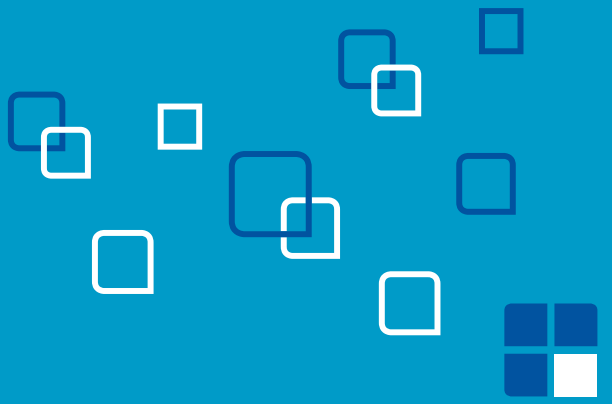
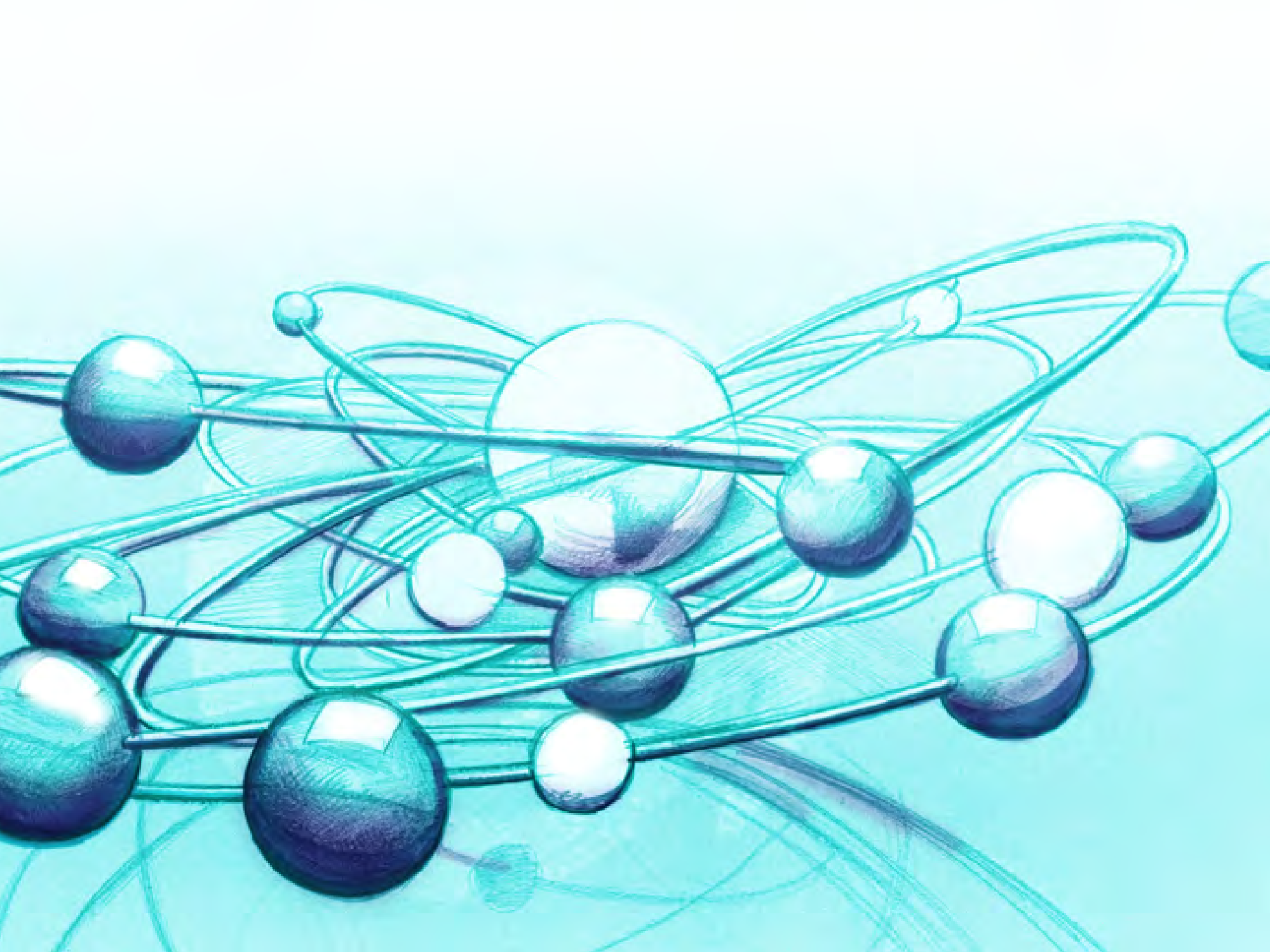
Radiopharmaceuticals





ÚJV Řež, a. s.

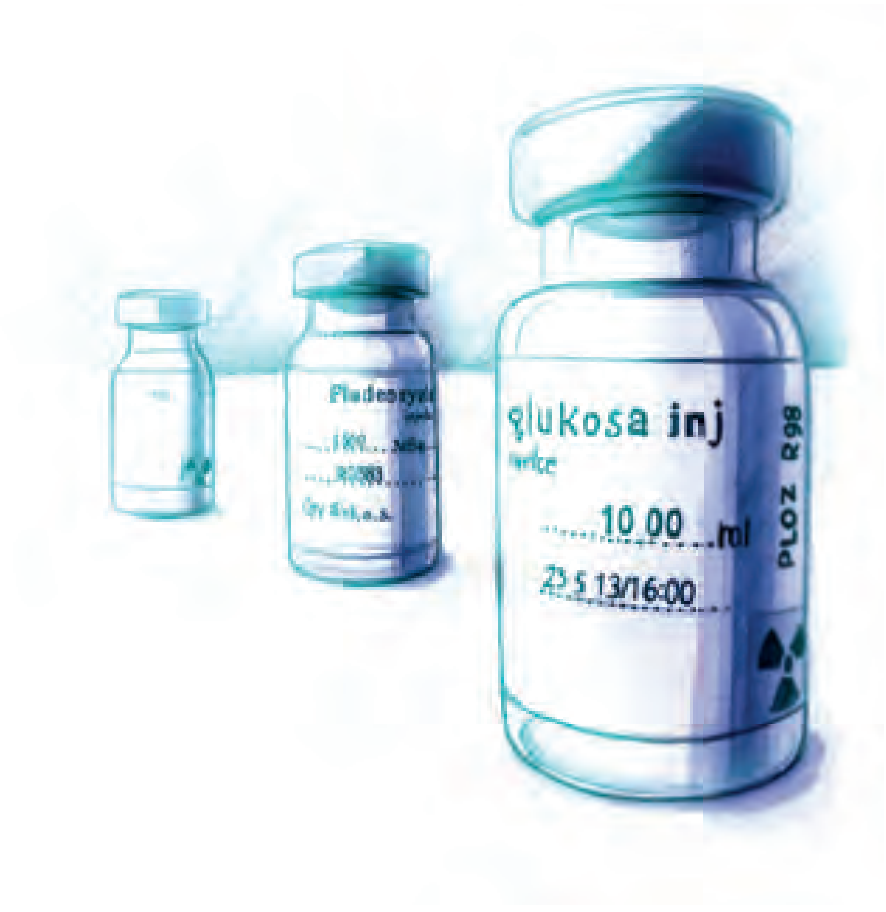
ÚJV Řež, a. s., is a renowned research & development and engineering company focused on nuclear technologies and their applications. The founding of the company dates to the year 1955. Besides safety evaluation, operation checking and nuclear facility testing, ÚJV Řež, a. s., focuses also on securing a long-term operating of nuclear power plant blocks, optimization of their operation and increasing their performance. A key field of interest is also healthcare. Through it s Radiopharmaceuticals Division, the company operates in the field of production, quality control, research and development of radiopharmaceuticals for more than 35 years.

