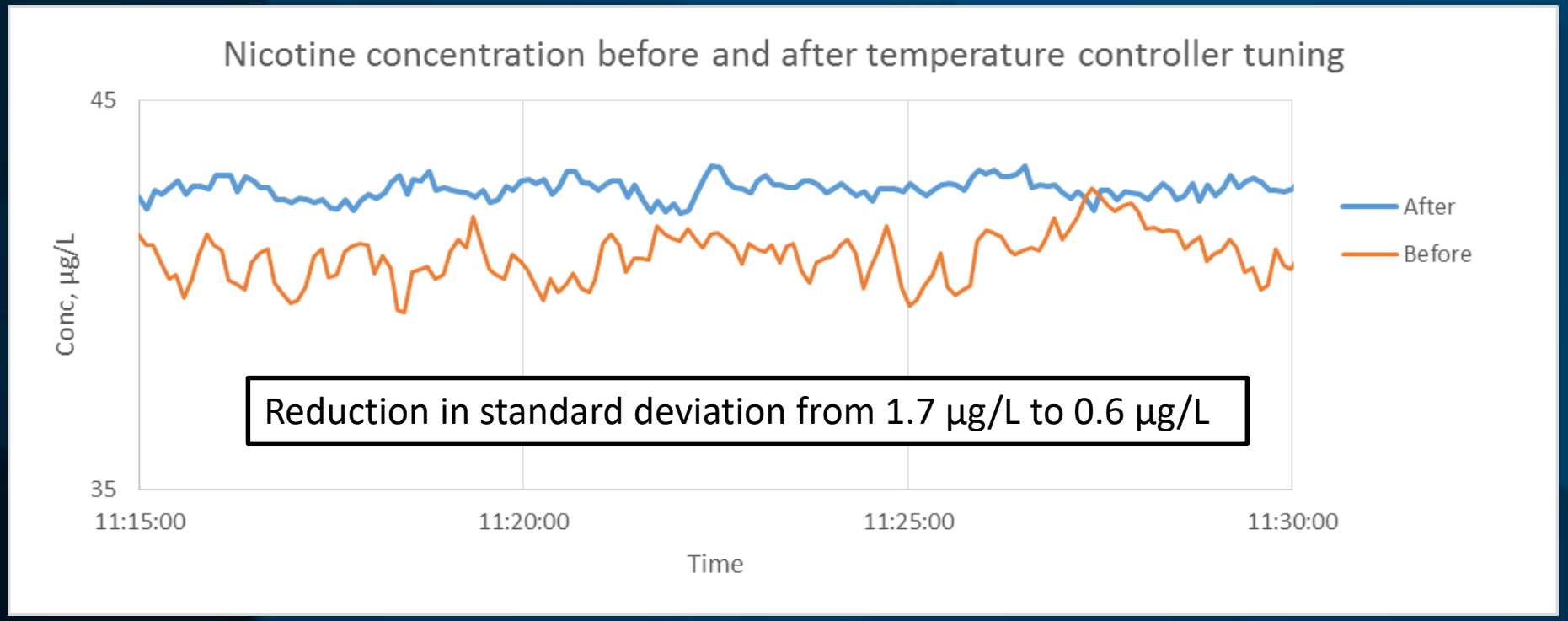


- Aerosol generated by nebulization of a mix of Nicotine and phosphate-buffered saline (PBS) using Collison nebulizer.
- Unstable nicotine concentration was found to be due to changes in the liquid level of the solution in the reservoir of the nebulizer bottle.

