Radiopharmaceuticals: Production and Availability

A. Introduction

1. The use of specific radiotracers called radiopharmaceuticals for imaging organ function and disease states is a unique capability of nuclear medicine. Unlike other imaging modalities such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Ultrasonography (US), nuclear medicine procedures are capable of mapping physiological function and metabolic activity and thereby giving more specific information about the organ function and dysfunction (1). The mapping of the radiopharmaceutical distribution in vivo provides images of functional morphology of organs in a non-invasive manner and plays an important role in the diagnosis of many common diseases associated with the malfunctioning of organs in the body as well as in the detection of certain type of cancers. The widespread utilization and growing demands for these techniques are directly attributable to the development and availability of a vast range of specific radiopharmaceuticals.

B. Radioisotopes for Radiopharmaceuticals: History and Growth

2. Radiopharmaceuticals are medicinal formulations containing radioisotopes which are safe for administration in humans for diagnosis or for therapy. Although radiotracers were tried as a therapeutic medicine immediately after the discovery of radioactivity, the first significant applications came much later with the availability of cyclotrons for acceleration of particles to produce radioisotopes. Subsequently, nuclear reactors realised the ability to prepare larger quantities of radioisotopes. Radioiodine (iodine-131), for example, was first introduced in 1946 for the treatment of thyroid cancer, and remains the most efficacious method for the treatment of hyperthyroidism and thyroid cancer.

3. One of the major goals for setting up nuclear research reactors was for the preparation of radioisotopes. Among the several applications of radioisotopes, medical applications were considered to be of the highest priority. Most of the medium flux and high flux research reactors now are routinely used to produce radioisotopes for medical, and also industrial, applications. The most commonly used reactor produced isotopes in medical applications are molybdenum-99 (for production of technetium-99m), iodine-131, phosphorus-32, chromium-51, strontium-89, samarium-153, rhenium-186 and lutetium-177 (2).

4. The early use of cyclotron in radiopharmaceuticals field was for the production of long lived radioisotopes that can be used to prepare tracers for diagnostic imaging. For this, medium to high energy (20-70 MeV) cyclotrons with high beam currents were needed. Isotopes such as thallium-201, iodine-123 and indium-111 were prepared for use with single photon emission computed tomography (SPECT). With the advent of positron emission tomography (PET), there has been a surge in the production of low energy cyclotrons (9-19 MeV) exclusively for the production of short lived PET radionuclides such as fluorine-18, carbon-11, nitrogen-13 and oxygen-15. Figure 1 shows such a machine. The majority of the cyclotrons (~350) worldwide are now used for the preparation of fluorine-18 for making radiolabelled glucose for medical imaging (3).

Fig. 1: A 13 MeV cyclotron (indigenous product) in operation in Chosun University, Republic of Korea.

C. Radiopharmaceuticals Production Aspects and Challenges

5. Currently there are over 100 radiopharmaceuticals developed using either reactor or cyclotron produced radioisotopes and which are used for the diagnosis of several common diseases and the therapy of a few selected diseases, including cancer. Radiopharmaceuticals production involves handling of large quantities of radioactive substances and chemical processing. Aspects which need to be addressed in radiopharmaceuticals production, including the management of radioisotope production, include import, operation and maintenance of processing facilities, complying with the codes of current good manufacturing practices (cGMP), ensuring effective quality assurance and quality control (QA & QC) systems, registration of the products with national/regional health authorities and radioactive material transport etc.

6. Radiopharmaceuticals production, unlike conventional pharmaceuticals production, is still on a relatively small scale and implementing the cGMP guidelines which are applicable for the drugs industry is both difficult and expensive. Ensuring cGMP compliance is a demanding task for a small scale manufacturer, as it involves taking care of several aspects prior to, during and after production. These include the development of well qualified personnel, use of controlled materials and procedures, availability of qualified equipment, production of the products in designated clean areas, applying validated processes and analytical methods, full documentation of the process and release of the final product by a qualified person. Application of clean room requirements in radioisotope laboratories in general and hot cells in particular (Fig. 2), is technically demanding to be compatible with the requirements for both radiological and pharmaceutical safety. The Agency assists its Member States to improve the radiopharmaceuticals production to meet cGMP as adaptable to radioactive products by providing appropriate documents, conducting training courses and supporting technical cooperation projects (4).