Radiopharmaceuticals Division Then and Now

The Radiopharmaceuticals Division has a long tradition and successful history. The production of first radiopharmaceutical drug took place here as early as in 1974. The product range was then oriented to production of radiopharmaceuticals in the form of radioactive injections usable for SPECT diagnostic examinations, as well as kits for preparation of these radiopharmaceuticals.

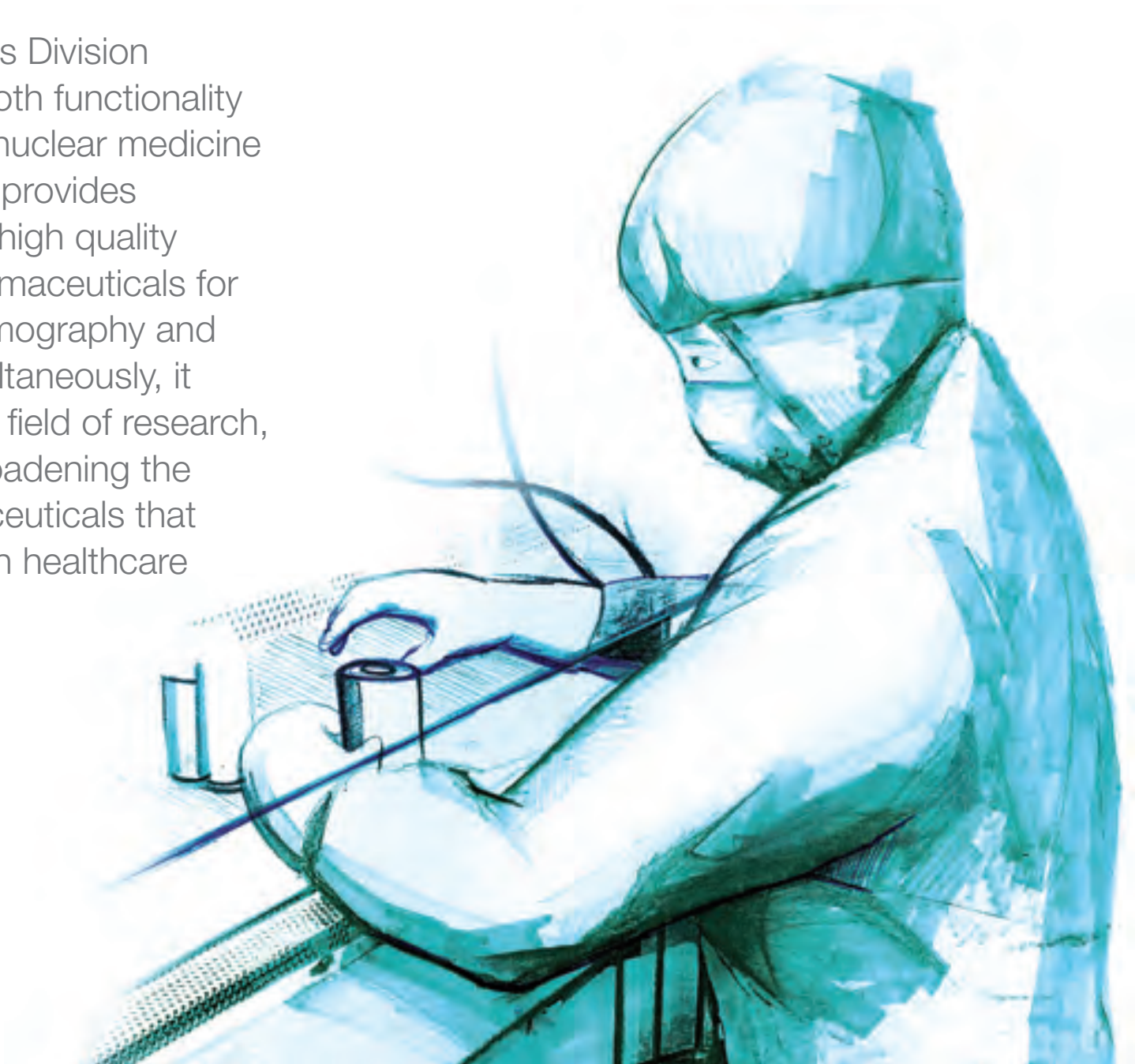
In 2001, a routine production of ^{18}F-fluorine labelled glucose, FDG in short, was established. This radiopharmaceutical allows for performing examinations by a state-of-the-art diagnostic method called positron emission tomography (PET). This was preceded by building and establishing the first PET centre for Central and Eastern Europe in Prague, by the Na Homolce Hospital, with both production and diagnostic part. This model project of the International Atomic Energy Agency (IAEA) became crucial for the development of new diagnostic method in Czech Republic. In 2008, the ÚJV Řež, a. s. celebrated the opening of second PET centre by the Masaryk Memorial Cancer Institute in Brno, with the objective to ensure the same potential in PET diagnostics also for the

Moravian part of the country. In 2012, the Radiopharmaceuticals Division finished the construction of a third PET centre, situated in the seat of the company itself, the purpose of which is mainly research and development of new radiopharmaceuticals. The product portfolio of the Division currently consists of a routinely produced radiopharmaceuticals (mainly FDG) and kits for preparation of radiopharmaceuticals. The focal point is also the R&D field with special emphasis on new radiopharmaceuticals labelled by ultrashort-living nuclides.



