PRELIMINARY REPORT ON SUPPLY OF RADIOISOTOPES FOR MEDICAL USE AND CURRENT DEVELOPMENTS IN NUCLEAR MEDICINE

ESTABLISHED BY AN INTERNAL EUROPEAN COMMISSION AD HOC INTERSERVICE GROUP
TABLE OF CONTENTS

1. WHY THIS REPORT?

2. CURRENT USE OF RADIOISOTOPES FOR MEDICAL PURPOSES
   2.1.1 IN VIVO NUCLEAR MEDICINE PROCEDURES IN NUMBERS
   2.1.2 CURRENT IN VIVO NUCLEAR MEDICINE DIAGNOSTIC PROCEDURES
   2.1.2.1 "CONVENTIONAL" DIAGNOSTIC NUCLEAR MEDICINE
   2.1.2.1.1 TECHNETIUM-99M
   2.1.2.1.2 POTENTIAL SHORT-TERM REPLACEMENT OF TECHNETIUM–LABELLED RADIOPHARMACEUTICALS
   2.1.2.2 MORE RECENTLY DEVELOPED DIAGNOSTIC METHODS: PET
   2.1.3 THERAPY
   2.2 OTHER APPLICATIONS OF RADIOISOTOPES
   2.3 RADIATION SAFETY CONSIDERATIONS IN RELATION TO NUCLEAR MEDICINE
   2.4 HEALTH IMPACTS OF THE RECENT SUPPLY SHORTAGE IN VARIOUS COUNTRIES
   2.5 PREVIOUS SHORTAGES IN RADIOISOTOPE SUPPLY

3. CURRENT SUPPLY SITUATION

4. AVAILABLE PRODUCTION CAPACITIES
   4.1 NUCLEAR REACTORS
      4.1.1 RADIOISOTOPES PRODUCTION BY FISSION ROUTE
      4.1.2 PRODUCTION OF RADIOISOTOPES BY LOW ENRICHED URANIUM TARGETS
      4.1.3 RADIOISOTOPES PRODUCTION BY ACTIVATION ROUTE
   4.2 PARTICLE ACCELERATORS
      4.2.1 PRODUCTION OF MOLYBDENUM-99
      4.2.2 PRODUCTION OF TECHNETIUM-99M
      4.2.3 PHOTON ACTIVATION AND FISSION
   4.3 ACCELERATOR-DRIVEN SUBCRITICAL REACTORS
   4.4 OVERVIEW OF CURRENT PRODUCERS AND REACTORS
      4.4.1 MOLYBDENUM-99 PRODUCERS
      4.4.2 NUCLEAR REACTORS PRODUCING MOLYBDENUM-99

5. TRANSPORT OF RADIOISOTOPES

6. PRODUCTION AND DISTRIBUTION OF RADIOPHARMACEUTICALS

7. INTERNATIONAL COOPERATION

8. OUTLOOK
   8.1 CURRENT DEVELOPMENTS IN NUCLEAR MEDICINE, POTENTIAL ALTERNATIVE METHODS AND ESTIMATED FUTURE NEEDS IN REACTOR RADIOISOTOPES
8.1.1 Qualitative Approach and Discussion

8.1.2 More Quantitative Approach

8.1.2.1 Development Trends

8.1.2.2 Diagnosis

8.1.2.2.1 Expected Use of the Various Imaging Modalities in Clinical Practice in the Future

8.1.2.2.2 Dynamics of Innovation

8.1.2.2.3 Summary

8.1.2.2.4 Conclusion

8.1.2.3 Therapy

8.1.2.4 Quantitative Estimates of Evolution of Demand for Medical Radioisotopes

8.1.2.4.1 Conventional Nuclear Medicine Procedures Using Molybdenum-99 / Technetium-99M for the Period 1990-2020

8.1.2.4.2 Estimated Evolution of Demand for Medical Radioisotopes Globally (Including Tc-99M)

8.2 Prospected Future Production Capacities of Radioisotopes for Medical Use

8.2.1 Europe

8.2.2 U.S.

8.2.3 Other Parts of the World

8.2.4 IAEA Initiative for Small Scale Production of Molybdenum-99

8.2.5 Improvement in the Production of Molybdenum-99 through Activation

8.2.6 Homogeneous Aqueous Solution Nuclear Reactors for Radioisotopes Production

9. Lessons Learnt

10. Possible Future Initiatives

10.1 In the EU

10.2 Internationally

11. Summary and Conclusions

Explanatory Notes

List of Abbreviations

References

Annex 1: Nuclear Reactor Produced Radionuclides in Use and of Importance for Future Research Applications

Annex 2: Statement by the European Association of Nuclear Medicine on Supply of Radioisotopes for Medical Use – Supply of Molybdenum-99 in Europe
ANNEX 3:  Statement by the Association of Imaging Producers and Equipment Suppliers on the Global Supply of Molybdenum-99 in June 2009

ANNEX 4: Extract from "Lessons learned from the shutdown of the Chalk River reactor" (A report submitted in May 2008 to the Canadian Minister of Health by an Ad Hoc Health Experts Working Group on Medical Isotopes)

ANNEX 5: Composition of the internal European Commission ad hoc Interservice Group on Sufficiency in Supply of Radioisotopes for Medical Use

Disclaimer

This report expresses solely the current views of the ad hoc Interservice group of the European Commission's services on sufficiency in supply of radioisotopes for medical use. Readers should not regard these views as a statement of the official position of the European Commission.
1. **WHY THIS REPORT?**

The EU Health ministers, at their meeting of 8-9 September 2008, because of a shortage in supply of radioisotopes for medical use (Molybdenum-99 / Technetium-99m) had occurred in the EU in autumn last year following an incidental shut down of all three nuclear reactors in which radioisotopes are produced in the EU, addressed to the Commission with the request to take a role in exchanging information on the situation. They called for an emergency meeting of the EU Health Security Committee to be convened in order for the Committee to exchange on the situation and discuss on possible actions which could be taken to counter the lack of medical radioisotopes.

The European Commission convened an emergency audio-conference of the EU Health Security Committee on 11 September 2008 on the issue. The item was further discussed in audio-conferences of the EU Health Security Committee of 30 September and 28 October and in plenary meetings of the Committee of 5-6 November 2008 and 18 June 2009. The members of the EU Health Security Committee called upon the European Commission to take a role in the coordination of EU wide actions to respond to the shortage.

The European Medicines Agency (EMEA), in order to further elaborate on a strategy to address the supply shortage of radiopharmaceuticals, has setup a Task Force which is composed of representatives of the European Commission, Heads of Medicines Agencies of the EU Member States and EMEA. The first meeting of this Task Force was held on 2 October 2008. EMEA has produced a report, with status as of 24 October 2008, to the European Commission on the Supply Shortage of Radiopharmaceuticals. The report has been published by EMEA ([http://www.emea.europa.eu/pdfs/human/press/pus/5118309en.pdf](http://www.emea.europa.eu/pdfs/human/press/pus/5118309en.pdf)). EMEA undertakes further activities with the view to address the place of radiopharmaceuticals, labelled with radionuclides produced in nuclear reactors, in clinical practice in the EU in the longer term.

The Health ministers of the G7+, at their meeting in Brussels of 5 December 2008, concluded that the issue of security in supply of radioisotopes for medical use is a question of global concern and should be looked at urgently within the Global Health Security Initiative of the G7+.

Following the deliberations and discussions at the political and technical level and on the background of fragility in supply of radioisotopes for medical use (e.g. Molybdenum-99 (Mo-9m) / Technetium-99m (Tc-99m) continuing to exist worldwide the European Commission services established an ad hoc interservice group on the issue at the beginning of 2009 which has produced the present report.

The EU Health Ministers, at their meeting of 6-7 July 2009, took note of the conclusions of the present report. Health ministers expressed the view that the situation should be monitored closely and cooperation between actors be strengthened.

At the time when this report has been finalised (October 2009) a severe shortage in supply of Mo-99 / Tc-99m has occurred again and is ongoing, because of an unplanned shut down since mid-May 2009, following a leak in the water system, of the "NRU" nuclear reactor in Chalk River, Canada, in which about 40% of the
worldwide production of these radioisotopes takes place. The operator of the "NRU" nuclear reactor has announced that the reactor might return to service during the first quarter of 2010. In addition, the operator of the "High Flux Reactor (HFR)" in Petten, The Netherlands, has communicated that it is obliged to undertake repairs to the reactor which are expected to start in early 2010 and take up to 26 weeks. The "HFR" reactor will be shut down during this time period. This situation affects the nuclear medicine sector severely.

Preliminary remark

In the present report aspects of nuclear reactor produced isotopes are emphasized and other related aspects are only mentioned briefly.

2. CURRENT USE AND RELEVANCE OF RADIOISOTOPES IN MEDICINE

Radio-isotopes (radiopharmaceuticals) play an important role in medicine, where they are used routinely in the clinics for the non-invasive diagnosis and treatment of various diseases, including some of the most important and frequent ones, like cancers and cardiovascular diseases.

They can be used in 2 forms: as sealed sources (ie radio-isotopes incorporated in solid substances and/or sealed in an inactive capsule) or as unsealed sources.

Sealed sources are used by radiotherapists (the medical specialty concerned in this case), essentially for the (increasingly) localised treatment of cancers, like prostate or breast cancer. This is called brachytherapy (or Curie-therapy by some) and is developing. Conversely, sealed sources are less and less frequently used for external beam cancer therapy, at least in developed countries where better even though more expensive alternatives exist to produce better beams.

Unsealed radio-isotopes are a crucial component of the radiopharmaceuticals that are used by Nuclear Medicine, the medical specialty concerned.

The main medical radio-isotopes are Nuclear Reactor-produced.

2.1. NUCLEAR MEDICINE

Nuclear medicine plays a growing role in diagnosis and therapy (like also brachytherapy) and has done so since its early developments. It essentially started in the 1940s.

Radio-isotopes are a crucial component of the radiopharmaceuticals that are used routinely in the clinics for the non-invasive diagnosis and treatment of various diseases. These radiopharmaceuticals are specific biological molecules tagged (or "labelled") with medical radioisotopes. They are also called "tracers", because they only need to be administered in very small quantities (traces) thanks to the high sensitivity provided by nuclear radiations and they allow to trace biological processes.

Nuclear medicine is non-invasive and covers two main aspects:
• *In vitro diagnostic analyses* (e.g. of hormone levels in the blood) which belong to in-vitro molecular diagnostics. They concern about 15 million medical analyses of biological samples per year in Europe and are medically important. The most commonly used radioisotope for the radio-immunoassays is Iodine-125. It is nuclear reactor produced. The quantities of radioisotopes used per analysis are of course much lower than per in vivo study of a patient, and hence so are the total quantities involved. Therefore, and not because they are not important, we will not further deal with these in vitro aspects in this report.

• *In vivo procedures* (nearly 10 million patient examinations every year in Europe);
  - 90% are Diagnostic (imaging);
  - 10% are Therapeutic (essentially for cancers; like the metabolic radiotherapy of thyroid tumours with Iodine-131).

Imaging provides a rich portrait of what is happening in a patient's body and a wealth of useful information to help doctors and patients decide on treatment plans. The *in vivo* nuclear diagnostic procedures are currently the second most used imaging technique in the clinics, after X-rays (X-ray scanner or Computed Tomography (CT)) and before MRI (Magnetic Resonance Imaging). They are used to image metabolism and other functional processes in the human body.

They can be separated in two groups:
  - SPECT (Single Photon Emission Computed Tomography) and planar scintigraphy that use gamma-emitters (gamma-emitting radionuclides, or radioisotopes). They are often, and probably partly misleadingly, called "conventional". Because both of these use the same isotopes, they will be grouped, for the purpose of this report, under the term of "SPECT", without further distinction between the two (unless explicitly stated).
  - PET (Positron Emission Tomography) that uses positron emitters. PET was developed more recently (since 1970s) and is more sophisticated, complex and costly. PET uses radioisotopes produced by accelerators/cyclotrons, not by nuclear reactors (at least as of today).

### 2.1.1 IN VIVO NUCLEAR MEDICINE PROCEDURES IN NUMBERS

Over 10,000 hospitals worldwide use radioisotopes in medicine, and the vast majority of the procedures (over 90%) are for diagnosis [1].

35 million *in vivo* procedures are performed annually in the World, including 20 million in the USA, 9 in Europe, 3 in Japan and 3 in the rest of the World [2]. So, about 30 000 in-vivo diagnostic and 3000 therapeutic procedures involving radioisotopes are currently performed in the European Union per day, and about 60 000 in North America.

One out of two persons living today should benefit from in vivo nuclear medicine during their life, in developed countries. And this probability is rising.
2.1.2 Current in vivo nuclear medicine diagnostic procedures

90% of all in vivo nuclear medicine procedures are carried out for diagnostic purposes (with gamma emitters being used in the vast majority of cases).

Most are used for serious and often life-threatening medical conditions. These mainly include heart disease and cancer, but also bone or hormonal disorders (in particular of the thyroid, but not only) and diseases of brain, lungs, kidneys, liver and other organs.

Indeed, nuclear medicine gives diagnostic information, essentially by imaging biological processes in the body: It is essentially a molecular and functional imaging technique. It can provide metabolic or functional imaging of specific organs and inform on their alterations during disease and disorders. It allows physicians to identify at a metabolic and cellular level what is going on inside a person’s body. In addition to pinpointing the underlying cause of disease, physicians can actually see how disease is affecting other functions in the body.

Diagnostic radiopharmaceuticals can be used to examine blood flow to the brain, functioning of the thyroid, liver, lungs, heart or kidneys, to assess bone metabolism and growth (e.g. traumatology, rheumatic diseases), to detect lymphatic pathways of tumours (e.g. to plan for tumour surgery, like breast cancer surgery, including intra-operatively) and to confirm or complement other diagnostic procedures.

Molecular imaging can also show how active a tumour is, allowing doctors to offer patients highly targeted therapies and delivering higher doses of medicine more precisely to problematic cells in the body.

Another important use is to predict the effects of surgery and to monitor treatment, i.e. to see how effective treatment is by assessing changes after treatment early in the process, so that treatments can be adjusted and optimised quickly.

Diagnostic techniques in nuclear medicine use radioactive tracers (or radiopharmaceuticals), i.e. molecules labelled with a radioisotope that is generally short-lived. A radioisotope used for in vivo diagnosis must produce gamma rays of sufficient energy to escape from the body so that it can be detected from the outside (with a gamma- or a PET-camera that will produce an image). It must also have a half-life that is long enough to allow for logistics and preparations before the imaging can take place, and short enough for it to decay during the imaging procedure and disappear soon after it is completed.

In conventional nuclear medicine, the radioisotopes used emit gamma rays directly; in PET they emit positrons that are then converted into gamma rays. The radioisotopes are linked to specific chemical compounds to produce radiopharmaceuticals which permit the desired specific physiological processes to be examined. The radiopharmaceuticals can be administered by injection, inhalation or orally.

The amount of the radiopharmaceutical given to a patient is just sufficient to obtain the required information (images of good enough quality) before its decay. The radiation dose received is essentially medically insignificant (and this dose is normally smaller with SPECT than with PET; of course, like for any medical procedure, potential risk/benefit has to be considered, and not just that of radiation). The patient experiences no discomfort during the test and after a short time there is no trace that the test was ever done.
Nuclear medicine images provide a map (image) of the position and concentration of the radioisotope within the body, and can also indicate its variations in time (if a series of images is taken). All of these, when altered, can reveal organ or tissue dysfunction. The non-invasive nature of this technology, together with its ability to observe an organ functioning from outside the body, makes it a powerful diagnostic tool.