FIG. 2 Hot cells with manipulators used for radioisotopes/radiopharmaceuticals production available from commercial sources.

7. The last decade has seen an increase in the use of PET in regular diagnostic imaging, and a commensurate use of PET radiopharmaceuticals, particularly fluorine-18 in the form of fluorodeoxy glucose (18F-FDG). The associated 511 keV high-energy radiation needs thicker shielding and more sophisticated handling devices. In view of the short half-lives, the emphasis is also increasingly on process validation and strict adherence to approved procedures in handling of all steps of manufacture, rather than relying on the final QC test results alone. The need for rapid, remote and reliable synthesis of PET radiopharmaceuticals has led to the introduction of microprocessor controlled automated synthesis modules. This experience has also led to the development of similar automated synthesis module systems for other radiopharmaceuticals.

D. Technetium-99m Radiopharmaceuticals and their Kits

8. Technetium-99m is the most widely used radioisotope in diagnostic nuclear medicine, it being estimated that over 80% of the nearly 25 million diagnostic nuclear medicine studies carried out annually are done with this single isotope. This percentage share is expected to remain for the foreseeable future, notwithstanding the introduction of new diagnostic radiopharmaceuticals with other radionuclides. The availability of the short lived technetium-99m (a half-life of 6 hours) as the daughter product of the long lived molybdenum-99 (a half-life of 66 hours) is one of the major factors which have promoted the universal use of this radioisotope. The Agency has supported Member States in the local production of molybdenum-99 – technetium-99m generator technologies, thereby enhancing the availability of technetium-99m for diagnostic studies. (Fig. 3)

9. The parent radionuclide molybdenum-99 can be prepared in abundant quantities by the fission of uranium-235 in a nuclear reactor with a fission yield of about 6%. There are only a limited number of industrial companies and national centres producing molybdenum-99 from fission products, but collectively they have adequate capacity to meet the world's demands for molybdenum-99. More than 95% of the molybdenum is currently produced using highly enriched uranium (HEU) targets. At the request of concerned Member States, the Agency is supporting the adaptation of technology for the production of molybdenum-99 using low enriched uranium targets.

FIG. 3. A 99Mo-99mTc Generator production facility built under an IAEA Technical Cooperation project in Bangladesh.

10. Technetium-99m radiopharmaceuticals are often formulated from cold kits, so called because they do not contain radioactivity. When treated with sodium pertechnetate solution eluted from a technetium-99m generator, the final product for patient injection is directly formed. Cold kits are prepared in such a manner as to have a long shelf life, ranging from several months to a few years, and may be transported at room temperature and then stored under refrigeration to ensure stability. Large-scale preparation of the cold kits requires special techniques and facilities and is mostly done by industrial companies and in national laboratories. The IAEA has supported a number of developing Member States in setting up cold kit production facilities through technical cooperation programmes as well as by developing and transferring technical know-how through various Coordinated Research Projects.

E. Diagnostic Uses of Technetium-99m Radiopharmaceuticals

11. The early technetium radiopharmaceuticals were developed by taking advantage of physiological properties such as adsorption, distribution, metabolism and excretion of various technetium-99m complexes, and were used for imaging the thyroid, liver, bone, kidneys etc. Careful design of new technetium-99m complexes led to the discovery of agents for imaging the blood flow (perfusion) in the muscular tissue of the heart (myocardium) and the brain. Currently, SPECT imaging using technetium-99m products is often an important component of evaluation of patients with known or suspected coronary artery diseases.

12. The primary role of radiopharmaceuticals in cancer treatment will be towards the follow-up of patients with a known disease. Technetium-99m-MDP (methylene diphophonate) is a widely used radiopharmaceutical to detect bone metastasis associated with many forms of cancer. It has also been discovered that some of the technetium-99 radiopharmaceuticals used for renal and cardiac studies also accumulate in some forms of primary cancer, which has led to the use of technetium-99m

radiopharmaceuticals for imaging primary cancer other than that of the thyroid. A majority of current investigations in development of cancer imaging agents mostly use peptides and antibodies as carrier molecules to target tumour sites. Radiopharmaceuticals can provide useful information about the function and molecular biology of the tumour by measuring several of the causal factors of the tumour. In future, specific roles of technetium-99m radiopharmaceuticals for imaging in oncology may include for example, the lymphatic system, development of new blood vessels and monitoring gene therapy.