The Mission

Radiopharmaceuticals Division contributes to a smooth functionality and development of nuclear medicine in Czech Republic. It provides reliable, on-time and high quality supplies of radiopharmaceuticals for positron emission tomography and other methods. Simultaneously, it pursues objectives in field of research, development and broadening the offer of radiopharmaceuticals that are available to Czech healthcare institutions.



Market Position – What Distinguishes Us From Competitors

We are a stable supplier of radiopharmaceuticals for many nuclear medicine departments both in Czech Republic and abroad. We are the only manufacturer in Czech Republic who owns three cyclotrons for positron emitter production.

- Through the three PET centres we cover the majority of PET radiopharmaceuticals market in Czech Republic
- We own a unique technical and technological know-how (clean premises, semi-hot cells, synthesis modules, quality control laboratories etc.
- We have our own research and development facility for radiopharmaceuticals in the newly built PET centre Řež
- We offer research and development collaboration, utilizing our long and rich experience in solving R&D tasks
- We have permissions for production of medicinal products and investigational medicinal products, as well as distribution of radiopharmaceuticals

- Our team consists of highly qualified experts
- Thanks to the Laboratory of Biological Testing, we are the only facility in Czech Republic that can, based on permissions from the overseeing authorities (State Institute for Drug Control and State Office for Nuclear Safety), offer to perform various types of tests and studies including the Good Laboratory Practice regime

What We Can Offer

We are running three PET centres in the Czech Republic, and based on a long-time practical experience, we offer the following services to our partners:

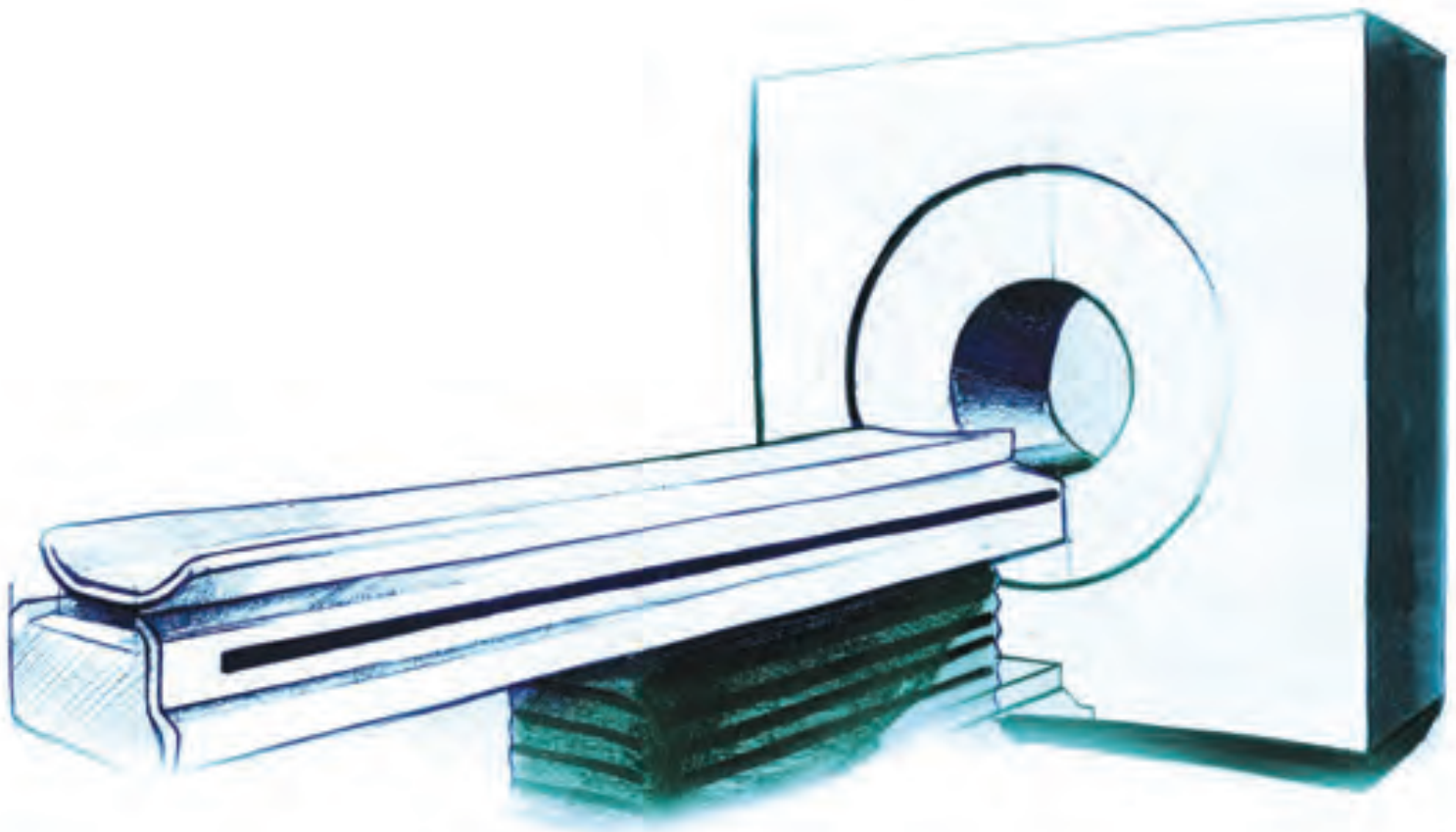
Construction of PET Centres

- Turn-key construction of PET centres
- Creating a complete project documentation (both structural and technological)
- Choice of suitable suppliers
- Consulting in choosing the technologies
- Obtaining the permissions and certificates necessary for running the facility
- Acceptance tests and equipment qualification
- Launching the operation of the facility

Operating PET Centres

With regard to our experience with production and supplies of the most used PET radiopharmaceutical (FDG) to all PET-equipped healthcare institutions in the Czech Republic, we offer practical consulting in the following fields:

- Transferring PET radiopharmaceuticals to routine production
- Organization of production and distribution in regard to the various requirements of customers
- Optimization of movement of PET radiopharmaceuticals at the nuclear medicine departments
- Solutions for crisis supply scenarios
- Validation of equipment