Having the radiation source within the body makes a fundamental difference between nuclear medicine imaging and many other imaging techniques, X-rays in particular.

A distinct advantage of nuclear imaging over X-ray techniques, and some others, is that the accuracy of tests is independent of structural abnormalities, e.g. post surgery, and that, being essentially a functional technique, diseases may be detected before structural or macroscopic morphological/anatomical changes appear (eg in bones), ie earlier.

2.1.2.1 "CONVENTIONAL" DIAGNOSTIC NUCLEAR MEDICINE (GAMMA/SPECT IMAGING)

This includes by far the largest number of diagnostic procedures performed today worldwide. A list of the most frequent diagnostic nuclear medicine procedures is given below in the part on potential short term replacement.

Like for medical applications in general, the main radio-isotopes used in in vivo diagnosis are Nuclear Reactor-produced.

Technetium-99m (Tc-99m), is the isotope used for over 80% of all nuclear medicine procedures performed around the World. It is used in 90% of all diagnostic procedures in Europe, according to EANM, in 2008.

The total number of in-vivo diagnostic procedures using Tc-99m approached 30 million in the World in 2008, of which approximately 6-7 million in Europe, 12-15 million in North America, 6-8 million in Asia / Pacific (particularly Japan), and 0.5 million in other World regions [2].

2.1.2.1.1 TECHNETIUM-99M (TC-99M)

Tc-99m is produced by nuclear reactors, via molybdenum: it is the decay product of Molybdenum-99. Molybdenum-99 and Technetium-99m hardly exist in nature. Molybdenum-99 is formed during the nuclear fission of Uranium-235 (and consequently exists in 'used' fuel or uranium targets irradiated for radioisotope production). The Molybdenum-99 is then extracted and placed in generators that are sent to hospitals. It decays into Technetium-99m, which is extracted from the generators and then combined to a product to form a radiopharmaceutical that can be administered to patients.

Technetium-99m is the favourite (close to ideal) radioisotope for "conventional" nuclear medicine.

Indeed, it offers many advantages with respect to many other radio-nuclides, due to its very good physical and chemical characteristics. Among other things, the gamma radiation emitted has the appropriate energy (neither too low nor too high) to provide a good image whilst keeping low radiation dose to the patient (also because Tc is a nearly pure gamma emitter: 89%).
Its 6-hour half-life is appropriate (neither too long nor too short) for a medical examination and a good image quality. It is long enough to allow labelling of a number of molecules, and short enough to allow the patient to leave the hospital shortly after the examination.

It is a decay product of Molybdenum-99 which has a 66-hour half-life and can be shipped under the form of a Mo-99/Tc-99m generator, which gives enough time for the logistics (transport, preparation, etc) and to be sent at far distances, including to developing countries.

Tc has a versatile and well-known chemistry. It can easily and quickly be bound to many different chemical compounds, and so can be used to label various molecules of interest for many diagnostic applications. This also shortens new ligand development times.

In about 10% of examinations other radioisotopes are favoured because of their specificity for particular use (like Iodine for the thyroid, or Thallium for some heart studies).

But otherwise, the other isotopes, and hence potential alternatives to Tc, tend to have one or more drawbacks compared to it, like higher radiation dose to the patient, non-ideal gamma energy, lability of the chemical bonds, more difficult production and/or manipulation, logistics (eg need of a cyclotron at reasonable distance, due to short half-life) and/or higher cost.

2.1.2.1.2 POTENTIAL SHORT TERM REPLACEMENT OF TECHNETIUM-LABELLED RADIOPHARMACEUTICALS

The most frequent diagnostic nuclear medicine procedures in the World are:
- cardiac imaging (12 million/year; mainly Tc-99m, some with Thallium-201),
- bone scintigraphy, including tumour metastases (10 million/year ; mainly Tc-99m),
- lung investigation (5 million/year ; mainly Tc-99m),
- thyroid (5 million/year ; Tc-99 or Iodine-123/-131)
- kidney function analysis (Tc-99m).
- tumour staging (PET, 18F-FDG)

The balance can be a little different when looking at European countries only, in particular because of more cardiac studies in the US than in Europe. The future tendency will likely be in that direction in Europe too.

In case of shortage in Tc supply, replacement of Tc-99m-labelled radiopharmaceuticals can be envisaged for short term situations and for a limited number of patients. However, known replacements have one or more disadvantages compared to Tc-99m, as seen above. Also, these isotopes and the corresponding radiopharmaceuticals may only be available in enough quantity for limited periods and/or limited number of patients (eg the most urgent ones but perhaps not even all of them) and/or limited geographical locations (eg if substitution is with PET, which needs appropriate equipment, like PET cameras, and a cyclotron nearby, or for geo-politico-economic reasons).

Alternative radioisotopes (here we only cite the radioisotopes, not the more numerous radiopharmaceuticals), and some of their drawbacks, are mainly: Thalium-201 (TI-201) and Indium-111 (In-111) (but they give higher radiation dose and poorer image quality), Iodine-123 (I-123) (but more expensive and less available than Tc-99m can be), Krypton-
81m (Kr-81m) (but for limited studies and much more expensive) and Fluorine-18 (F-18-FDG, ie Fluorine-18 Fluoro-deoxyglucose) with PET (but need PET camera, radiochemistry and cyclotron nearby).

No alternative exists today for some other Tc-labelled compounds, like colloids (eg for sentinel lymphnode determination for cancer surgery), MAA for lung perfusion, DMSA for kidney function investigation and HAS for gastro-intestinal bleeding or cardiac studies.

So, in general and when they exist, alternative procedures are less effective, often more costly or not universally available (including because of cost) [3].

2.1.2.2 More Recently Developed Diagnostic Methods: PET

Positron Emission Tomography (PET) is a more recently developed diagnostic nuclear medicine technique. It uses positron emitters produced in a cyclotron, like Carbon-11 (C-11) or Fluorine-18 (F-18). A positron-emitting radionuclide is usually bound to a molecule to form a radiopharmaceutical, which is administered, usually by injection, and reaches and accumulates in the target tissue. As it decays the radionuclide emits a positron, which promptly annihilates with a nearby electron, resulting in the simultaneous emission of two 511 kilo-electron-Volt (keV) gamma rays in opposite directions. These are detected by a PET camera, giving a precise indication of their origin and good quantitation.

The most common radiopharmaceutical in PET clinical imaging is Fluorine-18-labelled Fluoro-deoxy-glucose (F-18 FDG), which is readily incorporated into the cells that take-up glucose, and is a good indicator of cell glucose metabolism.

PET’s most important clinical role today is in oncology, with 18F-FDG as the tracer. This has proven to be a very good and sensitive non-invasive method of detecting and staging many cancers. PET is also used in cardiac and brain imaging, and in various research applications.

Globally, it is used in about 6-7 % of diagnostic procedures today, and this fraction is increasing, like the total number of clinical PET examinations.

New equipment combines PET with CT in a PET/CT scanner, which co-registers the two images and enables up to 30% better diagnosis than with stand-alone PET (or CT) imaging [communication by EANM].

Most, if not all, positron emitters currently used in clinical PET have a short half-life; F-18 has one of the longest ones, with just under 2 hours (110 minutes). They are produced with accelerators (mostly cyclotrons), that must therefore be available within close enough distance (2 hours for 18-F) of the patient and the PET camera.

Apart from directly cyclotron-produced PET radio-nuclides, some others can interestingly be extracted from generator systems (eg Ge-68/Ga-68 generator), where the parent radionuclide (here Ge-68) is produced with accelerators, like a cyclotron. These are not much used in the clinics yet, but may be more in the future (also see later section about the future). The most interesting one may be the Ge-68/Ga-68 system, since Ga-68 (half-life ca. 1 hour) can be coupled to various organic compounds, such as peptides. Nevertheless, this would require extensive radiopharmaceutical developments. Another interesting generator is Sr-82/Rb-82, since Rb-82 could substitute for traditional
myocardial perfusion agents. This is the only PET-generator that is currently commercialised (in the USA) for the clinics, to our knowledge.

PET will not be considered further in this part of the report since it uses radioisotopes produced by accelerators, not by nuclear reactors. It will be reconsidered in the discussion about future techniques.

2.1.3 Therapy

In a number of medical conditions, and cancers in particular, the aim of the treatment is to destroy pathological or cancerous cells (while damaging normal tissues as little as possible). Ionising radiations are one of the potential tools to do so. They are used in radiotherapy and nuclear medicine as one of the main curative treatment of cancers. They are also important for non-curative or palliative treatment. For instance they can improve the patient's quality of life and decrease pain from bone metastases, which can be very intense (and in some cases where even morphine doesn't work).

Indeed, rapidly dividing cells are particularly sensitive to damage by radiation, so that some cancers can be controlled or eliminated by irradiating them. A possibility is to use external irradiation or internal sealed sources.

Nuclear medicine uses internal (or molecular) radiotherapy with unsealed sources. The radioisotope that emits the ionising radiation localises to the site of pathology in the same way as for diagnosis - through a radioactive element following its usual biological pathway, or through the element being attached to a suitable and specific biological compound. In most cases, it is beta-emitters that are used to cause the destruction of the pathological cells (via beta-radiation).

However, an ideal therapeutic radioisotope is a beta-emitter which also emits just enough gamma rays to enable imaging, like Lutetium-177 or Iodine-131, allowing to follow its distribution in the body and target tissue.

Iodine-131 is commonly used as an unsealed source to treat thyroid cancer. It is also used to treat non-malignant thyroid disorders.

Although nuclear medicine therapy procedures are less common than diagnostic ones, they are nevertheless widespread, important and growing.

All radioisotopes currently used for therapy are nuclear-reactor produced, and many potential future ones also are (see list in Annex 1).

In addition, external gamma beam irradiation can be carried out from a radioactive source, typically Cobalt-60, but in developed countries the much more versatile linear accelerators are now being utilised as a source of high-energy x-rays (gamma- and x-rays are physically much the same).

Internal radiotherapy may also use sealed radiation sources, usually of gamma or beta emitters, by implanting them in the target area. For instance, Iridium-192 implants are used especially in the head, prostate and breast.

So, various other radio-nuclides are used (by the radiotherapy specialists, not nuclear medicine ones) for external irradiation and brachytherapy with sealed sources, essentially for cancer treatment too. These important radio-nuclides include Ir-192, Pd-103, Co-60,
Sr-90, I-125, Cf-252, and others. They are often also mentioned as a matter of concern during reactor-radioisotope supply crises [2].

2.2 OTHER APPLICATIONS OF RADIOISOTOPES

Many other reactor radio-nuclides, which can have their supply jeopardized, are used for other specific needs, like in industry and research. Some are used in biomedical research, with potential future clinical applications.

For instance, SPECT and PET are also used in various biomedical research applications in animals and humans.

Molecular imaging techniques, and perhaps nuclear medicine ones in particular, also have an important potential role in drug development (eg as biomarker or for pharmacokinetic and pharmacodynamic studies). Indeed, pharmaceutical companies are increasingly interested in these techniques and a number of them have their own molecular imaging centres, which include more and more frequently nuclear medicine modalities.

A speech published in 2008 by the American DOE said [4]: "Industrial applications for isotopes have also grown in areas such as instruments for analysis and characterization of materials and environments, sealed samples for irradiation applications including sterilization of medical supplies and pharmaceutical and food packaging, and for processes like cross-linking in the development of materials. Cobalt-60 is widely used for these purposes. Application for technologies needed to meet national security requirements has also increased the demand for a number of isotopes, such as Nickel-63. The demand for Californium-252 for applications such as online analyzers for optimizing coal-fired power plants and other production facilities, treatments for certain cancers that are not responsive to other radiation therapies, oil exploration, and radiography of aircraft to detect metal fatigue, is yet another example."

2.3 RADIATION SAFETY CONSIDERATIONS IN RELATION TO NUCLEAR MEDICINE

Since the nuclear medicine procedures involve exposure to ionizing radiation of the patient, of the staff involved in the procedure and of other people who are in contact with the patient, appropriate arrangements for radiation protection of the exposed individuals shall be in place. The radiation protection arrangements implemented in the EU Member States shall be in line with the EURATOM Community legal requirements in this area, as defined by:

- COUNCIL DIRECTIVE 96/29/EURATOM laying down the basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation, and

- COUNCIL DIRECTIVE 97/43/EURATOM on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure.

Quoted Directives define the general principles for radiation protection of the members of the public, the occupationally exposed individuals and the patients. Exposure of patients forms the main part of the exposure associated with the nuclear medicine procedures, and for it those general radiation protection principles can be interpreted, as follows:
- **Justification**: The procedure shall show a sufficient net benefit, weighing the total potential diagnostic or therapeutic benefits it produces against the individual detriment that the exposure to ionizing radiation might cause. All new types of practices shall be justified in advance before being generally adopted. All individual exposures shall be justified in advance taking into account the specific objectives of the procedure and the characteristics of the individual involved.

- **Optimization**: All doses due to medical exposure for diagnostic purposes shall be kept as low as reasonably achievable consistent with obtaining the required imaging information, taking into account economic and social factors.

Radiation protection of the staff participating in the nuclear medicine procedures and to members of the public, who may be exposed due to being in contact with a nuclear medicine patient, should also be optimized. The principle of *limitation of the doses* also applies to those individuals, who shall not receive doses exceeding the legally established dose limits.

Since the nuclear medicine procedures involve the use of radioactive material, some radioactive waste will be generated in result of preparing the radiopharmaceuticals and implementing the procedure. Therefore, the potential of the specific nuclear medicine practice to generate radioactive waste and the availability of management routes for that waste shall be taken into account when deciding on the adoption of the practice. In general, the shorter the half-life of the radioisotopes used in the procedure, the easier the management of the resulting waste. However the use of shorter-living radioisotopes may be not always favourable to the radiation protection of the patient and will normally require that the radioisotopes are produced in the hospital.

All the aforementioned safety considerations in relation to the implementation of the nuclear medicine procedure shall be taken into account when deciding to adopt one or another alternative technique. Those considerations shall be judged together with other aspects as safety of the production and supply route, effectiveness of the procedure, security and sustainability of the considered options, costs, etc.

In general the new techniques provide for better image quality, faster and better diagnosis and provide significant contribution to the improvement of the health care. However, the new techniques may also expose patients to higher doses of radiation and may be misused or overused. Therefore the systematic implementation of the justification principles to the type of practice before being generally adopted and to its individual implementation in each case is of utmost importance. This is especially relevant to the constantly growing implementation of PET and PET/CT.

### 2.2.1.5 Health Impacts of the Recent Supply Shortage in Various Countries

A shortage in supply of Molybdenum-99 / Technetium-99m in particular, which is quantitatively the most important radioisotope for medical use, occurred in Europe in autumn 2008 – early 2009. This was because the nuclear reactor in Petten (The Netherlands) could not re-start after the summer maintenance due to a technical problem in the cooling system, while the two other major radioisotope-producing nuclear reactors in the EU, in Saclay (France) and Mol (Belgium), were on routine maintenance. In addition, the nuclear installation in Fleurus (Belgium) where radio-isotopes from the nuclear reactors in Saclay and in Petten are purified for further medical use was closed down end of August after an accidental (even though small) release.
**Affected Isotopes**

Annex 1 lists currently used nuclear-reactor-produced medical radioisotopes and new ones that seem most promising for the future.

Technetium-99m (Tc-99m) is the isotope used for over 80% of all nuclear medicine procedures. It is produced by nuclear reactors (via Molybdenum). Normally, more than 80% of the Molybdenum-99 supply for Europe comes from nuclear reactors located within the EU (70% of which from the High Flux Reactor (HFR) in Petten). The rest is imported essentially from South Africa or Canada.