13. Currently an area of high interest is for developing technetium-99m products for SPECT imaging of receptors in brain which would help managing patients with movement disorders. Advances in novel labelling techniques and identification of appropriate carrier molecules have strengthened the efforts in this direction.

F. Radiopharmaceuticals for Positron Emission Tomography Imaging

14. The evolution of PET as a clinically useful imaging modality has its origin in the synthesis of fluorine-18 fluorodeoxyglucose (18F-FDG) in 1976 at the Brookhaven National Laboratory. Fluorine-18 is the positron emitting radioisotope. The initial application of 18F-FDG was for mapping glucose metabolism in the brain in the understanding and monitoring neurological diseases. While it is also useful for studying myocardial viability, due to the greater utilisation of glucose by the proliferating cells, the major use of 18F-FDG subsequently emerged in the detection, staging and treatment follow up of various types of cancers. Currently PET studies using 18F-FDG account for 10% of all imaging performed using radiopharmaceuticals. A number of other fluorine-18 labelled radiopharmaceuticals are being developed and a few of them are under clinical investigations (1).

15. Increasing clinical demand for 18F-FDG has triggered technological advances in various fields such as accelerator technology, radiochemistry, automated processing modules, detector systems, and imaging software. A typical cyclotron-PET centre nowadays includes a dedicated medical cyclotron together with automated radiochemistry modules and a number of PET or PET-CT units. Daily large scale production of 18F-FDG in the early morning hours for extensive and rapid distribution to medical centres is becoming common practice in several countries.

F.1. Generator produced PET-radiopharmaceuticals

16. The availability of PET radionuclide generators would facilitate PET studies by those centres that do not have a cyclotron. In addition, it can also enhance the range of studies at existing cyclotron/PET centres. The PET isotope gallium-98 can be obtained from germanium-68 – gallium-68 generator. The parent germanium-68 prepared using 30-60 MeV energy and high current cyclotron has a long half life (271 days) and hence the generator can be transported over very long distances and useful for periods of up to one year. In addition to infection imaging, gallium-68 is finding use in cancer imaging when labelled with peptides. The ultra short-lived rubidium-82 (a half-life of 75 seconds), available from a strontium-82 – rubidium-82 generator, and useful for PET imaging of blood flow to myocardium, has high potential in managing heart patients.

G. Therapeutic Radiopharmaceuticals

17. Radionuclide therapy employing radiopharmaceuticals labelled with beta emitting radionuclides is emerging as an important part of nuclear medicine. In addition to the management of thyroid cancer, radionuclide therapy is utilized for bone pain palliation, providing significant improvement in the quality of life of cancer patients suffering from pain associated with bone metastasis as well as for the treatment of joint pain, as in rheumatoid arthritis. Though the sale of therapeutic radiopharmaceuticals is currently much lower compared to that of diagnostic products, a steep increase over the next 5-6 years is predicted (5,6), since several new products for treating lymphoma, colon cancer, lung cancer, prostate cancer, bone cancer and other persistent cancers are expected to enter the market. Development of sophisticated molecular carriers and the availability of radionuclides in high purity and adequate specific activity are contributing towards the successful application of radionuclide therapy.

G.1. Radiopharmaceuticals for bone pain palliation

18. Persons suffering from breast, lung and prostate cancer develop metastasis in bones in the advanced stage of their diseases and therapeutic radiopharmaceuticals containing radionuclides such as strontium-89, samarium-153 and rhenium-186/188 are used for effective palliation of pain from skeletal metastases. The IAEA has initiated a programme for the development and clinical application of lutetium-177 based radiopharmaceuticals for bone pain palliation. It can be prepared in large quantities for bone pain palliation application in low/medium flux research reactors, which are available in several countries. The long half-life of lutetium-177 provides logistic advantages for production and testing of the products as well as the feasibility to supply the products to places far away from the production site.