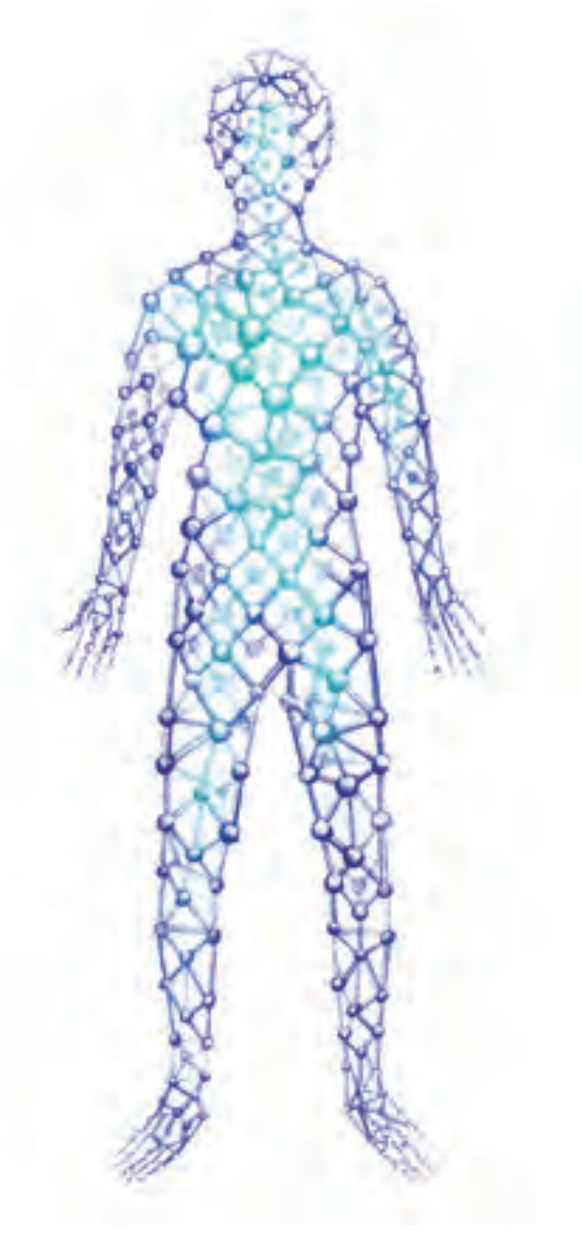


Training PET Centres' Staff

We can provide the training of staff for operating a PET centre, both in theoretical and practical field. We will accommodate to individual requirements for training, from beginners to people already acquainted with pharmaceutical production. Thanks to the mastered process of transferring technologies and processes between individual worksites and an effective system of experience transfer to the trainees we achieve significant reduction of maintenance costs of the operated equipment. Trained employees are operating and perform maintenance of the manufacturing technologies in an extent that allows to reduce the need for externally-provided maintenance.

The training focuses on the following:

- Operating a cyclotron
- Production of radiopharmaceuticals
- Quality control
- Radiation safety assurance
- Quality management system



Services of the Laboratory of Biological Testing

Our laboratory of biological testing, as the only one in Czech Republic, holds both the certificate of Good Laboratory Practice (issued by State Institute for Drug Control) and the permission for working with sources of ionizing radiation (issued by State Office of Nuclear Safety) Thanks to it, the laboratory can perform various special tests and studies, such as tests of physiological distribution of radiopharmaceuticals, cultivation of cell cultures, application of cell cultures to mice or toxicity studies of new medicinal products. As the only facility in Czech Republic, we can perform preclinical studies of new radiopharmaceuticals. These studies are essential for subsequent marketing authorization and routine use of a medicinal product.

Legislation Counselling

- Implementation of State Institute for Drug Control instructions (Good Manufacturing/Laboratory/Distribution Practice) into the process of production of radiopharmaceuticals, their distribution and release to market, as well as studies of physiological distribution and preclinical drug testing.

- Assurance of the State Office for Nuclear Safety requirements in production, quality control and distribution of radiopharmaceuticals as ionizing radiation sources.

Logistics Support Counselling

- Dispensation of radiopharmaceuticals
- Cooperation between manufacturer and customers in order to achieve the optimum in transport of PET radiopharmaceuticals and providing required equipment

Other services

- Distribution of drugs
- Qualified person (QP) services

Performing Clinical studies

- After the installation of PET scanner and launching of the medical facility in full operation (PET Centre Řež,2015), it will be possible to perform contractual clinical studies with PET radiopharmaceuticals, thanks to the necessary infrastructure and production possibilities

