[11C]-choline is an effective PET tracer used for imaging of neoplastic lesions and metastases of the prostate cancer. However, its production can be a challenge for manufacturers, as it has not yet been described in Polish or European pharmacopoeia. In this study the technical aspects of [11C]-choline production are described and detailed process parameters are provided. The quality control procedures for releasing [11C]-choline as solutio injectabilis are also presented. The purity and quality of the radiopharmaceutical obtained according to the proposed method were found to be high enough to safely administer the radiopharmaceutical to patients. Application of an automated synthesizer makes it possible to carry out the entire process of [11C]-choline production, isolation and purification within 20 minutes. It is crucial to maintain all aspects of the process as short as possible, since the decay half-time of carbon-11 is 20.4 minutes. The resulting radiopharmaceutical is sterile and pyrogen-free and of a high chemical, radiochemical, and radionuclide purity proved by chromatographic techniques. The yield of the process is up to 20%. [11C]-choline PET scanning can be used as accurate and effective diagnostic tool in all centers equipped with [11C]-target containing cyclotron.
Isotope production

The starting point of the production of Carbon-11-labelled radiopharmaceuticals is the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ nuclear reaction [16] – it takes place on the gaseous target of the Cyclone 18/9 (IBA) cyclotron with protons of 18 MeV energy.

The radioisotope is produced by proton irradiation (target current = 38 µA) of a gas N₂/O₂ mixture (the nitrogen target gas contains 0.5% oxygen, filling pressure equals 19 bar) with the proton beam energy of 18 MeV. The in-target activity of $^{11}\text{C}$-CO₂ peaks at 20–25 minutes of beam time, yielding 68 GBq.

Synthesis of $^{11}\text{C}$-methyl iodide

The $^{11}\text{C}$-CO₂ produced in a cyclotron is trapped on the molecular sieve of the synthesis module. To increase their efficiency, the molecular sieves are conditioned. This process involves removing moisture from the filling volume by heating it to a temperature of 250°C and simultaneously purging with nitrogen. The first conditioning should last 60 minutes, and before each subsequent use of the molecular sieves, the conditioning can be shortened to 20 minutes. The Bioscan synthesis module is used for preparation of $[^{11}\text{C}]$-choline. It consists of the Mel-PLUS™ unit adapted for the synthesis of $[^{11}\text{C}]$-methyl iodide and the Reform-PLUS™ unit in which the $[^{11}\text{C}]$-CH₃I precursor’s synthesis, isolation, purification, and final product collection take place. The modules are installed in hot cells to decrease the operator’s exposure to ionising radiation. Since Carbon-11 is produced in the form of a gaseous $[^{11}\text{C}]$-carbon dioxide, the chamber is adapted to collect potentially radioactive air from inside of the chambers.

The release of $[^{11}\text{C}]$-CO₂ into the reaction vial is performed identically as the conditioning: by heating the molecular sieves of the Mel PLUS™ unit to a temperature of 250°C for 90 seconds while purging the sieves with a nitrogen gas flow of 15 ml/min. Using a vial, $[^{11}\text{C}]$-CO₂ is reduced to methanol with LiAlH₄ in a tetrahydrofuran (THF) environment. After the evaporation of THF from the reaction mixture, a 57% solution of hydriodic acid is added to the reaction vial – it reacts with $[^{11}\text{C}]$-MeOH and forms $[^{11}\text{C}]$-CH₃I [17]. Figure 1 shows the radioactivity and oven temperature changes taking place during the subsequent stages of the $[^{11}\text{C}]$-Mel synthesis.
Synthesis, isolation and purification of \([^{11}C]\)-choline