The shortage in Molybdenum-99 / Technetium-99m supply of September 2008-February 2009 resulted in significant effects for nuclear medicine procedures in Europe. But a shortage in supply of other reactor-produced isotopes than Mo—99 / Tc-99m could also be of medical concern, in particular in case of prolonged decrease in nuclear-reactor production capacities. Radioisotopes of concern would be for example Iodine-131 and Samarium-153, which are mainly used for (cancer) therapeutic purposes.

**Affected Countries**

The European Association of Nuclear Medicine (EANM) investigated, by means of a survey amongst its members, the impact of the in supply of Mo-99 / Tc-99m of autumn 2008 for nuclear medicine in European Countries.

The results of the survey, which were presented in January 2009 and kindly provided by EANM, are summarised in figure 2.1.

![Figure 2.1: Impact of Supply Shortage that started in September 2008 on 34 European Countries, according to EANM Supply Survey of January 2009 (information and authorisation to reproduce kindly provided by EANM). n/a= information not available.](image)
The 34 countries (ie not just EU ones) for which information was available were distributed as follows:

- 14 countries were seriously affected: Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Iceland, Ireland, Lithuania, Netherlands, Slovakia, Switzerland, United Kingdom.
- In 9 countries there was some impact: Austria, Bulgaria, Denmark, Italy, Luxembourg, Malta, Portugal, Slovenia, Turkey.
- 11 countries were not affected: Cyprus, Estonia, Finland, Israel, Latvia, Norway, Poland, Romania, Russian Federation, Serbia, Ukraine.
- For 5 countries there was no information available.

The survey showed no major discrepancy in supply between different departments (university departments, private practices, etc.) in a majority of countries. The discrepancies depended on the delivering company.

Various non-European countries have also been affected, like Korea where it had "significant effects" [3].

**Health Impact**

Potential medical consequences of radioisotope shortage are obvious in the case of therapeutic radioisotopes, namely absence of the most appropriate treatment (eg of tumours, pain palliation, etc.).

Potential consequences of delay in diagnosis, which is often crucial for the management of patients and treatment decisions in (acute) life-threatening conditions, include more myocardial infarcts and cardiac death, and delayed or non-optimal treatment in cancer patients, resulting in more complications and increase in non-fatal and fatal diseases.

Delayed diagnosis also causes results in additional stress in all patients (also orthopaedic ones and others) and delay in appropriate treatment.

On 27 August 2008 (just after the HFR shutdown), The President of the North American Society of Nuclear Medicine (SNM), Robert W. Atcher, said ([http://interactive.snm.org/index.cfm?PageID=7977&RPID=969](http://interactive.snm.org/index.cfm?PageID=7977&RPID=969)): "The impact on the patients who are in need of diagnostic tests using these radioisotopes is very serious".

On 29 August 2008 "Nature on-line" news reported that “Isotope shortage could delay cancer treatments. Reactor shut downs mean patients will go without diagnostic imaging.”

In December 2008, both EANM and SNM indicated that the situation for diagnosis and treatment of patients in nuclear medicine was not critical (yet), but that the quality and frequency of diagnosis and treatment could not be maintained at the same level as before the supply shortage occurred.

**Socio-economic Impact**

On top of impact on patients' health, a supply shortage has an economic impact on hospitals and healthcare systems, including because of the cost of alternative methods, which are often more costly and/or less efficient, and not always easily available.
Closure of nuclear medicine departments could also happen. It did in some countries, but not in Europe, to our knowledge (at least in the public sector), in the recent crisis.

2.5 PREVIOUS SHORTAGES IN RADIO-ISOTOPES SUPPLY

Shortages in nuclear-reactor-produced medical radioisotopes, and in particular Mo-99m / Tc-99m, already occurred before. Here is a probably non-exhaustive list:

- In 1995: Strike of Canadian air-flight personnel produced problems in shipping Mo-99 from Canada, which is the World’s main producer.

- 11 September 2001: following the New York terrorist attack flights were perturbed and the shipping of radioisotopes to/from North America was disrupted for some days.

- 2002: HFR reactor in Petten (NL) shuts down for 42 days because of reactor operation safety concerns.

- 2006: NRU reactor (Canada) shuts down for about 6 days because of a technical problem.

- In 2007: the Australian isotope-producing nuclear reactor was temporarily shut-down for upgrades. This was planned, but Australia reported it expected to face shortages.

- November-December 2007 (for about a month): the NRU reactor at Chalk River in Canada, which is the main producer of Mo-99 in the World (with about 40%), mainly for Canada and the USA, shuts down to address safety concerns. This sparked a crisis in Ottawa (Canada) and a worldwide medical shortage. The isotope shortage lasted for a few months and strongly affected North America. It forced the cancellation and delay of diagnostic testing for life-threatening conditions affecting tens of thousands of patients throughout the U.S. and Canada [5]. Some nuclear medicine departments were forced to close and, by mid-December, emergency services in some regions were compromised.

The SNM warned in a public statement that “Patients’ lives are now at risk”. “The practice of nuclear medicine across North America is in serious danger. An increasing number of hospitals and imaging centres across the United States and Canada are prioritizing their patient lists and may be unable to appropriately treat many patients with cancer, thyroid, heart, and kidney disease.” (The Journal of Nuclear Medicine, 17N-18N, Vol. 49, No. 1, January 2008).

- End August 2008 – February 2009: The HFR reactor in Petten (The Netherlands), which is the main European supplier, had to shut down because of anomalies detected during a routine maintenance. During part of this period the two other nuclear reactors in the EU which produce Mo-99, in Saclay (France) and Mol (Belgium), were out of service in September and October 2008 because of planned maintenance. The Institute for Radio-elements in Fleurus (Belgium) in which Molydenum-99 produced in Saclay and in Petten is purified, was shut down from mid-August until mid-November 2008 due to an unplanned (even though small) release into the environment. Consequences are partly described elsewhere and triggered this report.

On 27 August 2008, the American SNM Expressed Serious Concerns as Isotope Shortage Loomed (http://interactive.snm.org/index.cfm?PageID=7977&RPID=969):
"Another Worldwide Shutdown is the Latest Hiccup in the Precarious Supply of a Critical Tool. A shutdown announced late this month at a nuclear reactor facility at Petten in the Netherlands threatens the ability of countries across the globe to access and obtain radioactive isotopes, which are critical for performing many common nuclear medicine procedures in the United States and worldwide. The shutdown at the High Flux Reactor in Petten comes after a similar shutdown last December of the National Research Universal reactor in Chalk River, Canada by Atomic Energy of Canada Limited. "SNM has serious concerns about this most recent outage," said SNM President Robert W. Atcher. "A combination of anticipated outages at other production reactors, coupled with unanticipated shutdowns, is simply devastating. The impact on the patients who are in need of diagnostic tests using these radioisotopes is very serious. The United States and other countries are not prepared to adequately deal with the current situation, let alone anticipate other situations as they continue to arise". "Following the shutdown of Canada's Chalk River facility late last year, we simply cannot afford to sit and wait as the situation continues to worsen," added the emerging medical technology team leader at the Los Alamos National Laboratory in New Mexico."

- 4 to 15 December 2008: initially planned shutdown of NRU (Canada) had to be unexpectedly prolonged for repair.

In December 2008, there was on average a lack of 20-30% of normal supply in European countries. The majority of 479 members of the American SNM selected for a survey by the society in November 2008 reported that the supply was below 75% of the normal supply situation. Both the EANM and SNM indicated that the situation for diagnosis and treatment of patients in nuclear medicine was not critical, but that the quality and frequency of diagnosis and treatment could not be maintained at the same level as before the shortage in supply occurred.

- 30 March 2009: the HFR reactor in Petten (NL), the main European supplier, had a “delay in the restart due to technical problems during the routine start up check-out procedure, concerning the drive coupling of one of the six control rods. HFR engineers did a great job, they had to dismantle, find the problem, make the repair and rebuild the whole core. They managed it in less than 36 hours. Unfortunately it was not a cheap repair.” So, it could restart on 1 April.

- 14 May 2009: Shut down for at least until first quarter of 2010 of the 51-year-old NRU reactor in Chalk River after discovery of a leak in the heavy water system (state at the time of drafting of the present report). Shortage in supply of Mo-99 is expected to occur soon in the U.S. and Canada (and seems real as of 25 May). It is likely that the U.S., Canada and Japan will be hit hardest. The prognosis is that Europe will be affected, also due to additional buying by North American radiopharmaceutical companies of Molybdenum-99 from the European market. There seems to be real cause for concern amid increasing speculation that the NRU reactor could be closed down for good, given its record of recent high unreliability. There are currently no reliable long-term substitutes to NRU to ensure continuity in supply of medical radioisotope worldwide.

**Analysis of previous shortages**

The above list is probably not exhaustive. Nevertheless, it seems to give some general indications concerning the shortages:
- The causes for shortages can have various origins.
- They are sometimes completely independent from the radioisotope production and supply chain (e.g. due to geographical, geo-political or economic reasons which might not be under European control).
- Most situations of shortages are unpredictable
- They seem to become more frequent and more severe; this is not completely surprising considering the age of concerned nuclear reactors (essentially 40 to 50 years old).
- There seems to be little incentive for private companies to invest in additional production capacities for medical radioisotopes in the current market;

Therefore, if nothing changes and nothing is done, further shortages and possibly more severe ones will occur.

3. CURRENT SUPPLY SITUATION

Just five nuclear research reactors produce most of the worldwide supply of Molybdenum-99, from which then Technetium-99m is derived. These are the High Flux Reactor in Petten, the Netherlands; BR2 in Mol in Belgium; Osiris in Saclay, France; NRU in Chalk River, Canada; and Safari-1 in Pelindaba, South Africa. These facilities range in age from 42 to 51 years.

Several countries have expressed an interest in building modern research reactors, often seen as a stepping stone to a full-blown nuclear power programme in addition to other capabilities such as isotope production. However, it can take ten or more years from the planning phase for research reactors to become operational and ‘teething’ issues during the early years of operation can add additional, unanticipated challenges.

Projects to initiate Molybdenum production from an existing facility, not originally conceived for that purpose, can also take five or more years to become operational depending on available equipment and facilities at the specific reactor site.

The vulnerability of the global medical isotope supply chain, which depends on a limited number of ageing nuclear research reactors for isotope production and a complex processing and distribution chain for delivery of short-lived isotope products to the health system, continuous to exist. The vulnerability of the chain has manifested itself in several regional and global supply disruptions over the last decade which were due to reactor outages and various complications in the processing and distribution system (see list in the previous chapter).

At the time when this report is drafted, the NRU reactor in Chalk River, Canada, is shut down for at least three months following a leak in the heavy water system. This unplanned shut down effects the worldwide supply situation of Molybdenum-99. It is foreseen to cause a shortage of Mo-99 in North America rapidly. It is expected to have indirect effects for the European market, in the sense that North American radiopharmaceutical companies, in their efforts to compensate a lack of this radioisotope in that region, will buy additional Mo-99 from the European market and thus could cause a shortage of this radioisotope here as well.
4. AVAILABLE PRODUCTION CAPACITIES

Radioisotopes for medical use are produced both in nuclear reactors and in particle accelerators. Different processes include:

- Fission of uranium in special targets in a nuclear reactor or by means of photons in a particle accelerator. This results in fission products which can be separated from uranium by chemical processes.

- Activation: irradiation with neutrons (nuclear reactor), protons or photons (accelerators). This results in radioactive nuclei of the irradiated element (usually in reactors) or of a different element (usually in accelerators). In the second case the radioactive nuclei can be separated chemically from the target material.

The nuclear reactions that are necessary for the production of radioisotopes depend on different attributes, i.e. the type of bombarding particle (e.g. neutron, proton), the energy of the particle, the number of particles present (neutron flux, density of the proton beam) and the probability that the nucleus undergoes a reaction (cross section).

4.1. NUCLEAR REACTORS

Nuclear reactors, as well as neutron generators and isotopic neutron sources provide the neutrons needed for the nuclear reactions. The neutron fluxes typically achieved in nuclear reactors are several orders of magnitude higher than those of other neutron sources. The quantity of radioactivity from the generated radioisotopes is directly proportional to the neutron flux, which explains the importance of nuclear reactors for the production of radioisotopes.

4.1.1. RADIOISOTOPES PRODUCTION BY FISSION ROUTE

The process of nuclear fission consists in the splitting of the nucleus of the isotope $^{235}\text{U}$ following the collision with a thermal neutron in two fragments. The resulting fission products can be important as radioisotopes, such as $^{99}\text{Mo}$.

The abundance of $^{235}\text{U}$ (isotopic abundance) in natural uranium is approximately 0.7%. By means of isotopic enrichment the abundance of the isotope $^{235}\text{U}$ can be increased. When the quantity of $^{235}\text{U}$ is above 20%, we talk about "highly enriched uranium, HEU", while below that threshold it is "low enriched uranium, LEU".

Currently $^{99}\text{Mo}$ is produced mainly by means of HEU targets (approximately 92% enriched in $^{235}\text{U}$). The use of HEU has implications for what concerns non proliferation issues, and it is therefore limited to countries that conform to the directives of the International Atomic Energy Agency (IAEA). Radioisotopes production via the fission routes is usually done by irradiation of special uranium targets, rather than by direct irradiation of the reactor fuel. Special irradiation rigs are therefore required, which are designed to assure efficient and safe irradiation procedures. The fission route is used for producing radioisotopes as $^{99}\text{Mo}$ and $^{131}\text{I}$.

4.1.2 PRODUCTION OF RADIOISOTOPES BY LOW ENRICHED URANIUM (LEU) TARGETS

Between 95 and 98 percent of the world’s supply of Molybdenum-99 is produced by just four organizations (NNSA/ANSTO, 2007), all of which use highly enriched uranium
(HEU) targets. A recent study [Medical Isotope Production Without Highly Enriched Uranium Committee on Medical Isotope Production Without Highly Enriched Uranium, Nuclear and Radiation Studies Board Division on Earth and Life Studies National Research Council of the National Academies, The National Academies press, Washington, DC, 2009] has examined the possibility of eliminating HEU as reactor fuel and as target material for the production of medical radioisotopes. The study concludes that there is sufficient evidence that LEU targets can be used for production of more than 1000 Ci/ week (6 days). Although eliminating HEU targets is therefore possible, the use of LEU encounters resistances from the large producers, since:

- The new chemical process to separate and purify the Mo-99 would require to be approved by the competent authorities;
- The targets conversion from HEU to LEU would require significant financial investments (tens of millions €) and time (ranging from a few months to about 13 years).

4.1.3 RADIOISOTOPES PRODUCTION BY ACTIVATION ROUTE

Activation consists in the capture of a neutron by the nucleus of a stable element, which is transformed into an unstable (radioactive) nucleus of the same element. In nuclear reactors, this route is followed for the production of radioisotopes like Lu-177 and Ir-192. This process can be used for producing Molybdenum-99, but the resulting specific radioactivity (radioactivity per unit mass) is several orders of magnitude lower than in the case of the fission route and the residual non-activated Mo-99 poses medical problems.

4.2 PARTICLE ACCELERATORS

Considerable research has been performed to investigate the feasibility to produce Mo-99 and Tc-99m by means of cyclotrons, which are much more widespread than nuclear reactors. Either Mo-99 or Tc-99m can be produced in a particle accelerator.