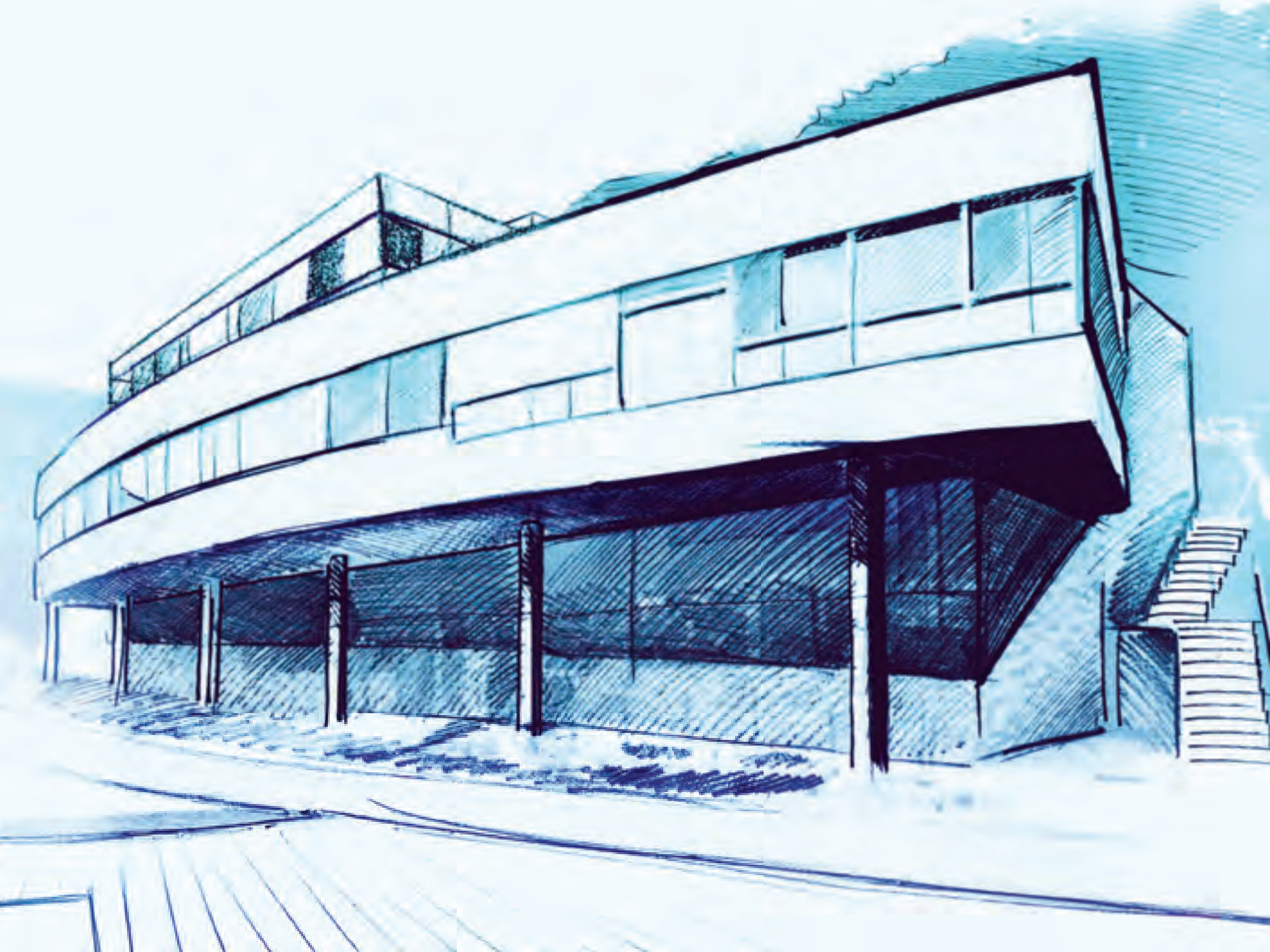
Research and Development

Besides the routine production, the Radiopharmaceuticals Division also deals with the research and development, especially in the field of PET. The research projects focus on introducing new PET radiopharmaceuticals, labelled mainly by fluorine ^{18}F or carbon ^{11}C to the market and diagnostic practice. We also focus our attention to the possibilities of using other radionuclides for PET purposes. The radiopharmaceuticals we develop are used in diagnostics of oncologic diseases, in neurology (Parkinson or Alzheimer disease) and cardiology. The cyclotron equipped with the solid target external beam-line allows us to work also in biomolecule labelling (peptides or antibodies) and therefore participate in development of methods of biological treatment.

Our PET Centres

R&D PET Centre Řež – year 2012

PET centre is located in the premises of ÚJV Řež, a. s., and it was launched into operation in year 2012 for the purpose of providing new capacities for research, development and implementation of new prospective PET radiopharmaceuticals, as well as training of staff of PET Centres. Currently, another construction is underway here – the diagnostic part with a planned installation of required technology including own PET scanner. After the construction is finished, this PET Centre will perform, in collaboration with a healthcare institution, the research, development and application of new PET radiopharmaceuticals and clinical studies will be performed here as well. This project is co-financed from the European Regional Development Fund (ERDF) and the state budget of Czech Republic under the framework of Operational Programme Business and Innovation (OPBI). This project finished third in the Investor of the Year 2010. It was awarded by the Greatest Innovation Potential Award by CzechInvest in cooperation with the Ministry of Industry and Trade of the Czech Republic and the Association for Foreign Investment (AFI)

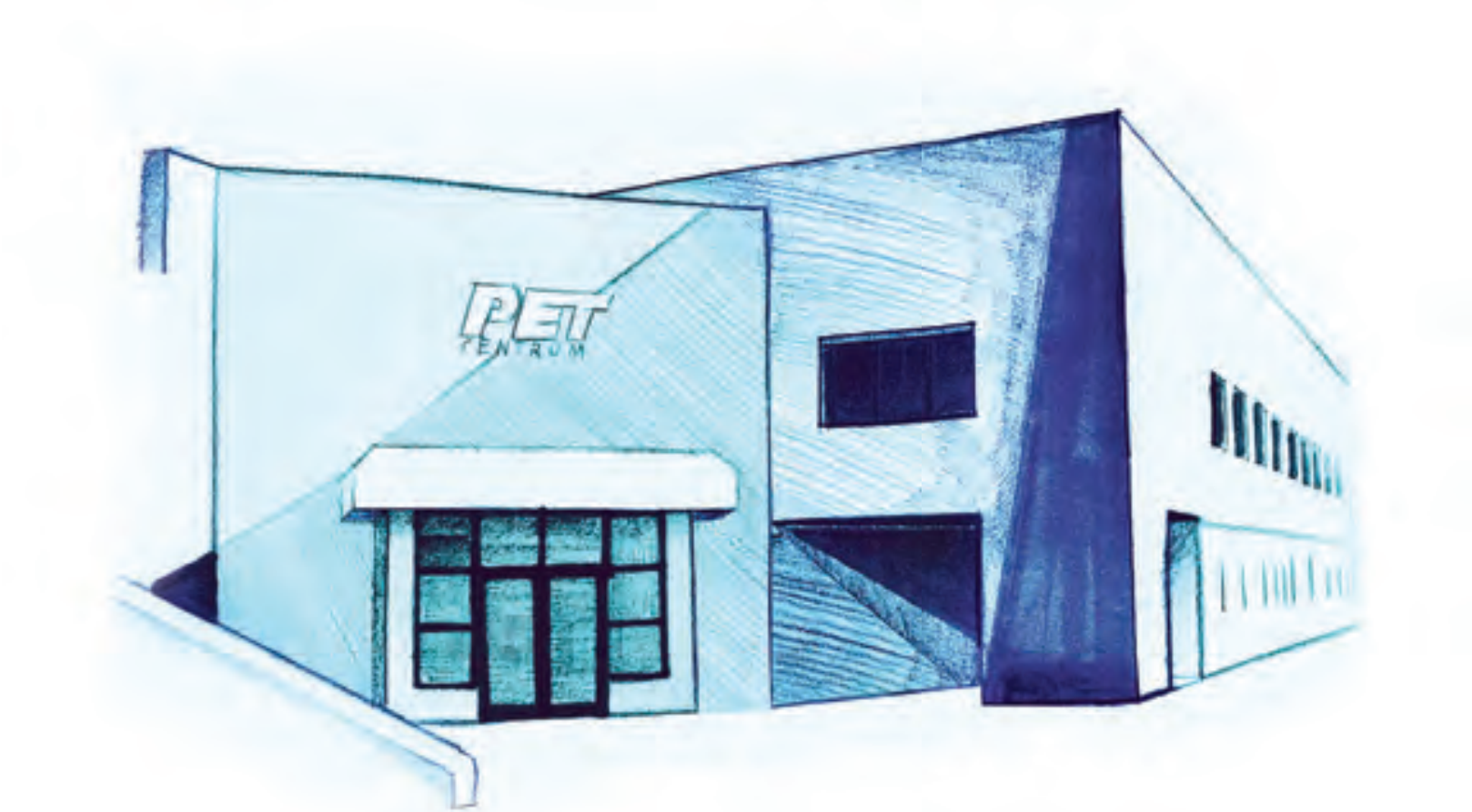


PET Centre Brno – year 2008

PET Centre Brno is located by the Masaryk Memorial Cancer Institute in Brno and it provides Fludeoxyglukosa inj. (FDG) supplies primarily for the Moravian regions.