G.2. Radiopharmaceuticals for primary cancer treatment

19. Targeted radionuclide therapy involves the use of radiopharmaceuticals to selectively deliver cytotoxic (toxic to cells) levels of radiation to a disease site, as this would potentially deliver the absorbed radiation dose more selectively to cancerous tissues. Advances in tumour biology, recombinant antibody technology, solid phase peptide synthesis and radiopharmaceuticals chemistry have led to investigations on several new radiotherapeutic agents. Radiolabelled peptides as molecular vectors are being developed for targeted therapy. When labelled with therapeutic radionuclides, peptide molecules have the potential to destroy receptor-expressing tumours, an approach referred to as peptide receptor radionuclide therapy (PRRT). Yttrium-90 and lutetium-177 are frequently used as radionuclides in such PRRT studies.

20. During the development, the assessment of the relative effectiveness of different radiopharmaceuticals for cancer therapy is complex because of the large number of variables to be considered, some related to the biological carrier and others to the radioisotope. Comparing the therapeutic efficacy in patients is not feasible in most cases, and so development of laboratory methods that can be used for reliable and efficient comparative evaluation of promising therapeutic radiopharmaceuticals is an important need.

G.3. Radiopharmaceuticals for radiosynoviorthesis

21. Radiosynoviorthesis or radiosynovectomy is a technique wherein a radiopharmaceutical is delivered into the affected synovial compartment (the interior of joints that is lubricated by fluid) of patients suffering from joint pain, as in the case of rheumatoid arthritis. Beta-emitting radiolabelled

colloids are widely used for this purpose. Several radiopharmaceuticals have been developed using phosphorus-32, yttrium-90, samarium-153, holmium-166, erbium-169, lutetium-177, rhenium-186, etc. and some of them are registered for human use. The radiation properties of each therapeutic isotope determine their respective use and applicability for the joint size.

H. Radiopharmaceuticals Market and Future Trends

22. A number of Member States through the Agency's technical cooperation programme have developed capacities for radiopharmaceuticals production, manufacturing products regularly to meet local demands. The assured local availability of radiopharmaceuticals has greatly contributed to the growth of nuclear medicine practices in such countries, in addition to ensuring price stability of radiopharmaceuticals imported from large manufacturers. Local production and distribution of radiopharmaceuticals has also helped to reduce the number of radioactive consignments that need to be transported across international borders.

23. Problems and delays in transport of radioactive materials; the need for compliance with transport regulations; the denial of shipments by some carriers etc., often affect the end use of the imported products. For example, if a shipment of the raw material molybdenum-99 is affected by any delay, it leads to a cascading negative impact, as several users of technetium-99m generators are then affected for the subsequent period. Some countries follow a practice of holding up all the cargo in airports at times for a pre-destined period (say 24 to 48 hours) before being loaded on the plane, as part of measures for enhancing security. This procedure also affects the radiopharmaceuticals due to additional decay losses apart from the delays caused, especially when dealing with short-lived radioactive materials. The decay loss during a 'cooling' (waiting) period of 24 hours amounts to nearly 20 to 22% of radioactivity in the case of thallium-201 and technetium-99m generator consignments, in addition to causing disruptions to the patient appointments. The IAEA has hence tried to create necessary awareness through informed discussions towards better understanding of the various aspects involved, so that denials and delays in shipments of radioactive materials are not unduly affecting the availability and use of radiopharmaceuticals.

24. A process of formal 'Approval or Registration' after screening by competent national authorities is necessary for marketing authorisation of radiopharmaceuticals, for both those produced locally and imported from commercial sources. For example, centralised radiopharmacy units in Scandinavia, usually under the auspices of the drug administration authority, carry the responsibility for the control and supply of radiopharmaceuticals around the country. All radiopharmaceuticals which are to be procured or imported are formally assessed before being passed on to the end-users. The Good Manufacturing Practice (GMP) status of each supplier is to be established and a dossier on each product submitted as a pre-requisite before entry into distribution chain. Such a system could be very useful for many Member States that at present do not have a formal market authorization system in place for radiopharmaceuticals, as even smaller countries benefit from similar approaches. Those countries that already have formal systems paralleling normal medicines are increasingly feeling the impact of the present prohibitive costs associated with formal market authorisation process for radiopharmaceuticals.

25. There is a considerable variation in the extent of local availability and utilisation of radiopharmaceuticals in different parts of the world. However, consistent with an overall growth in health care systems in many developing economies, the demands for the use of diagnostic and

therapeutic radiopharmaceuticals are increasing including in developing countries and in turn, in the number of requests for strengthening capabilities through the Agency's technical cooperation support.