**[\(^{11}C\)]-CH\(_3\)I distillation and reaction with the precursor**

The \([^{11}C]\)-methyl iodide distilled from the MeI PLUS™ unit is then transported into the vial by a constant flow of nitrogen (10 ml/min). The vial, which is a part of the ReFORM PLUS™ kit, contains the precursor, dimethylaminoethanol (DMAE) dissolved in dimethylformamide (DMF) in the ratio of 10 µl DMAE : 200 µl DMF. The reaction of \([^{11}C]\)-CH\(_3\)I with DMAE takes place almost instantaneously at room temperature, according to the formula [18]:

\[
\begin{align*}
\text{H}^3&\text{C} - \text{N} - \text{OH} + \text{[^{11}C]\text{CH}_3} + \text{I}^- \\
\rightarrow \text{H}^3&\text{C} - \text{N} - \text{OH} + \text{H}^3&\text{C} - \text{N} - \text{OH} + \text{I}^- \\
\end{align*}
\]

(1)

Competitive reactions with water, saline, or ethanol may also take place because methyl iodide is highly reactive. Such reactions are facilitated by the diffusion of the mentioned reagents into the ReFORM PLUS™ tubing assembly. Thus, the valves of the ReFORM PLUS™ kit should be carefully checked and closed. The reagents may be loaded after double-checking the valves.

**Isolation and purification of \([^{11}C]\)-choline**

The isolation and purification process is a four-step procedure conducted by the ReFORM PLUS™ unit. First, 1 ml of ethanol is added to the reaction vial to homogenise the mixture. Afterward, the whole mixture is extracted to solid phase on a cation exchange resin (Sep-Pack Accell Plus CM; Waters [8]). As the ionic compound, \([^{11}C]\)-choline is captured by the SPE column, and the remaining components of the reaction mixture are removed. To confirm the proper purification of the product, especially from the insoluble substances present in organic solvents, the SPE column should be washed twice with 5 ml of water. The final product is released from the SPE column using 0.9% saline solution and collected in a sterile, pyrogen-free vial with septum enclosure after the previous filtration on a 0.22-µm membrane sterile filter. Figure 2 shows the changes of the system radioactivity during the reformulation process.

In our first attempts at the synthesis of \([^{11}C]\)-choline a SPE SCX Maxi-Clean (Alltech) column was used instead of a Sep-Pack Accell Plus CM. However, the product could not be released from SCX Maxi-Clean cartridge with saline.

In a series of eleven subsequent approaches \([^{11}C]\)-choline was obtained with the yield up to 20%, as measured relative to the activity of \([^{11}C]\)-CO\(_2\) captured on molecular sieves.

The synthesised and purified product is a sterile, colourless solution of pH 7.5–8.5. Its sterility is determined by an accredited laboratory.

**Quality control**

The Polish and European Pharmacopoeia do not provide any guidelines on \([^{11}C]\)-choline quality control. However, some quality parameters can be customised on the basis of the general information from the pharmacopoeial chapters [19]: Potentiometric determination of pH (2.2.3), Gas chromatography (2.2.28), Identification and control of residual solvents (2.4.24), Sterility (2.6.1), and Bacterial endotoxins (2.6.14).

The quality control procedures based on the mentioned chapters are described in the subsequent points.

**Chemical and radiochemical purity**

The chemical and radiochemical purity are controlled using UHPLC apparatus DIONEX Ultimate 3000 with UV-VIS DAD, scintillation detector, and Corona CAD.

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**Fig. 2. System radioactivity changes during the reformulation process**
This study applies two analytical approaches to serve different application purposes. The first method, described by Boschi et al. [20], uses a phase-reversed C18 column (µBondapack® C18; 3.9 × 300 mm; Waters) and a mobile phase, which is a mixture of 3 mM sodium 2-naphthalenesulfonate (in place of 2-naphthalenesulfonic acid) with the addition of 1 mM H3PO4, with a flow rate of 1 ml/min.