PET Centre Prague – year 2001

PET Centre Prague is located by the Na Homolce Hospital and it was the first PET Centre in Czech Republic. Thanks to this centre, the PET method became available in Czech Republic and a new era of this diagnostic method began. The centre provides routine production of Fludeoxyglukosa inj. (commercial name of the ^{18}F-fluorodeoxyglucose produced by ÚJV Řež, a. s.).



Technologies

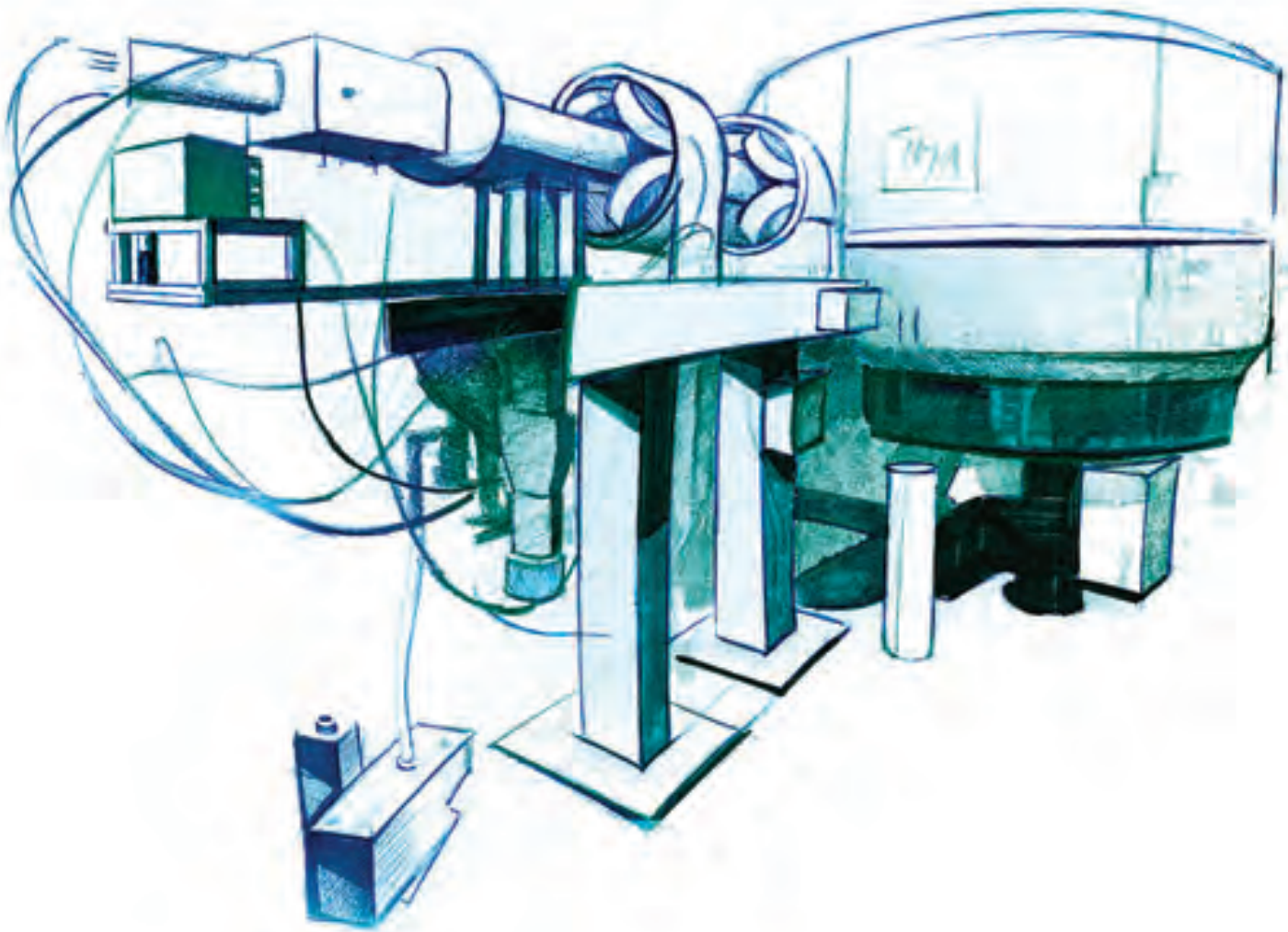
The Radiopharmaceuticals Division of ÚJV Řež, a. s., has a complex technological infrastructure for production and development of PET radiopharmaceuticals and their implementation to production.