4.2.1 PRODUCTION OF MOLYBDENUM-99

Even by irradiation of Molybdenum 100% enriched in the isotope Molybdenum-100 (natural isotopic presence is 10%), the quantity of resulting radioactive Mo-99 is two orders of magnitude lower that via the fission route in a nuclear reactor, and the chemical separation of the accelerator product introduces a further loss of the active component. The final Mo-99 is chemically less pure that the one obtained by nuclear reactors, leading to higher radioactive doses to the patient and to less precise imaging.

4.2.2 PRODUCTION OF TECHNETIUM-99M

Direct production of Technetium-99m is possible in accelerators (reaction 100-Mo(p, 2n)99m-Tc), and the resulting quantity of radioactive Tc-99m is approximately half what can be obtained in the same period of time via the fission route in a nuclear reactor. Since the half life of Tc-99m is only 6 hours, the radioisotope cannot be transported and it has to be produced in the immediate vicinity of the utilization. In principle each hospital should have its own cyclotron, and the capacity to separate/purify the accelerator product, which makes this way of production highly unlikely. The purity of the end product (approximately 25% Tc-99m and 75% Tc-99) also poses problems from a medical standpoint.
Both, for producing Mo-99 and Tc-99m, the Molybdenum has to be enriched in the Mo-100 isotope, a very expensive process, of which just a small quantity is finally used for the analysis. Separation and recycling of he remaining Mo-100 is in practice not possible.

Most of the radionuclides of interest for the PET (e.g. C-11, N-13, O-15, F-18) can only be produced in cyclotrons.

4.2.3 PHOTON ACTIVATION AND FISSION

An alternative approach in particle accelerators is to use an electron beam to generate high intensity photons which in turn initiate an activation reaction on enriched Mo $^{100}$Mo($\gamma$,n)$^{99}$Mo or a fission reaction $^{238}$U($\gamma$,n)$^{99}$Mo.

A recent report {Making Medical Isotopes, Report of the Task Force on Alternatives for Medical-Isotope Production, TRIUMF University of British Columbia Advanced Applied Physics Solutions, Inc. 2008} analyses in detail this route, which is in particular attractive for non proliferation considerations.

The challenges for both photon induced reactions is the need for very high intensity beam to overcome the factor of about 1,000 smaller cross section for this reaction versus neutron fission of U-235 in nuclear reactors. A large number of accelerators would be needed to produce a significant amount of Mo-99: the report estimated that half a dozen machines would be necessary to cover 30%-50% of North American demand.

4.3 ACCELERATOR DRIVEN SUBCRITICAL REACTOR (ADS OR ADSR)

An ADS provides protons and neutrons for various R&D applications. It consists of a proton accelerator coupled to a subcritical fast core. The neutrons could be used, in similarity to what is done in nuclear reactors, to bombard uranium targets for the production of Mo-99. In Europe, the MYRRHA (Multi-purpose hybrid Research Reactor for High-tech Applications) is currently being studied at Mol, Belgium. The current plan is to have the MYRRHA operational by 2018. Although the characteristics in terms of neutron flux would allow MYRRHA to produce neutron-rich radioisotopes, its operating schedule and its currently foreseen focus (research, transmutation) leads to question its actual use for significant commercial production.

4.4 OVERVIEW OF CURRENT PRODUCERS AND REACTORS

Between 95 and 98 percent of the world’s supply of Mo-99 is produced by just four organizations (NNSA/ANSTO, 2007), all of which use highly enriched uranium (HEU) targets: MDS Nordion, Mallinckrodt, Institut National des Radioéléments (IRE), and Nuclear Technology Products Radioisotopes (Pty) Ltd. (NTP).

The remaining world supply of Mo-99 is provided by a small number of organizations that make Mo-99 primarily for local use. These producers collectively produce only about five percent of the world supply of Mo-99. The short half life for Mo-99 (66 hours) prevents it from being stockpiled for use, so Mo-99 producers must schedule the production of this isotope to meet projected demand. It can therefore be reasonably assumed that Mo-99 production is equivalent to the world demand.

Several estimates of the global supply for Mo-99 (usually expressed as weekly quantities) have been published {e.g., Bonet and Ponsard, 2005; Von Hippel and Kahn,
2006; NNSA/ANSTO, 2007}. It is not possible to verify the accuracy of these estimates because Mo-99 producers do not publicly disclose their production data. The most recent and likely the most reliable of these estimates is provided in NNSA/ANSTO (2007). According to that report, the 2006 production of Mo-99 for medical diagnostic imaging was approximately 12,000 6-day curies per week.

4.4.1 MOLYBDENUM-99 PRODUCERS

An overview of the producers using highly enriched Uranium (proportion of U-235 is higher than 25% -HEU) and low enriched Uranium (proportion of U-235 is lower than 25% - LEU) targets is given respectively in figure A and B [Ref. Cristina Hansell Nuclear medicine's double hazard - Imperiled Treatment and the Risk of Terrorism. Nonproliferation Review, Vol. 15, No. 2, July 2008].

All of the organizations that currently produce Mo-99 utilize government-owned research/test reactors to irradiate targets. In some cases also the Mo-99 recovery/processing facilities are government-owned.

The principal producers are described briefly in the following sections, starting with the large producers.

MDS Nordion (Canada)

MDS Nordion provides approximately 40 percent of world supply. It obtains raw Mo-99 from the Atomic Energy of Canada Limited (AECL), a Canadian government-owned Crown Corporation. AECL is responsible for (HEU) target fabrication, target irradiation, and target processing to recover a solution containing Mo-99. Irradiation takes place in the NRU reactor at the Chalk River Site in Ontario, Canada. The targets are processed at their Chalk River. The separated Mo-99 is shipped to MDS Nordion’s plant in Ottawa for purification and preparation for distribution.

Mallinckrodt – Covidien (The Netherlands)

Mallinckrodt produces approximately 1/4 of world supply. Production is carried out at the Petten Site in the Netherlands in a joint venture with NRG (Nuclear Research and CConsultancy Group) the reactor operator. The HEU targets are irradiated in the HFR reactor, which is located at the Petten Site. The BR2 reactor, which is located in Belgium, and the Osiris Reactor, which is located in France are used as backup. After irradiation, the targets are processed in a facility at the Petten Site.

Institut National des Radioéléments (Belgium)

IRE produces approximately 20 percent of the world supply of Mo-99. Its production takes place at Fleurus, Belgium. HEU targets are irradiated in three reactors: HFR, BR2, and Osiris. The irradiated targets are transported in shielded casks on trucks to the IRE facility for processing.

NTP Radioisotopes (South Africa)

NTP, part of the South African Nuclear Energy Corporation (NECSA), produces about 10 percent of the world supply of Mo-99. It produces Mo-99 from HEU (45% enriched) targets, which are irradiated in the Safari-1, located at the NECSA site in Pelindaba, and processed at that same site.
Comisión Nacional de Energía Atómica (CNEA; Argentina)

CNEA produces Mo-99 for its domestic market and for export to South American countries. It converted to LEU targets production in 2002. The targets are irradiated in the RA-3 reactor at CNEA’s Ezeiza Atomic Center (Buenos Aires). Irradiated target are processed at the same site. There are potentialities to significantly expand Mo-99 production.

Australian Nuclear Science and Technology Organisation (ANSTO, Australia)

ANSTO has been producing Mo-99 primarily to supply its domestic market, although it supplied Tc-99m generators to several countries in the Asia-Pacific area. After producing Mo-99 for 25 in the HIFAR reactor at Lucas Heights, it shut down its facility in 2007 in the frame of converting to a more efficient production process.

A new reactor (supplied by the Argentine company Investigaciones Aplicadas Sociedad del Estado (INVAP) was commissioned at the end of 2006. ANSTO plans to develop production in two phases:

- “Mini-moly”): supply Mo-99 to meet domestic and some export demand (mainly US). This phase would demonstrate the feasibility to produce large quantities of Mo-99 using LEU targets.

- “Mega moly” (pending favourable technical outcome of phase 1 and positive business case): extension of the facility to become global Mo-99 supplier. This step would take several years and large investments.

Test irradiations have started in November 2008, and commercial production is planned mid 2009.

Karpov Institute of Physical Chemistry (Russia)

The Karpov Institute of Physical Chemistry, located in Obninsk, Russia produces almost all the Mo-99 used in Russian. The HEU targets are irradiated in the WWR-TS reactor at Obninsk and processed at the site.
FIG. A: MOLYBDENUM-99 PRODUCERS USING HIGHLY ENRICHED URANIUM
4.4.2 NUCLEAR REACTORS PRODUCING MOLYBDENUM-99

An overview of the current nuclear reactors that are or could in principle be used for producing Mo-99 is given in figures C and D. Europe produces approximately half of the total word consumption; large industrialized countries such as US and Japan, although among the main consumers, have no production.

All the top 5 reactor for radioisotopes production are 40-50 years old. The NRU reactor in Chalk River has a valid operating licence until 2011, which is likely to be extended until 2015. Both BR2 and the HFR have to undergo a safety e-evaluation in 2015. The
operating licence of OSIRIS expires in 2015. It is in principle not sure if any of these 4 reactors will be in operation after 2015-2016.

As a general consideration, the whole world fleet of research reactors is ageing. Figure E [IAEAagereysreactors2008.pdf] shows the age distribution of research reactors in the IAEA Research Reactors Database.

<table>
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<tr>
<th>Country</th>
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<th>Location</th>
<th>Type</th>
<th>Power (kW)</th>
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<td>Jakarta</td>
<td>TRIGA II</td>
<td>30,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jakarta</td>
<td>Tank</td>
<td>2000</td>
</tr>
<tr>
<td>Italy</td>
<td>TRIGA RC-1</td>
<td>Rome</td>
<td>TRIGA II</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Lina TRIGA II</td>
<td>Parma</td>
<td>TRIGA II</td>
<td>250</td>
</tr>
<tr>
<td>Japan</td>
<td>JRR-4</td>
<td>Tokai-mura</td>
<td>TRIGA II</td>
<td>3500</td>
</tr>
<tr>
<td></td>
<td>TRIGA II Riky</td>
<td>Riky</td>
<td>TRIGA II</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Riky</td>
<td>Tank</td>
<td>50,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Riky</td>
<td>Pool</td>
<td>20,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>Pool</td>
<td>20,000</td>
</tr>
</tbody>
</table>

**Table 1: Research reactors producing radioisotopes**

**Fig. C: Nuclear Research Reactors in which Radioisotopes are produced**
<table>
<thead>
<tr>
<th>Reactor</th>
<th>Location</th>
<th>Owner</th>
<th>From</th>
<th>World share of Mo-99</th>
<th>Used by</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRU</td>
<td>Canada</td>
<td>AECL</td>
<td>1957</td>
<td>40%</td>
<td>Nordion</td>
</tr>
<tr>
<td>HFR</td>
<td>The Netherlands</td>
<td>European Commission</td>
<td>1961</td>
<td>30%</td>
<td>Mallinckrodt IRE</td>
</tr>
<tr>
<td>BR2</td>
<td>Belgium</td>
<td>SCK-CEN</td>
<td>1961</td>
<td>9%</td>
<td>Mallinckrodt IRE</td>
</tr>
<tr>
<td>Osiris</td>
<td>France</td>
<td>CEA/CEN Saclay</td>
<td>1966</td>
<td>3%</td>
<td>Mallinckrodt IRE</td>
</tr>
<tr>
<td>SAFARI-1</td>
<td>South Africa</td>
<td>NECSA</td>
<td>1965</td>
<td>10%</td>
<td>NTP</td>
</tr>
<tr>
<td><strong>Small producers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA-3</td>
<td>Argentina</td>
<td>CEA</td>
<td>1968</td>
<td>8%</td>
<td>CNEA</td>
</tr>
<tr>
<td>OPAL</td>
<td>Australia</td>
<td>ANSTO</td>
<td>2007</td>
<td></td>
<td>ANSTO</td>
</tr>
<tr>
<td>WWR-TS</td>
<td>Russia</td>
<td>Karpov Institute of Physical Chemistry</td>
<td>1964</td>
<td></td>
<td>Karpov Institute of Physical Chemistry</td>
</tr>
<tr>
<td><strong>Potential use for 99-Mo production</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MURR</td>
<td>USA</td>
<td>University of Missouri</td>
<td>1966</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.A. Siwabessy MPR</td>
<td>Indonesia</td>
<td>Badan Tenaga Nuklir Nasional</td>
<td>1987</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETRR-2</td>
<td>Egypt</td>
<td>Atomic Energy Authority of Egypt</td>
<td>1997</td>
<td></td>
<td></td>
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<tr>
<td>RP-10</td>
<td>Peru</td>
<td>Instituto Peruano de Energia Nuclear</td>
<td>1988</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECH-1</td>
<td>Chile</td>
<td>Comision Chilena De Energia Nuclear</td>
<td>1974</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MARIA</td>
<td>Poland</td>
<td>Institute of Atomic Energy</td>
<td>1974</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIGA II Pitesti</td>
<td>Romania</td>
<td>RAAN</td>
<td>1979</td>
<td></td>
<td></td>
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<tr>
<td>HANARO</td>
<td>South Korea</td>
<td>Korea Atomic Energy Research Institute</td>
<td>1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Future Reactors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jules Horowitz Reactor</td>
<td>France</td>
<td>2014</td>
<td></td>
<td></td>
<td>Mallinckrodt IRE</td>
</tr>
<tr>
<td>PALLAS</td>
<td>The Netherlands</td>
<td></td>
<td>2016</td>
<td></td>
<td>Mallinckrodt IRE</td>
</tr>
<tr>
<td>Medical Isotope Production System</td>
<td>USA</td>
<td>?</td>
<td></td>
<td></td>
<td>Babcock and Wilcox</td>
</tr>
</tbody>
</table>

Fig. D: Nuclear Research Reactors in which Molybdenum-99 is currently produced and those which potentially could be activated for Mo-99 Production
FIG. E: Age Distribution of Nuclear Research Reactors included in the IAEA Research Reactor Database
5. TRANSPORT OF RADIOISOTOPES

Medical isotopes are generated by reactor and accelerators. By their nature, these isotopes have a short life, and rely not only on a well-organised production, but also on a secure and reliable global distribution effort.

The transportation of this radioactive material places it outside of controlled facilities, in the public domain, and often entails movement between countries.

2.5 million packages containing radioactive material are estimated to be shipped annually across the European Union, which represents about 2% of all dangerous goods packages. Most of these packages (almost 90%) contain relatively small quantities of radioactive materials for medical purposes. By its radioactive nature, the use and handling of radioactive material (RAM), including its transport and in-transit storage, gives rise to radiological (and non-radiological) hazards with the potential for a variety of adverse consequences, such as human health effects and economical and environmental impact.

Radioactive material transport in the public domain is therefore subject to a comprehensive system of provisions and requirements agreed upon internationally that enables the beneficial uses of radioactive substances to be exploited while ensuring an appropriate level of protection and safety of people, property and the environment.

The applicable international provisions and requirements governing the safety and security during transport are essentially formed by a hierarchically structured and inter-related legislative and regulatory framework comprising four levels of (legally binding and non-binding) regulations and recommendations: i) IAEA Regulations for the Safe Transport of Radioactive Material (No. TS-R-1), ii) UN Recommendations for the Transport of Dangerous Goods (Orange Book) and the modal regulations and agreements (e.g. ADR, RID, ADN) of the specialised international transport organisations, iii) Community Regulations and Directives, and iv) a variety of international conventions, codes and agreements.

This comprehensive international regulatory regime is generally complemented by national provisions and requirements to address concerns of particular importance to that country, depending on and consistent with the established cultural, legal and institutional/political system. This has resulted in numerous national deviations from the applicable regulatory requirements and practices agreed upon internationally for the safe transport of radioactive material.