The second approach is especially suitable for quality assurance, impurity analysis, and trace-level residue analysis, and it suits qualitative, confirmative, and semiquantitative applications. The HPLC method, benefiting from an Acclaim® Trinity™ trimode column, is able to separate cations, anions, and neutral species in a single run. It is based on the method described by Crafts et al. [21] and combines an Acclaim Trinity P1 column (3.0 × 50 mm; DIONEX) – a high-purity silica column designed for pharmaceutical applications – and three mobile phases (with flow rate 0.7 ml/min): 200 mM of ammonium acetate (pH = 4) (A), distilled water (B), and acetonitrile (C) with gradients of 5% (A), 35% (B), and 60% (C) (gradient time from 0 to 10 min) and of 40% (B) and 60% (C) (gradient time from 10 to 25 min).

The radiochemical detection was carried out using a scintillation detector with a CsI crystal.

Both analytical methods identify [11C]-choline. However, the first technique suffers from a detection limit that is too high, although the resolution of the choline signal detected at the retention time of 9.5 minutes (on the UV-VIS detector tuned to the wavelength of 297 nm) is satisfactory (Fig. 3). In the second method (the detection performed using charged aerosol detector – Corona CAD) the retention time is 1.2 minutes and the resolution is worse, but the detection limit is over 10-times better (Fig. 4).

**Nuclide identification**

The radionuclide identification was based on the results of gamma radiation energy measurements [22] and the calculation of a radionuclide half-life.

For the positron emitting isotopes – such as Carbon-11 – the energy of the detected gamma quanta should be 511 keV, as the positrons annihilate with electrons. The expected half-life of Carbon-11 is 20.4 minutes [23]. The decay properties of Carbon-11 are shown in Table 1.

The gamma-ray spectroscopy was done using RAY-TEST MUCHA multichannel analyser with NaI 3 x 3” detector. The 511 keV photons and a sum peak of 1022 keV are observed in the gamma-ray spectrum, thus confirming the positron decay mechanism of the obtained radionuclide, as shown in Fig. 5.

The radotracer half-life was obtained using calibrated radiometric method and applying an ionisation chamber dose calibrator for the activity measurements. Each activity measurement lasts 15 minutes and is repeated every minute. The radionuclide half-life can be calculated using the following equation [24]:

$$T_{1/2} = -\ln \left( \frac{A_1}{A_0} \right) \frac{dt}{\ln \left( \frac{A_1}{A_0} \right)}$$  

where:

- dt – time difference, $A_1$ – ending activity, and $A_0$ – starting activity.

The half-life time equals 20.3 ±0.1 minutes and uniquely identifies the nuclide as Carbon-11.

**Table 1. Carbon-11 decay scheme**

| Parent nuclide | $T_{1/2}$ | Decay mode | $E_{\text{max}}$ | Relative intensity | $E_{\gamma}$ | Daughter nuclide |
|----------------|----------|------------|------------------|-------------------|-------------|-----------------|
| $^{11}$C        | 20.38 min| +          | 960.2 keV        | 99.759%           | 511 keV     | $^{11}$C        |

![Fig. 3. Chromatogram of choline chloride method 1](image1)

![Fig. 4. Chromatogram of choline chloride method 2](image2)
Bacterial endotoxin purity

The same bacterial endotoxin limit for \([^{11}C]\)-choline was accepted as \([^{18}F]\)-FDG, i.e. < 175 EU/dose; maximum dose 10 ml per patient [25].

The bacterial endotoxin test was performed using Endosafe®-PTS™ (Charles River) apparatus and the kinetic chromogenic LAL-test method [26] was applied, in accordance with the European Pharmacopoeia [25].

Residual solvents

The methodology for organic residual solvents testing was in accord with the pharmacopeial method [27]. However, some parameters (such as split ratio and total flow rate) were modified by a trial-and-error method, to adjust the procedure to the equipment used in the analysis.

A gas chromatography system equipped with an HP-Innowax column (30 m × 0.32 mm; film: polyethylene glycol 0.50 µm) was used. The adjusted parameters were as follows: the volume of sample injection was 1 µl; split 5.0 : 1 at a total flow of 16 ml/min with helium as a carrier. The column’s oven temperature: 50°C. Detection was carried out on an FID detector.