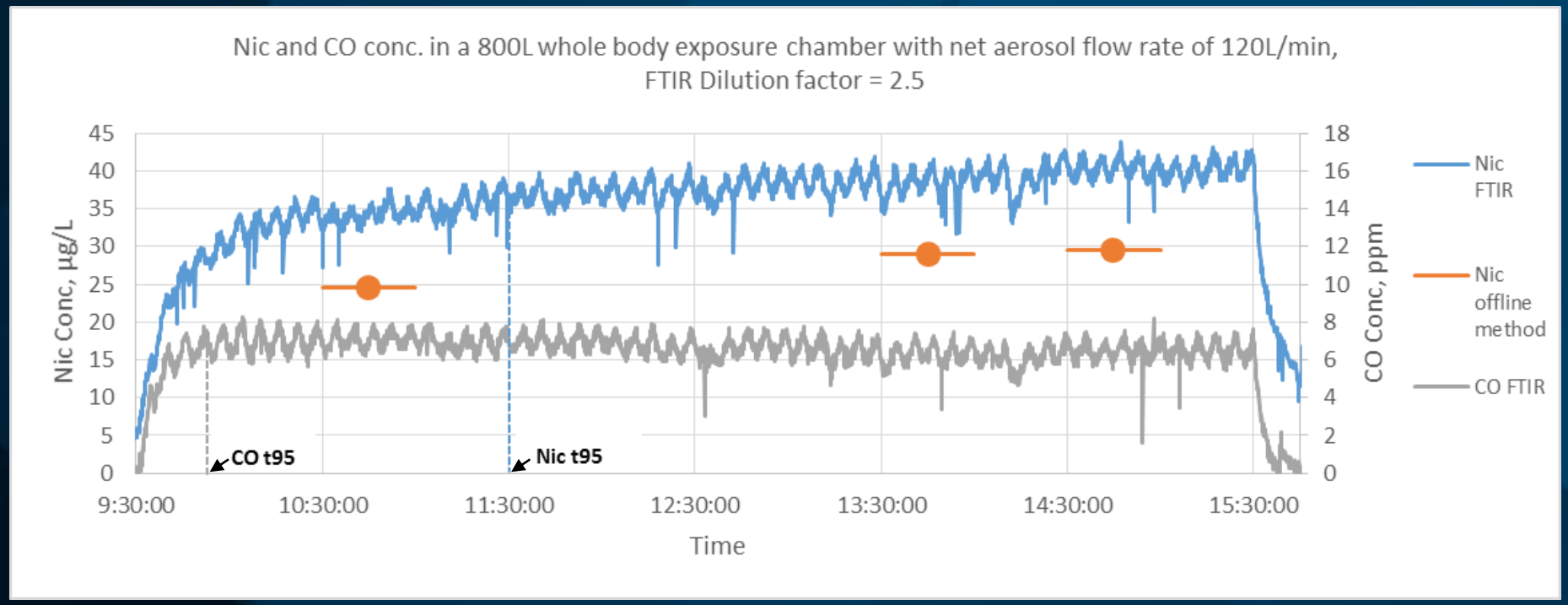
First and second picture from the right are from the nebulization of a Nic/PG/Gly/PBS solution and are used to illustrate the effect of liquid level on the spray pattern and nebulization efficiency. Nicotine/PBS solution is colorless, as depicted in the third picture, making it difficult to monitor the spray pattern and liquid level during operation.

# Case study 2: Influence of temperature on aerosol stability




- Aerosol generated by vaporization of a liquid solution using a temperature-controlled capillary aerosol generator.
- Before controller tuning: Temperature fluctuates around ±10°C from setpoint.
- After controller tuning: Temperature fluctuates around ±5°C from setpoint.

# Case study 3: Estimation of time to equilibrium (t95) in a whole body exposure chamber




- Aerosol generated from THS using rotary smoking machine and transferred to whole body exposure chamber (WBEC) containing animals and beddings.
- Sample taken from middle of WBEC.
- Carbon monoxide (CO): **t95 ~ 20 mins**.
- Nicotine: **t95 ~ 120 mins**. Cannot be derived from offline methods.

# Summary

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

- Nicotine concentration in nebulized diluted e-cig aerosol can be quantified continuously using the FTIR (within ±10% of results from offline method). Difference versus the offline method needs to be verified if the aerosol matrix changes (e.g., flavors).
- Results for propylene glycol and glycerin from offline methods are lower than those from the FTIR, possibly due to the lower trapping efficiency of filter pads.
- FTIR is sufficiently sensitive to be used for monitoring and troubleshooting the quality of diluted aerosol, as demonstrated by the ability to detect concentration changes due to:
    - Sub-optimal liquid level in nebulizer reservoir.
    - Variation in temperature of aerosol generator.
    - Time to reach equilibrium concentration.