The currently existing comprehensive and stringent transport regulatory framework has proven to be effective in minimising the radiological impact for normal and accidental conditions of transport. However, the national deviations and disparities in the regulatory requirements and practices, which often appear to be minor, can have a major impact on trans-boundary transport of radioactive material in terms of the extra effort, time and (technical/financial) resources required by transport operators to comply with the specific national duties and requirements.

Consequently, these can represent a major regulatory burden for shippers and carriers involved in intra-community and international radioactive material transport operations. These also increase the potential for non-compliances and shipment denials and affect adversely functioning of the Single European Market.
Currently, as stated at the 01/2009 NEA Workshop on the Security of Supply of Molybdenum-99 and Technetium-99m, there are indications that insufficient standardisation of international shipment standards or transport containers lead to repeated delays or denials with all related socio-economic consequences. Further, reduced commercial incentives for airlines to carry radioactive substances result in fewer carriers and fewer routes than historically available.

The denial of shipment by some carriers, sea ports and airports is a major issue for users of radioactive materials. There are problems with all modes of transport sometimes due to the perception of possible hazards rather than the reality. For example some maritime carriers and harbours have refused to transport and handle radioactive material, although the risk created by the material is very low:

The classification as ‘radioactive’ gives rise to a negative prejudgement that often makes it impossible or difficult to transport this kind of dangerous goods. Similar perception is not apparently frequent in the case of the other classes of dangerous goods.

The issue of denial of shipments is not just for specialists but affects the lives of millions of people around the world. The majority of the radioactive material shipped every day is used in hospitals for diagnostics and treatment of several illnesses. Any delay or denial of shipment may render the isotopes useless for their intended application.

In summary, the improvement in international coordination of research reactor production alone is not sufficient to solve the issue of global supply security. Also the transport of such radioactive materials is vital. Recently, following a three-year preparation period during which the Commission along with the help of independent experts looked into the Community acquis on the transport of radioactive materials, the health and safety aspects related to it and the implementation of Community legislation and international agreements on this topic in the Member States, a new Council Regulation on administrative procedures for the transport of radioactive material has been proposed. The proposed regulation intends to harmonise administrative procedures governing this practise, thereby making the safety standards laid down in the internationally recognised IAEA Transport Regulations and the international agreements based on it applicable in a universal and harmonised manner across the Member States of the European Union. It would introduce a Community carrier license, while increasing transparency of the existing rules by giving easier access to the information required by actors in this practise through a national contact point and a central internet site.
Currently there are over 100 radiopharmaceuticals developed worldwide 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, ensuring effective quality assurance and quality control systems, registration of the products with licensing authorities and radioactive material transport etc. Radiopharmaceuticals production, unlike conventional pharmaceuticals production, is still on a relatively small scale.

In the EU there are currently 7 radiopharmaceutical medicinal products on the markets which have received marketing authorisation centrally by the European Commission (ZEVALIN, NEOSPECT, QUADRAMET, YTRACIS, YTTRIGA, DATSCAN and LEUKOSCAN). In addition, there are radiopharmaceutical products on the market which have received marketing authorization by national agencies.

7. International Cooperation

The European Commission is participating actively in international initiatives which are aimed at contributing to securing supply of medical radioisotopes and looking at new developments in nuclear medicine at a global level.

The European Commission is leading together with Health Canada on the issue of supply of radioisotopes for medical use within the Global Health Security Initiative of the G7+.
It is cooperating with the OECD Nuclear Energy Agency (OECD / NEA) and the International Atomic Energy Agency (IAEA) on the question of security in supply of medical radioisotopes and on trends in nuclear medicine.

It contributed to an OECD / NEA workshop on the Security of Supply of Medical Radioisotopes of 29-30 January 2009. The Chairman's summary of the discussions was as follows:

Measures identified by participants to enhance short-term supply security:

- reactor owners and operators should continue to share information and to enhance co-ordination of reactor maintenance schedules, with a view to ensuring an uninterrupted global supply of isotopes;
- options for increasing production from existing reactors in times of global shortage should be further explored and encouraged;
- current economic conditions for irradiation services should be reviewed to provide better incentives to reactors operators, including where the main mission is research in support of national nuclear energy or scientific programmes;
- unnecessary impediments to the distribution of medical isotopes, such as restrictions in transport capabilities and denial of shipment by airline companies, should be removed;
- anticipative actions to avoid the dilemma between meeting nuclear safety requirements or meeting health care needs should be encouraged;
- radio-pharmacies, hospitals, health product regulators and the medical community should explore options for more efficient patient scheduling and utilisation of Mo-99/Tc-99m generators to make best use of currently available supplies of Mo-99 and/or other potential alternatives.

There was broad agreement between the participants of the workshop that increased transparency among reactor operators, isotope processors and distributors, government regulators, and health care professionals would facilitate all efforts. In particular, it is important that the health care community obtains early information from all participants in the supply chain concerning potential and real disruptions, including estimates of the timing, duration and severity.

Participants of the workshop expressed a wide range of views on the best means of ensuring adequate Tc-99m supplies over the longer term. Replacing or supplementing the ageing reactors that are used to produce Mo-99 would help to reduce supply disruptions arising from unplanned reactor outages. It was recognised that the uncertainties regarding the long-term global demand due to competing, although more expensive, techniques in the medical sector make the decision to invest in capital-intensive additional nuclear capacities, which are designed for around 50 years, difficult. A greater involvement of health authorities is needed to reduce these uncertainties. In addition, questions were raised regarding the long-term validity of the current economic model where the security of supply relies mainly on government-run reactors which typically charge only marginal costs for their irradiation services.

There was agreement, however, that governments have a responsibility for establishing an environment conducive to the private and/or public sector investments that may be required. There was recognition that it could take 5 to 10 years for
significant additional capacity to be developed. Participants also recognised that long-
term supply presents a global challenge that will require a global response. At the
same time, it was noted that regional co-operation has proved effective in some cases
and should be explored as a complementary vehicle.¹

In the area of pharmaceuticals, which include radiopharmaceuticals, the European
Commission and the European Medicines Agency (EMEA) have concluded bilateral
"confidentiality agreements" with the regulatory authorities of the US, Japan and Canada.
These confidentiality arrangements build on the previous cooperation and allow an
exchange of information between the parties as part of their regulatory and scientific
processes, both before and after a medicine has been approved by the European
Commission. Should a need arise to look for alternative sources in a situation of a
shortage of radioisotopes, an information exchange between those parties may also
become important. Recently, in particular the EU and Canada have expressed their
intention to cooperate further in the area of radiopharmaceuticals and discussions are
ongoing.²

8. OUTLOOK

8.1 CURRENT DEVELOPMENTS IN NUCLEAR MEDICINE, POTENTIAL ALTERNATIVE
METHODS AND ESTIMATED FUTURE NEEDS IN REACTOR RADIOISOTOPES

Past experience has shown that it is difficult to make predictions about the future.
Nevertheless, some likely predictions may probably be reached by considering a number
of facts, knowledge and various experts’ opinions, as we will do here.

A main question of this report is how important should the nuclear reactor production of
radioisotopes be for medical applications in the future. So this part of the report will deal
with how much these isotopes will probably be used, assuming they can be available in
sufficient quantity. Other parts will discuss potential alternative routes to their nuclear
reactor production.

This report concentrates on the current major user of medical radioisotopes, i.e. nuclear
medicine (which was also the most affected discipline in this and the previous supply
shortages), and mostly on its quantitatively most important diagnostic part which
currently concerns about 90% of nuclear medicine (NM) procedures.

Therefore, the main questions seem to be (for the foreseeable future):

- Is NM still evolving and what are the current developments and trends?
- Will NM still have a role, considering potentially competing imaging technologies
  (and taking into account its potential future evolutions)?
- Within NM, is PET likely to supplant single photon techniques, ie planar imaging
  and SPECT (and if it were the case, how rapidly)?

² http://ec.europa.eu/enterprise/pharmaceuticals/international/intercoopbi.htm#canada
- Within single-photon techniques, will Tc-99m remain an important isotope?

This last question was essentially already given a yes answer in the earlier part on current NM diagnostic procedures.

Before going into a more quantitative analysis, largely based on information, surveys and reports from various organisations, we would like to use a more qualitative approach, based on general broad reasoning. Such an approach can often give quite reliable, and sometimes better, indications (even for non-specialists) on trends. We will largely base it on knowledge of the authors (including on research trends and on projects supported by the EC in its research Framework Programmes).

### 8.1.1 Qualitative Approach and Discussion

The goal of modern healthcare is increasingly to prevent and/or predict pathological processes before they occur or at least before symptoms occur. Indeed, early detection of alterations allows early treatment which often allows reversing or curing disorders and preventing irreversible damage. This often reduces mortality and/or improves quality of life, and at the same time decreases treatment costs.

But pathological processes generally start at a molecular level, with molecular alterations occurring well before organ damage, anatomical alterations and appearance of symptoms (typical examples are cancer and diabetes). So, it is important for early detection to be able to identify molecular or cellular changes as soon as possible and therefore with high sensitivity. Whenever possible this should also be performed non-invasively, and with minimal or no pain and risk to the patient.

Therefore, the main solutions seem to be *in vitro* molecular diagnostics and *in vivo* molecular or metabolic imaging. Indeed, *Molecular Imaging*—the imaging of molecules, biochemical processes and physiological activity within the human body—is rapidly becoming one of the most powerful tools for diagnosis and staging of disease.

It is probably by considering this and the various other advantages of imaging techniques, like non-invasiveness, that a January 2009 article by Forbes [6] cites molecular imaging as one of "5 technologies set to change the decade (2009-2019)" and having "a good combination of scientific breakthrough and commercial potential", and says "This will surely be the decade of molecular imaging".

Various (molecular) imaging techniques exist (MRS, part of MRI, optical, etc.) that are based on different physical principles and can measure a wide range of physical parameters, eg for the detection of various biomolecules in vivo. Among these techniques, nuclear medicine ones (SPECT and PET) are at least currently the main tools. Indeed, they are by far the most sensitive, and they are also able to investigate the whole body, or large part of it, at once. The second most sensitive type of technique is optical imaging (100 to 1000 times less sensitive); It suffers from strong limitation in the depth of penetration in the organism, so essentially only applies to superficial processes (even though some optical imaging specialists believe they may improve on both these aspects of penetration and sensitivity).

So, only PET seems to be able to compete with SPECT for such a molecular sensitivity (PET is actually more sensitive), which as said above is a crucial aspect of current and future clinical molecular imaging. Indeed PET, like SPECT before, already demonstrated
its clinical and research utility and certainly still has a very promising potential: its current rate of expansion shows little doubts.

Will PET then replace SPECT? Most probably not, even though PET is likely to increase more than SPECT in the future. This increase in PET is partly linked to the fact that it has some advantages, but also that being quite a new technique, in particular in the clinics, it starts from close to zero (so absolute and relative increases are much easier).

In fact, PET and SPECT both have advantages and disadvantages with respect to each other.

For instance: PET is more sensitive allows accurate attenuation correction, which is necessary for quantification. Nevertheless, as opposed to what is sometimes assumed, quantitation is also possible with SPECT and further improved methods are still developing. PET currently has better resolution in humans, but the reverse is true for smaller animal systems, and could very well also become the case for human systems (in particular due to intrinsic limitation of PET resolution because of the path-range, of typically 1 to 10 mm depending on the isotope, of the emitted positron before it produces the 2 gammas). PET can normally label bio-molecules more physiologically. But PET is more expensive (both for the system itself and for each examination) and usually gives a slightly higher radiation dose to the patient. PET needs a cyclotron nearby for the production of the short-lived isotopes it uses (within 2 hours distance in most cases that use F-18, or usually much less for other radioisotopes). This last constraint may be partly circumvented, for some applications, by the development of new radioisotopes with a longer half-life, in particular if produced via generators (like Ge-68/Ga-68 and Sr-82/Rb-82). But then the advantage of more physiological labelling of molecules seems to disappear, except perhaps for thyroid tissue studies with I-124 (however, I-124 gives higher radiation doses than usual, mediocre image resolution and its large scale production is currently far from possible).

SPECT has better potential to image endogenous ligands such as hormones and antibodies (in particular due to their relatively easy labelling, for instance with Iodine, and to their relatively large size and hence usually slower kinetics). Remarkably, SPECT has the unique ability, compared to PET, to be able to probe 2 or more molecular pathways or targets simultaneously by detecting isotopes with different emission energies. This can be particularly useful to study complex molecular (pathways) interactions and the sequencing of cellular events, and has already shown its clinical potential. SPECT is also much better suited to measure slower kinetic processes, that occur over hours or days, due to the longer half-life of the commonly used isotopes (even though, as said above, it could become a future possibility for PET in some applications, with the advent of some new isotopes). This can be important for imaging some receptor ligands including those that become trapped in the cell or the cell nucleus (eg estrogen receptor, which is over-expressed in some tumours, like some breast, colon or prostate cancers) or for studying infection and inflammation processes (eg with labelled white blood cells, which slowly clear from the plasma and slowly accumulate in the infection site). The generally longer half-life of SPECT radiopharmaceuticals also makes them easier to work with. Furthermore, some SPECT radioisotopes, like Lu-177 or I-131, allow to image and treat patients with the same molecule. Nevertheless, this may also become possible with some PET isotopes, like Copper-64.
As a general consideration, up to now in history no imaging modality has been completely replaced (even planar X-ray techniques are still used after over a century). Indeed modalities tend to be complementary, also because they are based on different physical principles and because of cost. In fact, the range of modalities used has only been continuously expanding with time, with new modalities coming more as an addition allowing new applications than as a substitution of existing modalities. In particular, most other molecular imaging modalities tend to be more expensive than SPECT. This is important, were it only for less developed countries, many of which cannot afford PET systems due to cost, infrastructure and skill needs. Such countries already lack the much cheaper and easier to use SPECT.

Also, small and fast SPECT systems are currently developed for use in Nuclear Cardiology, which can be placed in out-patient facilities for cardio-vascular investigation. Together with Tc-99m-labelled flow tracers, this technology is expected to enjoy wide clinical acceptance. PET/CT on the other hand will grow in larger hospital facilities and develop to a standard procedure in oncology.

For all these reasons and more, it is nearly certain that SPECT and PET will coexist in the future and that each will serve different clinical indications and goals.

So, if SPECT remains an important technique as it seems, will it stop using Tc-99m and will other radionuclides take over? This is very unlikely in the foreseeable future, because of all the advantages of Tc-99m (as explained earlier). Also, 90% of current diagnostic procedures are based on Tc-99m and there is still great potential. Indeed, various Tc-99m-labelled biomolecules, especially for oncological applications, with highly promising properties have recently been developed, like vitamin analogues, peptides and antigen targeting constructs (cf. EANM Radiopharmacy Committee, personal communication). Using a different isotope would require to re-develop most radiopharmaceuticals; and any new such technology would need many years (more than 10-12) to become available at large scale, if possible at all.

8.1.2 More Quantitative Approach

The following discussion is mainly based on information provided by or reports and surveys from EANM (personal communication) or AIPES [2], other publications, and a 2009 report and survey by Technopolis [7]. Parts of the EANM, AIPES and Technopolis reports and data, including some figures and table, are used or reproduced here with permission (the text being occasionally slightly modified).

The Technopolis report [7] was written by experts in the field and largely based on opinions and interviews of experts from academia, including the clinics, and industry, and on an online Delphi survey. It is under review, at the time of writing (May-June 2009), by EANM that also supported it. It set out to answer the following questions:

- ‘What is the predicted market size of future imaging technologies for medical purposes – that is, between now and 2025 – and the relative share of technetium-based imaging applications in that market?’

