Validation of an in-house process for the production of Sodium [^{18}F]fluoride radiopharmaceutical

Marija Atanasova Lazareva[1,2*], Maja Chochevska[1,2], Katerina Kolevska[1,2], Maja Velichkovska[1], Filip Jolevski[1], Ana Ugrinska[1,3], Emilija Janevik Ivanovska[2]

[1]University Institute of Positron Emission Tomography, Skopje, North Macedonia
[2]Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia
[3] Faculty of Medicine, Ss. Cyril and Methodius University, Skopje, North Macedonia

[*]marija.atanasova@ugd.edu.mk

Background
An original in-house method for the synthesis of Sodium [^{18}F]fluoride radiopharmaceutical ([^{18}F]NaF) was designed and developed. The process validation of [^{18}F]NaF radiopharmaceutical production was performed with the aim of confirming the reproducibility of the process to produce a final product with consistent quality.

Materials and methods
The protocol for process validation was developed following the recommendations outlined in FDA Guidance for Industry Process Validation: General Principles and Practices and EANM Guidance on validation and qualification of processes and operations involving radiopharmaceuticals. Three consecutive batches of [^{18}F]NaF were produced on different days under the same predetermined conditions.
The production process (synthesis and dispensing) was carried out on the dispensing module Clio, using a modified single-use kit for dispensing. The modification involved installing a Y-connector and QMA cartridge on the kit. The quality of the final product should be in accordance with [^{18}F]NaF monograph of European Pharmacopeia.
The tested parameters were approximate pH value (pH strips), identification (half-life determination and difference in retention times), chemical and radiochemical purity (ion-exchange HPLC isocratic method with radiodetector and conductivity detector serial connected), radionuclidic purity (gamma-ray spectrometry), bacterial endotoxins (chromogenic LAL method) and sterility.

Results
The results of tested quality parameters for the three batches were within the defined acceptance criteria. The difference in retention times was 33.18, 32.76 and 32.82 s, and the measured half-life was 1.80,1.84 and 1.82 h. The approximate pH value was 6.5-7.0 for each batch. No chemical and radiochemical impurities were detected in the three batches. Only [^{18}F]fluoride peaks were detected on the radiochromatograms, while no fluoride peaks were observed on the chromatograms obtained from the conductivity detector. Radionuclidic purity testing showed a very low percentage of radionuclide impurities (0.0000883, 0.00000171 and 0.000001633 %), which indicates a high radionuclidic purity. The results from the bacterial endotoxins testing were < 5 EU/mL for each batch and all tested samples were found to be sterile.

Conclusion
The process validation results confirmed that the in-house designed production process for manufacturing [^{18}F]NaF radiopharmaceutical is capable of consistently producing a product that fulfils the quality requirements defined in the European Pharmacopoeia monograph (Ph. Eur. 01/2008:2100).