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Short communication

Cleaning validation of equipment used for aseptic production of [^{18}F]NaF radiopharmaceutical

Marija Atanasova Lazareva[1,2*], Katerina Kolevska[1,2], Maja Chochevska[1,2], Maja Velickovska[1], Filip Jolevski[1], Zlatko Filipovski[1,2], Nevena Manevska[1,3], Emilija Janevik[2]

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

Introduction

Radiopharmaceuticals are medicinal products containing one or more radioactive isotopes and are widely used for diagnostic and therapeutic applications (Ph. Eur. 10.0, 07/2016:0125, 2020). As most radiopharmaceuticals are sterile parenteral preparations, the prevention of microbiological contamination is critical to ensuring product quality and patient safety. (EudraLex, 2008).

Cleaning validation is an important part of the contamination control strategy in sterile radiopharmaceutical manufacturing, providing documented evidence that cleaning procedures can control microbiological contamination, bacterial endotoxins, and potential residues on critical equipment surfaces. Cleaning validation should focus on surfaces that come into direct contact with operators, starting materials, intermediates or finished products (EudraLex, 2015). In radiopharmaceutical production, cleaning validation studies may be performed under routine operating conditions but without radioactivity and final sterilization (Todde et al., 2017). The aim of this study was to evaluate, the effectiveness of the cleaning procedure, applied to the ^{18}F transfer line, the semi-automatic module (used for preparation and dispensing of the [^{18}F]NaF), and the lead-shielded cabinet (hot cell) where the module is placed.

Materials and methods

Materials used for cleaning validation included enriched [^{18}O]water, the Endosafe®-PTS system, sterile vials, sterile needles, sterile swabs, and settle plates. The production process for [^{18}F]sodium fluoride has been previously described by Atanasova Lazareva et al. (2025). This study focused on cleaning validation of critical equipment and surfaces used during [^{18}F]NaF routine production.

Cleaning validation was performed on the ^{18}F transfer line connecting the cyclotron to the dispensing module, on the external surfaces of the module, and in the hot cell. Three consecutive validation runs were performed under conditions representative of routine production, but without radioactivity and without final sterilization. The Kit Clio, Y connector, and QMA cartridge used for preparation and dispensing were sterile single-use components and were excluded from cleaning validation study.

The ^{18}F transfer line is an inaccessible part of the equipment that cannot be routinely disassembled. Cleaning with detergents or disinfectants is not

*marija.atanasova@ugd.edu.mk

possible due to the risk of contamination of the cyclotron target. The line is used only for the delivery of irradiated enriched sterile water and is cleaned by helium flushing. Therefore, no product or detergent residues are expected. Consequently, indirect sampling by the rinse method was applied. A 10 mL sample of water for injection was transferred from the cyclotron through the transfer line, collected in a sterile vial, and tested for total microbial count and bacterial endotoxins.

The effectiveness of cleaning of the module was assessed by direct surface sampling using sterile swabs from four predefined critical or difficult to clean locations. Swabbing was performed after completion of the cleaning procedure and before the next production run.

Viable air monitoring was performed using settle plates placed at predefined positions in the grade A chamber and the grade B pre-chamber of the hot cell and exposed for 4 hours after cleaning.

Results and discussion

All three rinse samples from the ^{18}F transfer line showed no microbiological growth, and bacterial endotoxin levels were below 5 IU/mL in all samples. These values were below the predefined acceptance criterion for bacterial endotoxins in intravenous sterile solutions, which was less than 17.5 IU/mL. The final rinse sample was collected four days after the last cleaning procedure, further supporting the microbiological control of the transfer line.

All surface swab samples collected from the module, pre-chamber (grade B), and chamber (grade A) of the hot cell showed no microbiological growth. The acceptance criteria for settle plates, as defined in EudraLex Volume 4, Annex 1, are the absence of microbial growth for Grade A and less than 5 cfu/4 hours for grade B (EudraLex, 2022). During the three cleaning validation procedures, all settle plates showed no microbiological growth. These results demonstrated that the applied cleaning procedure maintained the ^{18}F transfer line, module and hot cell in a microbiologically controlled state.

Conclusion

The absence of microbiological growth in rinse samples, surface swab samples and settle plates, together with bacterial endotoxin levels below the predefined acceptance criterion, confirmed the effectiveness of the applied cleaning procedure. These findings support the suitability of the cleaning procedure for routine production of [^{18}F]NaF radiopharmaceutical.

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