- ‘What new or developing medical imaging technologies may affect or supersede the technetium-based imaging technology in the period between now and 2025, both in terms of quality and quantity?’
The focus of the Technopolis report was on experts’ future expectations on whether and how far reactor isotopes will remain important in the future. In other words: Will the modalities that currently use reactor isotopes and particularly diagnostic imaging ones (SPECT, planar and multi-modality imaging) still be used in 2015 and 2025?

8.1.2.1 DEVELOPMENT TRENDS

Some important trends were identified, in relation to the range of modalities capable of causing shifts between technologies and potential substitution. The following ones were considered to be important:

- **Improvements in current modalities.** Current modalities are still being incrementally improved by further developments, including technological ones, such as increases in sensitivity and resolution, further software development for associated data processing and combinations of parameters. This will eventually increase scanning quality and lead to improved diagnostics or the wider usability of particular scanners. PET is a good example of a technology still in full development. Experts are still expecting great progress in this area, for example as a result of the discovery and testing of, or experiments with, new tracers, enabling the wider use of PET scanners. However, ‘older’ modalities such as SPECT continue to evolve too. New crystals and detectors are currently being developed, tested and applied, enabling higher SPECT resolution. Some experts expect that SPECT will eventually match PET resolution capacities, but others don't. We are here considering human studies, since in animal systems the current resolution of SPECT (0.4 mm or less in nano-SPECT) can be higher than that of PET.

Interviews showed that PET is one of the fastest growing modalities. Some of the interviewees in the Technopolis study, as well as a Canadian experts’ panel [5], expect PET to grow faster than SPECT. However, it is debatable whether this will lead to major shifts from diagnoses currently conducted by means of planar nuclear techniques and SPECT towards PET. Many of the developments will focus, in particular, on extending the possibilities for medical science, leading to improvements in the diagnostics of specific cases and thus to the use of PET as an add-on. Also, so far no imaging modality has disappeared.

- **Multimodality imaging (or hybrid imaging).** One of the most important developments running in parallel to single modality improvements is the combination of different imaging modalities. Currently PET/CT scanners are among the most frequently selling multi-modal scanners. Other combinations are still under development, including SPECT/CT, PET/MR and SPECT/MR scanners. The PET-MRI combination, in particular, is a physics-intensive modality. The greatest advantage of multi-modal scanners lies in the possibility of obtaining both metabolic and spatial/anatomic information (i.e. localisation) with a single equipment. In contrast, when measuring metabolism with a SPECT or a PET scanner alone, localisation in the body of the metabolic processes being investigated is less clear or precise. Such localisation is better established by means of CT or MRI. A combination of both modalities, like SPECT/CT, therefore achieves the best of both worlds.

Combinations of such modalities require further technological development, particularly in the area of equipment integration. They also require strong software
development, since sets of data obtained with different imaging modalities must be combined.

We will not enter here in a discussion of the (certain) benefit versus the potential risk of adding radiation doses when combining SPECT or PET with CT. Whatever, such a potential risk doesn't exist with MRI.

- **Development of new tracers, probes or contrast agents.** Tracing and representing certain processes (e.g. metabolism) or substances (e.g. certain proteins) requires tracers (eg radiopharmaceuticals) which go and/or bind to the right place in the body and which can subsequently be represented or imaged by means of a modality. New tracers act as modality enabling agents, by increasing its possibilities. Currently, many tracers and contrast agents are being developed, in particular but not only for PET, and expectations are high also for other modalities, like optical, MR and ultrasound. Nano-technologies and bionano-technologies further increase promises for new tracers and (bio)markers. Although new tracers and contrast agents might lead to shifts between modalities, it is not entirely clear yet as to which modalities will be stimulated most in the process. Furthermore, multi-modal tracers and contrast agents are also being developed.

- **Development of new treatments.** Although reactor isotopes are quantitatively mainly used for imaging purposes, they are undoubtedly of qualitative therapeutic importance. Reactor isotopes already play an important role in the treatment of thyroid and prostate cancer (by means of iodine-131 and iridium-192, respectively) and, together with the palliative treatment of bone metastases, appear to be quickly gaining in importance. For example, Lutetium-octreotate was first used some years ago as a radiopharmaceutical in the treatment of neuroendocrine tumours, which occur mainly in the stomach, intestine and pancreas, and spread harmful substances. The beauty of these applications lies in the fact that the administered substances move selectively towards the organs to be treated, in contrast to external beam radiotherapy which also exposes the surrounding tissue to radiation. This Lutetium treatment increases life expectancy by 4 years on average, with a relatively good quality of life [8].

- **Development of new equipment and modalities and time required.** Although there is currently no prospect of a totally new modality, an exploration into the future must include such a scenario of ‘unforeseen circumstances’. The Technopolis survey examined the time required for a new laboratory product to be developed for preferential clinical use. According to the respondents the average duration from the first research stage to clinical proof is 8 years. From this evidence to the preferential clinical use takes at least another 10 years. So, 8 years for the research phase and at least 10 years for the implementation. Therefore, if certain options have been overlooked in these explorations into the future because they have only very recently come under development, their preferential use will take another 18 years. The above averages were confirmed by experts, including from industry and academic clinics.
8.1.2.2 Diagnosis

8.1.2.2.1 Expected use of the various imaging modalities in clinical practice in the future [7]

The possible imaging modalities that might play a more prominent role in the future, their relative use and the expected trends for 2008, 2015 and 2025, as identified by experts, are shown in Fig. F.

Note that the figures express the share of one modality relative to the other modalities, rather than absolute numbers.

Figure F: Expert estimation of the relative use of modalities in 2008, 2015 and 2025 (reproduced with permission from Technopolis Group report).

These future expectations allow the following conclusions about imaging modality proportions:

- a relative (fairly steep) decrease in ‘regular’ CT;
- a slight decrease in the share of ‘regular’ MRI;
- a slight decrease in the share of ultrasound echography;
- a fairly substantial decrease in the share of ‘regular’ SPECT;
- a relatively substantial decrease in the share of other modalities: the ones that receive estimates of a few percent (planar nuclear techniques and optical ones in particular);
- a fairly substantial increase in the PET/CT share;
- a fairly substantial increase in the SPECT/CT share;
- a sharp increase in PET/MRI (non-existent as yet in the clinics: just being developed and not commercially available);
- after 2015: the advent and rise of SPECT/MRI.

In order to isolate trends for the imaging modalities that use reactor isotopes, the multi-modality percentage points and (some) basic modalities are summed in fig. G. The PET/CT share is summed both for PET and CT and the SPECT/MRI share for SPECT and MRI. This gives a picture of the total use of the basic modalities, although the total number of scanning applications exceeds 100%.

Figure G: Expert estimation of the use of imaging modalities in 2008, 2015 and 2025, categorised in base modalities (reproduced with permission from Technopolis Group report)

Figure G shows that a strong increase is expected in the combined use of PET and that of MRI. The decrease in stand-alone PET and MRI is substituted by their use in multi-modal systems. The combined use of CT is predicted to rise substantially, followed by a slight decrease, at the expense of multi-modalities including MRI. SPECT is expected to stay approximately the same. The considerable decrease in the share of SPECT alone (Fig. F) will be substituted by the use of multi-modalities: initially particularly by SPECT/CT, followed after 2015 by SPECT/MRI.
Figure H: Break-down of the shares of SPECT modalities (reproduced with permission from Technopolis Group report)

**8.1.2.2 Dynamics of innovation**

Implementations of innovative technologies are driven not only by technological but also by non-technological factors. Here technological factors concern, among other things, the resolution, and non-technological ones the problems of logistics and infrastructures connected to the use of radioisotopes. For reactor isotopes, the problems involve the purification and reprocessing of isotopes according to good laboratory practice, and transportation to hospitals. For PET radionuclides the problems involve infrastructures relating to cyclotron production, transportation to hospitals, as well as adequately trained personnel capable of dealing with the nuclides involved. In the medical domain and in hospitals various human aspects play an important role, such as the specialist skills of imaging assistants, convenience of use, costs (of a single action and/or of investment for a hospital to introduce a certain technology), contracts and effectiveness [9].

Of the four factors that seem particularly important, only higher resolution is a technological driver (note: the authors of the current report by the European Commission ad hoc interservice group believe that sensitivity also is an important one, which is further linked to resolution). Two factors concern human aspects: imaging assistant’s skill and human resources in general. The latter mainly concerns the highly trained personnel required for PET. The 4th important factor is infrastructure problems. This may involve Technetium supply problems and the infrastructural organisation of hospital cyclotrons. So, human factors also largely determine a technology’s success. Here, this also implies that the speed of wider PET application development depends particularly on adequately trained personnel and infrastructure. Cost is the next most important factor.
8.1.2.2.3 Summary [7]

On the basis of the identified trends and modality proportions it may be concluded that experts expect a strong increase in the choice of PET modalities in particular. Both industrial and end user interviewees indicated that this area currently shows the strongest development. Multi-modal developments appear to boost this increase in PET.

The share of SPECT modalities is expected to remain roughly the same. SPECT-alone scanning applications will decrease in the coming years, whereas the share of multi-modalities combining SPECT with other modalities will increase. Industrial interviewees indicated that a great deal of work is being done on the development of a SPECT/CT. Clinical practice expects this type of scanner to take up a substantial share.

As regards mixed modalities, it appears that reactor isotopes will continue to fulfil an important function. The fact that the share of SPECT remains the same leads to the conclusion that the relative demand for reactor isotopes (in proportion to the total number of scans) will remain about the same.

The implementation of a technology is determined by technological as well as non-technological factors. In the choice of a certain clinical modality, higher resolution turns out to be a technology driver, while human factors to an important extent determine technological success. In the present case this implies that the speed of wider PET application depends on adequately trained personnel and infrastructure.

Experts unanimously expect a sharp to very sharp increase in the total number of diagnostic imaging scanning applications in the future. This is also connected to the expected ageing of the population and increase in population in general.

As regards Technetium-based imaging modalities, no major replacement by non-technetium modalities is expected at least until 2015. Experts are divided in their opinions for the period after 2015; However, the average shifts from ‘probably not’ (ie no replacement) to more or less neutral for 2015, with a very slight tendency towards ‘probably’ for after 2015.

The total use of Technetium shows the same trend: the use of Technetium will certainly not decrease in the next few years; in fact, a slight increase is expected. For the period 2015-2025 the experts on average expect a very slight decrease (<10%) in the use of Technetium, but their opinions differ widely (from certainly to certainly not).

8.1.2.2.4 Conclusion

The following conclusions (mostly from the Technopolis report [7]) could be drawn (for imaging procedures):

- Medical use of imaging technologies has increased and is expected to continue to do so.
- There is currently a range of imaging modalities (in particular CT, MRI, SPECT and PET) available, each of which has specific applications in the medical domain. Technetium is used for SPECT and planar technology, which are preferentially used for bone (including bone metastases in oncology) and organ scanning (including the measurement of blood flow and heart muscle function in cardiology).
- Multi-modality imaging, which mainly combines nuclear and radiological techniques in a single device, is on the rise (e.g., PET/CT, SPECT/CT, etc.).
- There is currently no new technology at sight that might affect the use of Technetium. Even if such a technology existed, it would be expected to take at least 18 years before it can be preferentially used in clinical practice.
- Although high imaging resolution is a key technology driver, human factors (training, infrastructures, etc.) are important in determining the success of a technology.

**Expectations for the future**

- The total number of imaging/scanning applications will rise (sharply) in the future, with a particular development and increase in molecular/functional imaging ones. This rise has already started in recent years.
- Shifts are predicted in the use of modalities, with an expected decrease in single modalities in favour of multi-modalities.
- But it is expected that ‘old’ technologies will not disappear.
- A sharp increase in PET modalities is expected, particularly in combination with CT or MRI. Partly because of superior resolution, current applications of PET will be extended, but without affecting the total share of SPECT modalities. The speed of PET developments will partly depend on the development of new radiopharmaceuticals, infrastructure requirements and expertise.
- The relative share of SPECT modalities will probably remain the same, so that SPECT should increase in absolute terms, but stand-alone SPECT systems will in the long term be replaced by SPECT/CT, followed by SPECT/MRI (not yet available).
- It is unlikely that Technetium-based imaging will be replaced by other technologies in the medium term (up to 2015), although it might show a slight decrease in the period 2015-2025. The total use of Technetium, should remain the same for the time being, but slightly decrease (by less than 10%) in the period 2015-2025. Note that this is a conclusion of the Technopolis report [7]; Others expect an increase as discussed later. Some emphasize that up to now no imaging technology has been replaced and that the complete range of modalities has only been continuously expanding with time.

In short, all the data show that the demand for radiopharmaceuticals labelled with nuclear-reactor-produced radioisotopes, and hence the demand for these isotopes, will still be important at least until 2025 (the end of the forecast of the Technopolis report and beyond that of AIPES). The current fast development of PET will continue and this will result in a relative (but not absolute) decrease in the use of reactor isotopes. However, due to their low costs and relative simplicity, SPECT and planar nuclear technologies will persist and will be equally used.

**8.1.2.3 THERAPY**

Radiotherapy in general, including with radioisotopes, has been used for about a century for treatment, of cancer in particular but not only.

It has been for some time and still is by far one of the 2 major techniques, with surgery, for the treatment and particularly the cure of cancer. Its use is still expanding and is expected to continue to do so, with new developments.
With advances in molecular and cellular biology, many other and potentially alternative promising methods exist. But many of them have been promising for years or even decades. So, even though they are indeed still promising, it is very unlikely that they would substitute for radiotherapy or surgery in the next 15-20 years at least, and probably beyond. On the contrary, combining some of these new molecular biological tools or molecules with radioisotopes to produce new therapeutic radiopharmaceuticals also seems promising and already had some clinical success in recent years (with some commercially available treatments).

This seems to be confirmed by the fact that all experts’ opinions (in the Technopolis survey [7]) and the literature, without exception, point to the development and increase in the use of radiopharmaceuticals for therapeutic purposes in the future. All of these are at least currently based on reactor-produced radioisotopes. They are more and more frequently combined with new molecules coming from progresses in molecular and cell biology. In fact, radioisotopes can be attached to a wider and wider variety of specific molecules (antibodies, peptides, etc.) or molecular constructs being developed, that can target specific pathological processes. For instance, attaching radioisotopes to antibodies targeting tumour cells often shows an additional efficacy compared to the same antibody without the radioisotope. In some cases, the antibody is only used to target the tumour, ie to bring the isotope in the tumour, and the radioisotope is the one killing the tumour cells (eg a beta- or alpha- emitter).

No decrease is expected in any of these currently used or clinically envisaged (reactor-produced) therapeutic radioisotopes (Annex 1).

A clear increase is expected in the use of Lutetium-177 and Yttrium-90, which will start at present and continue until far into the future after 2015 (represented by + in figure L). The use of Holmium-166 and Samarium-153 should also increase, although not before 2010. The current use of Iodine and Iridium is not expected to increase a great deal (represented by 0 in fig. L) [7].

In fact, requirements for reactor radio-nuclides such as Sm-153 (used for pain palliation, bone cancer therapy), Y-90, Er-169 and possibly Re-186 (arthritis and synovitis therapy), and others, continue to grow, following the general trend towards widespread utilization of nuclear processes for therapy [2]. Also see figure L.