Radionuclide purity

Gamma spectroscopy [28] of the final sample was carried out in a Canberra-Packard gamma spectrometer equipped with a high-purity germanium (HPGe) detector. The spectral measurements were performed two days after the synthesis. The spectrum was measured for 180 minutes to integrate enough counts for high a signal-to-noise ratio (S/N) and to resolve the spectrum. The sample volume should be at least 1 ml. The gamma spectrum, shown in Fig. 6, was analysed using Genie 2000 software and the radionuclide content was determined to be below 0.1%.

Fig. 5. Gamma-ray spectrum of Carbon-11

Results

The highest activity output of Carbon-11 isotope produced in a cyclotron target took place in the first minute of irradiation. During the first minute of the process the Carbon-11 radioactivity reached about 3.7 GBq. A target irradiation for 25 minutes yielded about 68.45 GBq of Carbon-11 radioactivity. Saturation of the target was obtained after about two hours and the activity gained was 110 GBq. Then, the activity yield decreased – this was due to saturation of the target material and the decay processes of Carbon-11.

Within five minutes, the target was discharged and the product – \([^{11}C]\)-CO\(_2\) – was trapped on the molecular sieves. The operating time of the Mel PLUS™ unit, from the start of heating of the molecular sieves until the end of the \([^{11}C]\)-methyl iodide distillation was approximately 11 minutes, and the yield of the released \([^{11}C]\)-CO\(_2\) from the molecular sieves was between 85 and 90%. Reformulation and collection of the product in the final product vial took
six minutes. Thus, the total time required for production, purification, and packaging of $[^{11}C]$-choline equaled approximately a half-life time of Carbon-11, with a yield of up to 20%, as calculated on the basis of activity. In practice, when starting from an initial activity of 65 GBq, it was possible to obtain 14 GBq of $[^{11}C]$-choline in a form of sterile, pyrogen-free isotonic solution.

Table 2 summarises the quality control data of the final product (its chemical, radiochemical, radionuclidic, and biological purities). The results confirm the batch-to-batch reproducibility of the production process and identify a radionuclide as Carbon-11 by a match of measured decay characteristics to the listed values. The radiochemical purity, determined by liquid chromatography method, exceeded 99%, and the amount of radionuclide impurities was less than 0.1%. The levels of ethanol and dimethylformamide meet the pharmacopoeia requirements [29], as confirmed by gas chromatography.

Application of Corona CAD detector enhances the signal-to-noise ratio and chemical purity of the synthesised $[^{11}C]$-choline is at least 98%.

**Discussion**

Radiopharmaceuticals are only supplied for use in patients if they have been correctly processed, checked and stored in accordance with the defined procedures and released by a competent person. Thus, the quality control procedure is an important part of the production process. Control operations involve chemical purity control, radiochemical purity control, nuclide identification, bacterial endotoxin purity control, and residual solvent detection.

Chemical purity of radiopharmaceuticals refers to the amount of undesirable chemical species present. Chemical impurities include all nonradioactive substances that can either affect the radiolabeling process or directly produce adverse biological effects [30].

Radiochemical purity is defined as the percentage of the total radioactivity present in the desired chemical form in a radioactive pharmaceutical [31]. This kind of purity is a crucial issue in a diagnostic PET image interpretation, especially in case of short-lived radiopharmaceuticals – an unacceptable radiochemical purity can lead to radiopharmaceutical unspecific uptake, which may result in irradiation of critical organs and false diagnosis. The described $[^{11}C]$-choline manufacturing process allows eight doses of the radionuclide to be prepared for clinical applications, whereas total time required to produce one batch of the radiopharmaceutical, including quality control, is approximately one hour, which allows to produce three series per working day with a total number of 24 doses of $[^{11}C]$-choline.