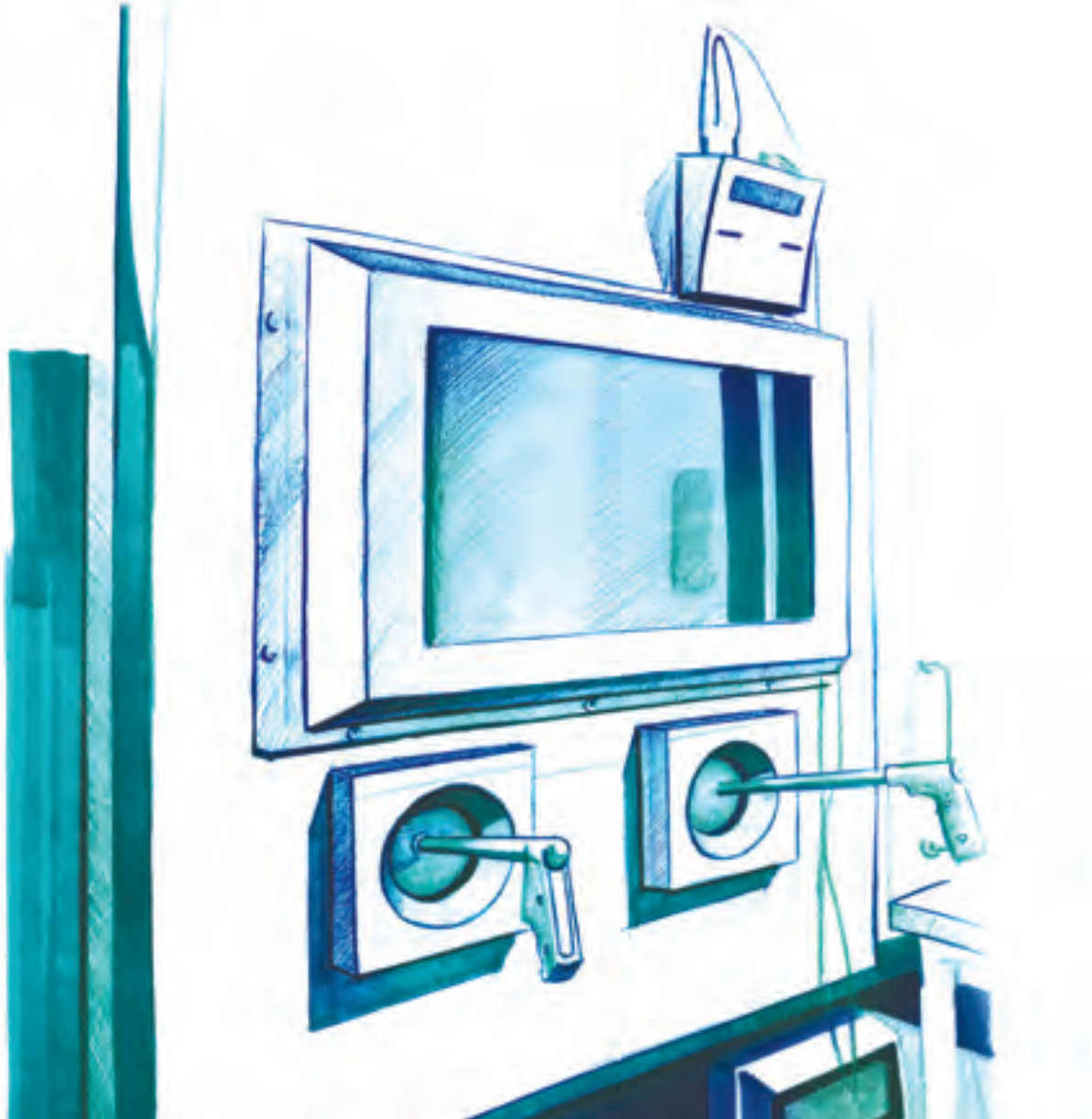
Cyclotron

The cyclotron is a device essential for production of PET radiopharmaceuticals and it determines the capacity of each PET production centre. All three centres of our company are equipped by the IBA Cyclone 18/9 (Belgium), constructed specifically for PET radionuclide production. This type of cyclotrons allows to be equipped by up to eight targets, a feature that enables a broad range of PET radionuclides to be produced.

Synthesis Units (Modules)

The radiopharmaceuticals are produced in automatized synthesis units manufactured by GE Healthcare or IBA. Nowadays, we produce not only the most used FDG (Fludeoxyglukosa inj.), but also other PET radiopharmaceuticals labeled by ^{11}C or ^{18}F.





Semi-Hot Cells (Shielded Boxes)

The production of PET radiopharmaceuticals takes place in semi-hot production cells (shielded boxes) in order to ensure the highest levels of safety when working with open sources of ionizing radiation. These cells are tailor-made for said worksite and process of production, from the arrival of activity to synthesis module to aseptic dispensation of the final product into vials.

Clean Premises

Premises with strictly defined requirements for purity of environment are an essential part of nuclear medicine departments that produce radiopharmaceuticals. The premises ensure high standard of purity during production of drugs intended for application by injection. After fulfilling and checking the legislative requirements for clean premises, a continuous monitoring and an annual validation by an external company. For each produced batch of radiopharmaceutical, the purity of environment is monitored. The monitoring of clean premises during the production encompasses particle count in the air, microbiological testing and measurement of temperature and humidity.

Laboratory of Quality Control

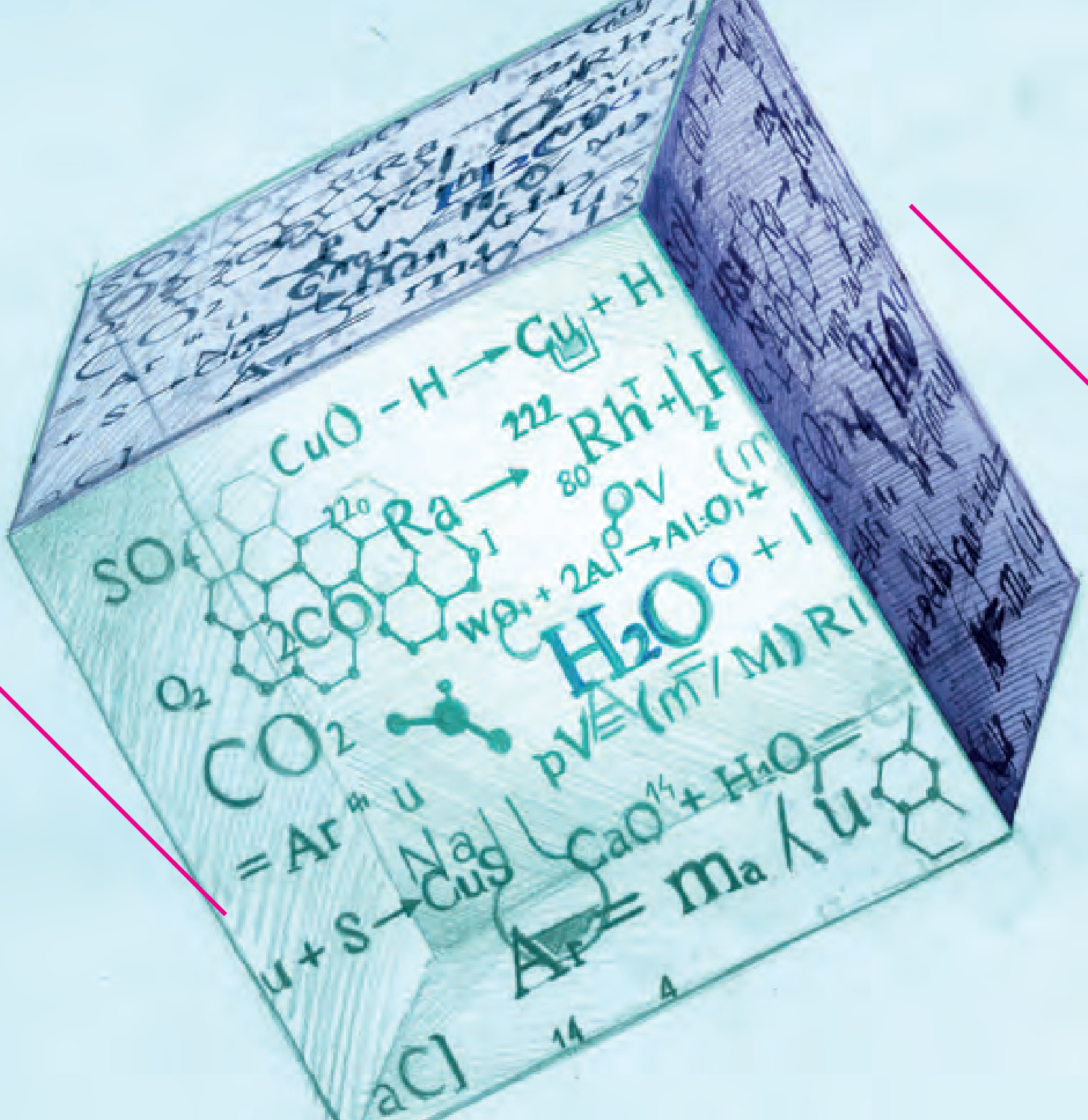
Each produced batch of PET radiopharmaceutical is subjected to strictly determined set of quality control checks, according to the approved procedures of Laboratory of Quality Control. In order to perform the tests, the laboratory is equipped by state-of-the-art equipment and apparatuses that are included in metrological system and verified or calibrated in predefined intervals of time. A part of the LQC is a microbiological laboratory including special box for performing sterility tests, laboratory premises for evaluation of these tests, for manipulation with microbiological testing material and performing tests on the presence of bacterial endotoxins – the so-called LAL tests. During the production of each batch, the LQC ensures monitoring of the environmental conditions by the prescribed standards. Thanks to this equipment, the quality of produced radiopharmaceuticals declared in approved dossier can be verified and the information about sterility and endotoxin content can be obtained.