*Figure L (from Technopolis report, reproduced with permission): Expert expectations for the application of therapy with reactor isotopes. (-- = large decrease, - = decrease, o = unchanged, + = increase, ++ = large increase).*

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<thead>
<tr>
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<tbody>
<tr>
<td>Iodine-131</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Strontium-89</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Iridium-192</td>
<td>O</td>
<td>O</td>
<td>O</td>
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<tr>
<td>Samarium-153</td>
<td>O</td>
<td>+</td>
<td>O</td>
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<tr>
<td>Rhenium-186</td>
<td>O</td>
<td>O</td>
<td>O</td>
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</table>
### 8.1.2.4 QUANTITATIVE ESTIMATES OF EVOLUTION OF DEMAND FOR MEDICAL RADIOISOTOPES

#### 8.1.2.4.1 CONVENTIONAL NUCLEAR MEDICINE PROCEDURES USING MOLYBDENUM-99 / TECHNETIUM-99M FOR THE PERIOD 1990-2020 [2]

The graph on Fig. K below provides estimates of the past and future use of conventional nuclear medicine procedures with Tc-99m/Mo-99 for the period 1990-2020, based on expert opinions of the major market actors (not the result of detailed surveys). Although those estimates must be used with some caution, they are believed to be reasonably representative of the development of nuclear medicine procedures using Tc-99m/ Mo-99 during the near past and for the medium term.

<table>
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<tr>
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<tbody>
<tr>
<td>Iodine-125</td>
<td>O</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Yttrium-90</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lutetium-177</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Holmium-166</td>
<td>O</td>
<td>+</td>
<td>O</td>
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**Fig. K: Estimates of the past and future use of conventional nuclear medicine procedures with Tc-99m/Mo-99 for the period 1990-2020 (reproduced with permission from AIPES report).**

**Note that:**

1. The global picture necessarily clouds some of the specific features of the major regional markets. For the purpose of this report (Fig. K), one distinguishes between 4 major regional markets:
   - Europe, comprising the European Union with Switzerland, Norway, Iceland, the Balkan countries and Turkey;
   - North America, comprising the three NAFTA countries;
Asia / Pacific, comprising Japan, South Korea, Taiwan, Australia;
Others: India, Pakistan, Middle East, Africa, South America and all world regions not mentioned above.

2. The report does not cover the Russian Federation, China and the central Asian countries, for which meaningful data are not available or not sufficiently reliable.

The strong growth experienced since the early 1970s is not expected to continue from 2010 onward. The forecast, with annual growth rate of 1%-2% (worldwide), suggests that a period of fast development is now followed by consolidation. This growth rate could become higher in case of fast growth of SPECT/CT systems or lower if a substitution in favour of e.g. PET radionuclides or other imaging technologies takes place on a large scale.

Since the supply chain for Tc-99m/Mo-99 and the use of Tc-99m in daily nuclear medicine procedures worldwide are well established, AIPES concludes that the prospect exists for further utilization of Tc-99m/Mo-99 within the forecast period of their report (2010-2020) and beyond [2].

The OECD / Nuclear Energy Agency (NEA) workshop of January 2009 [3] also concluded that demand for Tc-99m is expected to further increase, especially in USA, Japan and Europe.

It should be noted that potentially importantly growing markets exist in developing countries and particularly Asia. Some not necessarily European producers are already seriously considering them.

8.1.2.4.2 ESTIMATED EVOLUTION OF DEMAND FOR MEDICAL RADIOISOTOPES GLOBALLY (INCLUDING TC-99M)

For the reactor radionuclides other than Tc-99m, as used in therapy, pain palliation, diagnostics and research, demand is forecast to continue to increase, at varying rates depending on the specific nuclide [2].

AIPES [2] provides a tentative list of main nuclides with large scale (medical) use and production during 2010-2020, and possibly later, as based on industry specialists opinions (figure I). The list is not limited to reactor-produced radioisotopes. It also stresses the importance of physical and chemical properties of elements, and technical and logistical feasibility of large scale production and use for the suitability for medical purposes.
Fig. 1: Tentative list of main nuclides with large scale (medical) use during 2010-2020, and possibly later (reproduced with permission from AIPES report [2], page 12). The most common radionuclides produced in reactors for which supply is believed to be in jeopardy for the period 2010-2020 are in bold type.

<table>
<thead>
<tr>
<th>Imaging: conventional, single photon emission tomography SPECT, SPECT/CT</th>
<th>Imaging: positron emission tomography (PET, PET/CT, PET/MRI)</th>
<th>Therapy, pain palliation, radioimmunotherapeutics</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{67}$Ga (a)</td>
<td>$^{18}$F (a)</td>
<td>$^{67}$Cu (a)</td>
</tr>
<tr>
<td>$^{99m}$Tc/$^{99}$Mo (r)(g)</td>
<td>$^{68}$Cu (a)</td>
<td>$^{131}$I (r)</td>
</tr>
<tr>
<td>$^{11}$In (a)</td>
<td>$^{89}$Zr (a)</td>
<td>$^{152}$Sm (r)</td>
</tr>
<tr>
<td>$^{125}$I (a)</td>
<td>$^{89/90}$Sr (r)(g)</td>
<td>$^{153}$Sm (r)</td>
</tr>
<tr>
<td>$^{131}$I (r)</td>
<td>$^{99}$Y (r)</td>
<td>$^{165}$Re (r)</td>
</tr>
<tr>
<td>$^{133}$Xe (r)</td>
<td>$^{85}$Zr (a)</td>
<td>$^{185}$Re/186W (r)(g)</td>
</tr>
<tr>
<td>$^{201}$Tl (a)</td>
<td>$^{124}$I (a)</td>
<td>$^{188}$Re/189W (r)(g)</td>
</tr>
<tr>
<td></td>
<td>$^{125}$I (a)</td>
<td>alpha emitters, e.g. $^{213}$Bi</td>
</tr>
</tbody>
</table>

Production route: (r) = nuclear reactor, (g) = generator, (a) = accelerator

The major concerns expressed are about the supply outlook for the fission products I-131 and Mo-99/Tc-99m.

EANM also provides a list (Annex 1), but only concerning reactor-produced isotopes. For these AIPES and EANM basically agree. EANM further lists most promising isotopes for novel applications.

In general, the use of radionuclides for medical applications is estimated to increase by about 5-10% per year (10% according to reference [10]) [11]. The future increase is estimated to be about 3-10 % per year for Tc-99m globally [12] and about 10-20 % for other radionuclides, including positron emitters for PET. PET itself is estimated to increase by about 20% per year (but only in relatively recent years and considering that it started from very low levels).

"U.S. sales of diagnostic radiopharmaceuticals reached $1.93 billion in 2007 and are expected to rise to $4.06 billion by 2014. Radiopharmaceutical sales grew 9.0% in 2007, recovering from a temporary slowdown the previous year. However, growth should resume in the range of 11% 13% per year as new products are introduced for cardiology and oncology. Continued growth of PET imaging and sales of FDG will also contribute favourably." [13]

"Once a market is satisfied, growth continues at a 5-10% annual rate as further applications are developed. The growth of 99Mo best exemplifies this scenario. First introduced as a curiosity for research applications, the demand increased 20 fold over a 5-year period [in the 1970s] and then stabilized at a more reasonable growth rate." [14]

According to the 2009 report of the US Committee on Medical Isotope Production Without Highly Enriched Uranium of the National Academies [12]:

"Estimates of future demand growth for Mo-99 evaluated by the committee range from about 3 percent to 10 percent. These estimates are for both U.S. and global demand. The committee judges that demand growth for Mo-99/Tc-99m in the
United States could range from 0 percent to 5 percent per year for the next five years, with the most likely growth rate in the range of 3 percent to 5 percent per year. These estimates assume that there are no major disruptions in Mo-99/Tc-99m supplies and no major changes in health care policies or practices.

The demand growth for diagnostic imaging modalities will likely continue over the long term as the U.S. population ages. The extent that this will be reflected in demand for Mo-99/Tc-99m will depend strongly on whether other diagnostic imaging modalities take hold in the market.

During the next 5 years, imaging modalities (e.g., PET, CT, MR) that could potentially displace Tc-99m use for medical diagnostic imaging probably will not find widespread use in the United States. The current practice of favouring clinical use of Tc-99m radiopharmaceuticals will continue for the foreseeable future.

Global demand for Mo-99/Tc-99m could grow more rapidly than demand in the United States in the mid to long term as nuclear medicine technologies find more widespread application, especially in developing countries. At present, almost all of the Mo-99/Tc-99m produced in the world is consumed by developed countries. There is a huge potential market for these isotopes in those countries that hold most of the world’s peoples such as India and China. Their demand for Mo-99 will almost certainly increase substantially as the increasingly affluent segments of their populations demand improved healthcare. The relative low cost and ease of use of Tc-99m installations that rely on conventional gamma cameras will give these modalities a competitive advantage over PET, CT, and MR imaging.

What is not clear at this point is whether these developing countries will develop indigenous production of Mo-99 or will purchase this isotope on world markets. If countries choose to purchase Mo-99 there could be significant impacts on Mo-99 supplies, supply reliability, and prices in the United States. Although these impacts are likely to occur on timescales that are beyond the 5-year focus of this report, they should be of intense interest to Mo-99 producers who are contemplating conversion from highly enriched uranium- (HEU-) to low enriched uranium- (LEU-) based production or the construction of new facilities. It seems likely that, absent the development of truly superior imaging technologies, there will continue to be a flourishing long-term global market for these isotopes.

Finally, although it is beyond the scope of this report, decisions by developing countries to produce Mo-99 domestically also have implications for HEU minimization. It will be important for the U.S. government, especially the Department of State and the Department of Energy-National Nuclear Security Administration, as well as the International Atomic Energy Agency to encourage these countries to take the LEU path for Mo-99 production.

It should be noted that reactor-produced radioisotopes are normally cheaper than the others (about 11 $ per dose for diagnostic imaging, of typically 20 to 35 mCi, of Tc-99m sodium pertechnetate in the US in 2008 [12]).
8.2 PROSPECTED FUTURE PRODUCTION CAPACITIES OF RADIOISOTOPES FOR MEDICAL USE

8.2.1 EUROPE

At present in Europe Mo-99 and I-131 are produced in the HFR in the Netherlands, in BR2 in Belgium and in OSIRIS in France. Irradiations are taken place at the Institute for Radio-elements in Fleurus, Belgium. Replacement of the HFR is being studied, possibly leading to the realization of the future PALLAS reactor at the earliest in 2016. There are no plans to replace BR2 with another reactor, although there are plans to build an Accelerator Driven System (ADS), MYRRA (see later).

The new high flux reactor Jules Horowitz in France is scheduled to become operational in 2014. This reactor is intended in first instance to be used for research purposes, but it could be used for radioisotopes production as a back up reactor. Production of radioisotopes requires tailored duration of the operation cycle, which is usually not compatible with the research needs. A similar situation exists at present at the high flux reactor FRM-II in Germany.

8.2.2 U.S.

Following the last crises of radioisotopes availability, a lot of attention is given in the US to assuring sufficient supply in the future, in particular since in no capacity in present in the country to satisfy the demand. The possibility to use a network of smaller research reactors organized around a national program has been investigated. The research reactor of the University of Missouri in Columbia (MURR) has technical characteristics suitable for the production of 99-Mo from LUE, but at present it has not yet obtained the licenses from the Nuclear Regulatory Commission (NRC) necessary for demonstrating the irradiation and subsequent processing of the LEU. The plan of the MURR is to construct the irradiation facility in 2009/2010 and to enter commercial production in 2012/2013, aiming at covering 30-50% of the US internal demand of 99Mo.

The critical supply situation has led expert groups in the US to formulate clear advice to the US government. In the report {Advancing Nuclear Medicine Through Innovation (National Academy of Sciences report 2007), The National Academy Press, Washington, DC, USA, 2007} the following conclusions are formulated:

'RECOMMENDATION 1: Improve domestic medical radionuclide production. To alleviate the shortage of accelerator- and nuclear reactor-produced medical radio- nuclides needed for research, a dedicated accelerator and an upgrade to a nuclear reactor should be considered. This recommendation is consistent with other studies that have reviewed medical isotope supply in the United States and have come to the same conclusions'.

8.2.3 OTHER PARTS OF THE WORLD

In other parts of the world, the research reactors in South Korea (HANARO), Indonesia (BATAN) and Australia (ANSTO-OPAL) are in first instance intended for research purposes, but their relatively high neutron fluxes allow potential for commercial production of radioisotopes.
The new Advanced Research Reactor CARR in China should be operational in 2009/2010. Although no information is available regarding possible production of radioisotopes, the high reactor flux makes it a possible candidate to take up a substantial part of the world production. Once more the somewhat contrasting requirements of research and production would have to be solved.

8.2.4 IAEA INITIATIVE FOR SMALL-SCALE PRODUCTION OF MOLYBDENUM-99

Following the interest of a number of developing Member States that are seeking to produce Mo-99 to meet local nuclear medicine requirements, the IAEA has initiated in 2005 a “Coordinated Research Project (CRP) on Developing Techniques for Small-Scale Indigenous Production of Mo-99 using LEU or Neutron Activation.”

Two production methods are being investigated: The main method being studied is the LEU modified Cintichem process that uses LEU foil targets. Also being studied is a method involving neutron activation of molybdenum trioxide targets for producing a gel form of molybdenum called “gel moly”.

Seven institutions in five countries have been awarded research contracts:

- Chile: foil targets, LEU-modified Cintichem process
- Egypt: LEU fission moly, gel generators
- Kazakhstn: gel generators
- Libya: foil targets, LEU-modified Cintichem process
- Pakistan: foil targets, LEU-modified Cintichem process
- Romania (IFIN-HH): gel generators
- Romania (Pitesti): foil targets, LEU-modified Cintichem process

Seven institutions in six countries have been awarded research agreements:

- Argentina: LEU fission moly implementation
- Republic of Korea: development of LEU foil targets
- India: standardization of gel generators and feasibility of fission moly
- Indonesia: development of LEU foil targets, LEU-modified Cintichem process
- Poland: evaluation and implementation of LEU-modified Cintichem process (joined April 2007)
- U.S.: (Argonne National Laboratory, ANL): foil targets, LEU-modified Cintichem process
- U.S.: (University of Missouri Research Reactor): foil targets, LEU-modified Cintichem process; scope and level of work to obtain U.S. FDA approval for Mo-99 from LEU.

Many of the CRP participants have reactor facilities that could support large-scale LEU-based production of Mo-99 (e.g., Chile, Egypt, Indonesia, Pakistan, Poland and Romania; see), providing significant investments and strategic partnerships are found.

8.2.5 IMPROVEMENT IN THE PRODUCTION OF MOLYBDENUM-99 THROUGH ACTIVATION

Studies regarding improvement in the production of Mo-99 through activation are being carried out at Delft University (http://www.tudelft.nl/live/pagina.jsp?id=29b23a65-485b-44ee-9210-f460e363e2c6&lang=en). Researchers are examining the feasibility of using Szilard Chalmers reactions in order to produce radioisotopes with higher specific
activity. However, the yields from this process are likely to be small, and a great deal of development work would be required. It will take at least two years to verify the feasibility of this method for production on industrial scale. In case of success, this route would eliminate the need of HEU or LEU target for the production of Mo-99, and it would open the way for production at relatively small reactors.

8.2.6 Homogeneous aqueous solution nuclear reactors for radioisotopes production

Following a consultancy meeting held in June 2007, IAEA issued a report {IAEA TECDOC 1601, IAEA 2008} on the ‘state of the art’ of the technology related to homogeneous aqueous solution nuclear reactors (AHRs), especially in connection with the production of radioisotopes.