Another radiotracer with a similar use as $[^{11}C]$-choline is $[^{18}F]$-fluoromethylcholine, and its manufacturing processes is described elsewhere [8]. Due to $[^{18}F]$-labelling, the half-life of $[^{18}F]$-fluoromethylcholine is longer (109 minutes vs. 20 minutes in the case of $[^{11}C]$), whereas the $[^{18}F]$ positron range is shorter [32]. The longer half-life makes it possible to distribute the product away from the manufacturing site. However, the $[^{11}C]$-choline is preferred for prostate PET/CT imaging due to better distribution and higher assimilation of this tracer in the patient’s body as compared to $[^{18}F]$-fluoromethylcholine [33, 34] – the advantage of the latter is its nearly four-times longer half-life, which makes shipping possible and facilitates commercial availability of the choline containing tracer.

The purity and quality of the obtained radiopharmaceutical are high enough to safely administer it to patients. The production is also safe for the operator – due to the

| Test                     | Acceptance criteria | Batch 1 | Batch 2 | Batch 3 | Batch 4 | Batch 5 |
|--------------------------|---------------------|---------|---------|---------|---------|---------|
| pH                       | 4.5–8.5             | 8.23    | 8.16    | 8.27    | 8.19    | 8.29    |
| Appearance               | Clear, colourless   | Clear, colourless | Clear, colourless | Clear, colourless | Clear, colourless | Clear, colourless |
| EtOH                     | ≤ 5000 µg/ml        | 4251.36 µg/ml | 3017.87 µg/ml | 3981.82 µg/ml | 3964.24 µg/ml | 3682.47 µg/ml |
| DMF                      | ≤ 880 µg/ml         | 717.62 µg/ml | < 7 µg/ml | 730.56 µg/ml | < 7 µg/ml | 877.21 µg/ml |
| DMAE                     | 10 µg/ml            | < 7 µg/ml | < 7 µg/ml | < 7 µg/ml | < 7 µg/ml |
| Radiochemical purity     | ≥ 95% of $[^{11}C]$-choline | 99.09% | 99.36% | 99.20% | 99.32% | 99.30% |
| Gamma-ray identification | 511 ±10 KeV         | 511 keV | 512 keV | 514 keV | 514 keV | 510 keV |
| Radionuclidic purity     | ≥ 99.9%             | > 99.9% | > 99.9% | > 99.9% | > 99.9% | > 99.9% |
| Half-life                | 19.9–20.9 min       | 20.3 min | 20.3 min | 20.3 min | 20.4 min | 20.2 min |
| Bacterial endotoxin      | Ph. Eur. Conform (< 17.5 IU/ml) | < 10 IU/ml | < 10 IU/ml | < 10 IU/ml | < 10 IU/ml | < 10 IU/ml |
| Sterility                | Ph. Eur. Conform    | Sterile | Sterile | Sterile | Sterile | Sterile |
short half-life of Carbon-11, radiological contamination in the hot cell is reduced to a safe level within two hours. 

[11C]-choline-PET/CT may offer new hope to patients with prostate cancer and lymph node metastasis because current imaging modalities (including transrectal ultrasound, MRI, CT, and bone scan) demonstrate poor performance in the diagnosis and staging of this disease. [11C]-choline seems also to open a promising path for the study of genetic disorders involving metabolic alternations of choline-containing metabolites [35].

Conclusions
The described [11C]-choline manufacturing process allows eight doses of the radionuclide to be prepared for clinical applications.

The total time required to produce one batch of the radiopharmaceutical, including quality control, is approximately one hour, which allows the production of three series per working day with a total number of 24 doses of [11C]-choline.

The radiopharmaceutical purity and its quality are high enough to safely administer the radiopharmaceutical to patients. The production is also safe for the operator. All cyclotron-PET centres equipped with a [11C]-target containing cyclotron can consider using [11C]-choline because it has better diagnostic properties over Fluorine-18 analogue.

The authors declare no conflict of interest.

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