I. Centralised Radiopharmacy Services

26. Radiopharmaceuticals, unlike normal medicines which once produced undergo total quality control assessment before they reach the public, do not go through such procedures, especially the short-lived products prepared at the users' end. There is thus complete reliance on the robustness of quality assurance systems for the radiopharmaceutical release for patient administration to insure patient safety.

27. At a busy hospital level, the preparation of radiopharmaceuticals mostly involving the radioisotope technetium-99m, which has a half life of 6 hours, is done by the addition of technetium-99m from approved radioisotope generators to pre-sterile, validated approved commercial kits (see paragraph D. above) The process of simple "shake, mix or even heat" radiopharmaceutical formulation can technically be performed in a busy clinical setting. These radiopharmaceutical medicines are therefore mainly assembled within the conditions of the approved kit on-site in "Hot Laboratory- Radiopharmacy" for use within the hospital (7, 8). Under such a scheme, radiopharmaceutical injections are provided daily in accordance with their quality assurance systems. Any deviation from the approved method of preparation would require considerable validation before patient use.

28. Increasingly the national authorities in some Member States are requiring that this preparation be undertaken in compliance with GMP (good manufacturing practices) conditions overseen by a state registered pharmacist or "Authorised person/Qualified person". To address these requirements, nuclear medicine physicians are recommending the setting up of centralised radiopharmacies. In larger cities instead of each clinical nuclear medicine department having their own "Hot Laboratory", investment is recommended for the setting up of a self-funded, partially commercially supported, or totally private operated centralised radiopharmacy service (7, 8). Both from a legal and quality assurance perspective, the responsibility for the quality of the radiopharmaceutical then lies in the hands of the radiopharmacy.

29. Experience from such a model of a centralised radiopharmacy service suggests many advantages, such as:- delivery of the best products from all sources and services available; more efficient use of human resources; ability to dispense patient specific prescription; minimization of radiation exposure; simplification of regulatory and practice-based paperwork; maintenance of quality assurance requirements and reduction of risk e.g. radioiodine capsules; additional services e.g. white cell labelling for infection imaging (Fig. 4); same day delivery of products; simpler retrieval of radioactive waste and the maintenance of continuous and immediate pharmacy services.

FIG.4 Value added services e.g.radiolabelled white cells for infection imaging - Aseptic preparation by trained staff under Laminar flow hood - Kars El-Einy Nuclear Medicine Department, Cairo, Egypt

30. The overall impact of recent trends and changes in health care economics and operational viability of hospitals will result in nuclear medicine practitioners looking to the centralised radio-pharmacies to meet a larger portion of their radiopharmaceutical needs, as well as to value added services, such as education and research and development.

31. In Europe, centralised systems are driven more by the needs in meeting regulatory demands than by commercial interests alone, as the supplies from radiopharmacies are required to meet full GMP compliance, even for technetium-99m labelled radiopharmaceuticals.

32. A somewhat different situation for PET and other short lived radiopharmaceuticals applies. Regulatory authorities require high standards of compliance, independent of whether production is centralised or local.

33. Decentralised systems in this respect are necessary and play an essential role in clinical research in nuclear medicine, particularly if extremely short lived diagnostic radiopharmaceuticals labelled with carbon-11 or oxygen-15 are employed, and for the exploration of radiopharmaceuticals for therapeutic applications. Limitations of a centralised production system are the reduced flexibility for the nuclear medicine department to respond to acute clinical demand, and this situation will remain for ultra-short lived radionuclides and in the development or research activity for new radiopharmaceuticals.

34. There are increasing calls for radiopharmaceutical regulations, from both administrators and legislators in many countries, including the regulations for PET and for clinical trials. Whether this increase in regulation leads to a significant change in practice from decentralised to centralised radiopharmacy, based on commercial, semi-commercial or ‘not for profit’ co-operative models, remains to be seen. In the future, trends indicate that nuclear medicine practitioners will look to the centralised radiopharmacy model for an increasing portion of their radiopharmaceutical needs, with manufacturers ready and able to meet demands in a safe, timely, and cost efficient manner.

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