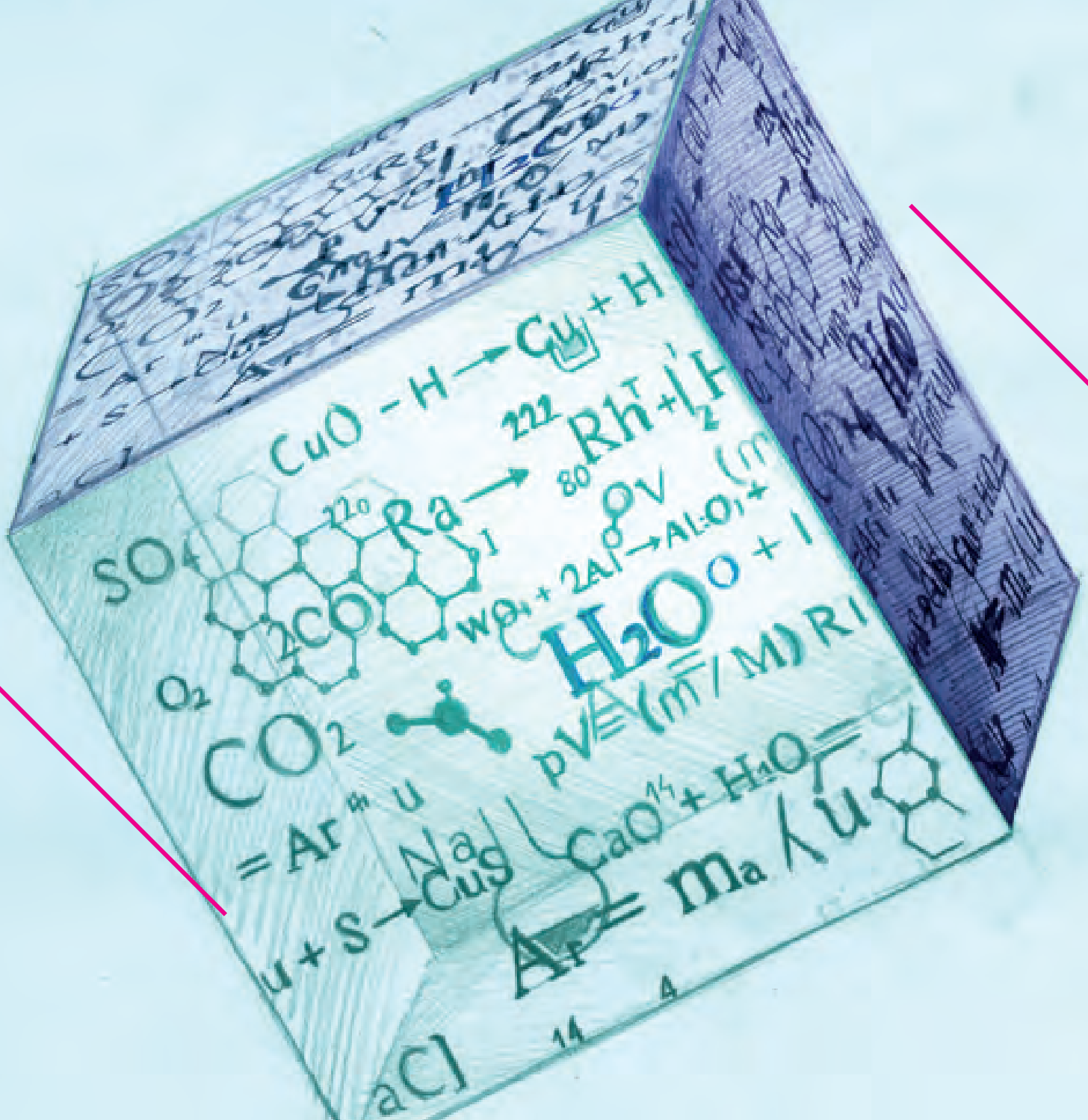
ÚJV Řež, a. s. – Summary

- Currently operating three PET centres for production and development of PET radiopharmaceuticals
- We have sufficient capacity to provide the supply of the most used PET radiopharmaceutical Fludeoxyglukosa inj. for the PET or PET/CT diagnostics all over the Czech Republic
- In 100% of the cases, we are able to back up eventual production failures of individual PET centres
- In accordance to our customers' wishes, we offer development and transfer of PET radiopharmaceuticals into production.

Hlavní 130, Řež, 250 68 Husinec
Czech Republic
www.ujv.cz

Design, production: TOP Partners, s.r.o., 2013


CuO - H → Cu + H
$^{220}_{86}Ra \rightarrow {}^{216}_{84}Po + {}^{4}_{2}He$
$^{222}_{80}Rh + {}^{1}_{2}H$
SO_4
CO_2
O_2
H_2O
$pV = (m/M)RT$
$= Ar \cdot u$
$u + S \rightarrow CuS$
$CaO + H_2O$
$A_r = m_a \cdot u$
aCl


CuO - H → Cu + H
$^{220}_{86}Ra \rightarrow {}^{216}_{84}Po + {}^{4}_{2}He$
$^{222}_{80}Rh + {}^{1}_{2}H$
SO_4
CO_2
O_2
H_2O
$pV = (m/M)RT$
$= Ar \cdot u$
$u + S \rightarrow CuS$
$CaO + H_2O$
$A_r = m_a \cdot u$
aCl

www.ujv.cz