The use of solution reactors for the production of medical isotopes is potentially advantageous because of their low cost, small critical mass, inherent passive safety, and simplified fuel handling, processing and purification characteristics. These advantages stem partly from the fluid nature of the fuel and partly from the homogeneous mixture of the fuel and moderator in that an aqueous homogeneous reactor combines the attributes of liquid fuel homogeneous reactors with those of water moderated heterogeneous reactors. If practical methods for handling a radioactive aqueous fuel system are implemented, the inherent simplicity of this type of reactor should result in considerable economic gains in the production of medical isotopes. The principal advantages of aqueous fuel systems include:

- Flexibility with respect to reactor parameter variation, fuel selection, and geometry;
- Inherent nuclear safety characteristics;
- Efficient neutron utilization for isotope production;
- Elimination of targets, less uranium waste generated per curie of 99Mo produced, and overall simpler waste management;
- Ability to process other isotopes such as 133Xe, 89Sr, 90Y, 131I more efficiently using offgas extraction;
- Less capital cost and potential lower operating costs.

Babcock & Wilcox Technical Services Group, Inc. (B&W TSG) has developed a concept of a 200kW Aqueous Homogenous Reactor fuelled by low-enriched uranium (LEU). B&W TSG recently signed an agreement with Covidien, a leading radiopharmaceutical supplier, to develop technology for the manufacture of molybdenum-99 (Mo-99).

9 Lessons learnt

From shortages of radioisotopes for medical use which occurred over recent years, one can identify the following lessons that were learnt by the EU and its Member States:

- Early communication between nuclear reactor operators, radiopharmaceutical producers and the nuclear medicine community is important for mitigating consequences that risk to result from a shortage of medical radioisotopes for healthcare;

- In a situation of shortage of supply it is essential to strive for equity of access, by the healthcare providers in the different Member States, to available radiopharmaceuticals
in order to allow for equal chances of access by patients to nuclear medicine diagnosis and treatment across the EU;

– It is important to have a framework for international cooperation in place by which a rapid exchange on the international situation and possible initiatives at a global level can be facilitated;

– It is essential to create backup capacity for radioisotopes production in time;

– Early coordination of information exchange on the situation and actions taken or planned to respond to a situation of shortage in supply of radioisotopes for medical use through an EU platform, e.g. EU Health Security Committee, has shown to be of particular value for better managing a situation of shortage in the EU.

Lessons which were learnt in Canada from shortages in radioisotopes for medical use following unplanned shut down of the Chalk River reactor of November/December 2007 are included in a report submitted by an Ad Hoc Health Experts Working Group on Medical Isotopes to the Canadian Minister of Health in May 2008 (see extract in Annex 4). Recommendations by the Canadian Health Experts Working Group are also valid, in an analogous manner, for European circumstances that occurred in the situation of shortage in supply of medical radioisotopes of autumn 2008.

10 Possible Future Initiatives

10.1 In the EU

Nuclear reactor capacities for production of medical radioisotopes

- The European Commission could offer to facilitate information exchange between the Member States on their plans for development of nuclear reactor capacities and thus help to achieve better coordination of plans.

- Creating backup capacity with the view to ensure more stable supply of Molybdenum-99 (Mo-99) / Technetium-99m (Tc-99m);
  
  * The construction of new research reactors with the aim to improve security and autonomy in supply of medical radioisotopes could be envisaged;

  * Possibly, the construction of an EU research reactor, as a common undertaking by EU Member States with the support of the EU, could be reflected on.

- Refurbishment of nuclear reactors in operation and increase of production cycles.

Radiopharmaceuticals

- Better knowledge of the real future need in radiopharmaceuticals;
  
  * Analysis of the future need in radiopharmaceuticals for nuclear medicine procedures is a central question to be looked at when planning for setting-up of sufficient production capacities for radioisotopes.
Nuclear medicine

- Constant review of the supply of Mo-99 / Tc-99m for nuclear medicine procedures in the EU;
- Improved communication between health professionals in nuclear medicine and suppliers of Mo-99 / Tc-99m, e.g. operators of nuclear reactors and installations where Mo-99 is extracted;
  * Better communication between the "users" (health professionals in nuclear medicine) and the “suppliers” on the needs and availability of Mo-99 / Tc-99m in a certain time period could help optimizing healthcare in the EU, e.g. better scheduling of diagnosis and treatment of patients, prioritisation of patients, re-direction of supply to healthcare institutions where it is most urgently needed.
- Investigation in alternative methods for diagnosis and treatment to traditional nuclear medicine procedures in which Mo-99 / Tc-99m are used;
  * A better understanding of the current state of development and maturity of alternative methods for diagnosis and treatment, by which the dependency on radioisotopes could be reduced, would be essential for future planning of a sufficient and adequate supply chain of medical radioisotopes.

10.2 INTERNATIONALLY

- Reinforcing cooperation between international partners on sufficiency in supply of radioisotopes for medical use and developments in nuclear medicine;
- Improved cooperation between agencies at the international level for marketing authorisations of radiopharmaceuticals could lead to more flexibility in the supply of radiopharmaceuticals in crisis situations. The possibility of a mutual recognition of such authorisations should be explored.

11. SUMMARY AND CONCLUSIONS

EU Member States and the European Commission should continue interacting for this work on the different aspects indicated in this report.

Regarding radioisotopes production:

- More than 90% of the total production of Mo-99 takes place in 5 nuclear reactors of which 3 are located in Europe. All these reactors are 40-50 years old, and it is in principle not sure if any of these 5 reactors will be in operation after 2015-2016.
- All the major producers of radioisotopes use research reactors that have been partly or totally built with government funding.
- With the currently available technology production of Mo-99 by means of particle accelerators is not suitable for large scale production. Although research is ongoing to improve the performance of this way of production, the construction and operation
costs together with the large number of facilities needed to have a significant production make currently unlikely that a business case could be made for this approach.

- Accelerator Driven Subcritical Reactors are currently in the conceptual stage. It is unlikely that they could provide a valid contribution to the radioisotopes supply in the foreseeable future.

- Homogeneous aqueous solution nuclear reactor specifically designed for radioisotopes production is a serious option for the future. Babcock & Wilcox Technical Services Group, Inc. (B&W TSG) has developed a concept and has signed an agreement with leading radiopharmaceutical supplier, to develop technology for the manufacture of molybdenum-99 (Mo-99). Considering the time needed for development, demonstration and licensing, this kind of reactors could play a role only in the long term.

- Multi-purpose reactors combining research and production can be used in networked operation as mutual backup for the production of radioisotopes. In general the operational schedule of a research reactor is not optimized for the production of radioisotopes; therefore this type of reactors can only have a backup function.

- In the mid-term the only option to assure security of supply of Mo-99 is the construction of one or more multipurpose reactors. This is also necessary in order to maintain the strategic independence of Europe in this critical medical field. The design of such reactors should be optimized since the beginning to assure a good balance between research and radioisotopes production.

- A standard for multipurpose nuclear reactors is not available. In order to assure the operational safety and to facilitate the design and licensing processes it is advisable to use a proven concept such as the reactor-in-pool type as a basis for new reactors.

- However, improvements on the side of research reactor production alone are not sufficient to solve the issue of global supply security. Also the transport of such radioactive materials is vital. Recently, a new COUNCIL REGULATION ON ADMINISTRATIVE PROCEDURES FOR THE TRANSPORT OF RADIOACTIVE MATERIAL has been proposed, intending to harmonise administrative procedures and making the safety standards laid down in the internationally recognised IAEA Transport Regulations and the international agreements based on it applicable in a harmonised manner across the EU Member States. The Regulation introduces a Community carrier license, while increasing transparency of the existing rules by giving easier access to the information required by actors in this practise through a national contact point and a central Internet site.

Regarding use of radiopharmaceuticals

Radiotherapy appears to offer promising new treatment possibilities in the future, e.g. for targeting tumour cells for diagnosis and treatment. Such added value for patients makes it necessary to ensure supply of radiopharmaceuticals for innovations and treatment options in the future. In areas where alternatives are available a replacement of radiopharmaceuticals could be foreseen.
As part of the Report by the European Medicines Agency (EMEA) to the European Commission (EC) on the supply shortage of Radiopharmaceuticals, dated 11 November 2008, the EU Task Force on Radiopharmaceuticals set-up by the EMEA concluded with reference to longer-term aspects that there is a need to further explore possibilities for alternatives to radiopharmaceuticals in the EU. In this regard, the Task Force made the following recommendations to the EC, after consulting the Committee for Medicinal Products for Human Use (CHMP), and the EC agreed for these recommendations to be taken forward:

“The CHMP during its preliminary discussions was of the view that consideration should be given to alternative diagnostic/therapeutic procedures (including those currently available as well as new emerging options) to better understand the place of radiopharmaceuticals in clinical practice in the EU in the longer term.

It is recommended that all stakeholders (nuclear physicians (e.g. European Association of Nuclear Medicine (EANM)), industry (e.g. Association of Imaging Producers & Equipment Suppliers (AIPES)), other clinicians (e.g. radiologists specialised in techniques such as MRI, CT and PET scan) are involved in such a discussion. If such recommendation is agreed upon, the EMEA proposes to make best use of the available scientific expertise in the EU by consulting the CHMP Scientific Advisory Group on Diagnostics, reinforced with additional experts e.g. from the former radiopharmaceuticals ad hoc group.

The Task Force could continue to be involved in such longer term aspects as per its agreed remit.”

Following this recommendation, the CHMP agreed an action plan in May 2009 involving the organisation of a workshop with experts in the field of clinical radiology and nuclear medicine (from academia, relevant learned societies, industry) with a view to address the place of radiopharmaceuticals, labelled with radionuclides produced in reactors, in clinical practice in the EU in the longer term and to shed light on the possible alternatives that are currently available and those that may become available in the future. The workshop will take place in February 2010 and a report, including recommendations made by the CHMP, is expected to be available end of April 2010.

Regarding the overall framework for radiopharmaceuticals

Following this report a consultation of relevant stakeholders should be initiated on the different issues raised by this analysis, including the adequacy of the current regulatory provisions for pharmaceuticals related to specific needs for the marketing authorisation, manufacturing, import and distribution of radiopharmaceuticals.

Regarding nuclear medicine procedures and use of medical isotopes

- The achievements of hybrid SPECT/CT systems, together with the existing broad spectrum of SPECT radiotracers, might provide a second life for imaging techniques using nuclides produced in reactors. The techniques and equipment relying on Technetium-99m are used today in the vast majority of nuclear medicine procedures. In principle, they will still be needed in the long term.

- There is however potential for substitution. The future expectations of the medical community and the mixed attitude of many public authorities towards the use of
nuclear reactors, even for medical purposes, might result in a shift towards non-reactor radionuclides for both imaging and therapy purposes, and pain relief. The events which have lead to the recent supply shortfall of major radionuclides could be far-reaching. They could entice the medical community and the industrial providers of technologies and services to gradually develop new strategic orientations and priorities. Such new orientations warrant detailed investigations, as they could necessitate profound adjustments of the current industry patterns.

- Alternative methods for imaging and therapy show a steep growth, e.g. positron emission tomography (PET, PET/CT), magnetic resonance imaging, ultrasonic echography and others.

- Until very recently, in the common view of practitioners and industrialists, these methods added only new layers of diagnostic, therapeutic or pain palliation technologies but were not to replace ‘conventional’ nuclear medicine procedures, i.e. using radionuclides produced by fission of uranium or by activation of materials in a nuclear reactor core. The recent supply crises of Molybdenum-99 could contribute to a change in perspectives. As a result of the mixed outlook for new reactor projects for the period under consideration, the alternative methods mentioned above are increasingly being considered by the medical community as substitutes for the conventional nuclear medicine procedures instead of as complementary methods, as previously.
EXPLANATORY NOTES

1. Numbers given are good approximations (some figures have been rounded) or best estimates. It was not always possible to capture exact numbers. Also, figures may come from different sources, which have been chosen since believed to be among the most reliable.

2. 6-Day Curies: Mo-99 is priced based on units of radioactivity (Curie) calibrated to a certain time. Time calibration is necessary because of radioactive decay. Usually the calibration time is six days after the product leaves the producer’s facilities (“6-day curies”). Mo-99 continues to be lost due to radioactive decay after the targets are removed from the reactor and during target processing. The amount of Mo-99 available for sale as 6-day curies is only a fraction of the isotope present in the targets at the end of irradiation in the reactor. The current global demand for Mo-99 is about 12,000 6-day curies per week. To produce this quantity of isotope, producers would need to irradiate enough U-235 targets to obtain about 69,300 curies of Mo-99 in the targets at end of irradiation. The weekly global demand for Mo-99 can be supplied by the fission of about 2 grams of U-235.

LIST OF ABBREVIATIONS

AIPES Association of Imaging Producers and Equipment Suppliers (European Industrial Association for Nuclear Medicine and Molecular Healthcare)
CT (X-ray) Computed or computerized Tomography
DOE US Department of Energy
EANM European Association of Nuclear Medicine
EC European Commission
EU European Union
MR Magnetic Resonance (or more appropriately “Nuclear Magnetic Resonance”)
MRI Magnetic Resonance Imaging
MRS Magnetic Resonance Spectroscopy
NM Nuclear Medicine
PET Positron Emission Tomography
SNM Society of Nuclear Medicine (North America)
SPECT Single Photon Emission Computed Tomography
US Ultrasound

References


[9] PET Gepast gebruik(t), ZonMW Doelmatigheidsonderzoek; January 2007


Annex 1

Nuclear Reactor Produced Radionuclides in Use and of Importance for Future Research Applications

**TABLE 1** List of Reactor-Produced Radionuclides currently used for radionuclide therapy and for future interest in (pre)clinical research applications

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erbium-169</td>
<td>• To treat rheumatoid arthritis</td>
</tr>
<tr>
<td>Iodine-131</td>
<td>• To diagnose and treat thyroid disorders including cancer and for basic biomedical research</td>
</tr>
<tr>
<td>Holmium-166</td>
<td>• In cancer therapy and to treat rheumatoid arthritis</td>
</tr>
<tr>
<td>Lutetium-177</td>
<td>• In cancer therapy and to label antibodies for cancer therapy</td>
</tr>
<tr>
<td>Molybdenum-99</td>
<td>• To produce technetium-99m, the most commonly used radioisotope in clinical nuclear medicine</td>
</tr>
<tr>
<td>Rhenium-186</td>
<td>• As a bone cancer therapeutic agent and to radiolabel various molecules as cancer therapeutic agents; also used to treat rheumatoid arthritis</td>
</tr>
<tr>
<td>Rhenium-188</td>
<td>• For treatment of medullary thyroid carcinoma and alleviation of pain in bone metastases</td>
</tr>
<tr>
<td>Samarium-153</td>
<td>• To radiolabel various molecules as cancer therapeutic agents and to alleviate bone cancer pain</td>
</tr>
<tr>
<td>Strontium-89</td>
<td>• To alleviate metastatic bone pain</td>
</tr>
<tr>
<td>Strontium-90</td>
<td>• Decays to yttrium-90, which is used in cancer therapy</td>
</tr>
<tr>
<td>Xenon-133</td>
<td>• For lung ventilation studies in selected cases</td>
</tr>
<tr>
<td>Tungsten-188</td>
<td>• Decays to rhenium-188 for treatment of cancer and rheumatoid arthritis</td>
</tr>
<tr>
<td>Yttrium-90</td>
<td>• To radiolabel various molecules as cancer therapeutic agents</td>
</tr>
</tbody>
</table>

**Especially the use of Lu-177 and Y-90 is expected to rise in the coming years**

*Note by authors of this EC report: as an exception to the table, these are diagnostic radionuclides*

**TABLE 2** List of promising Reactor-Produced Radionuclides for Research for novel Radionuclide therapy applications

<table>
<thead>
<tr>
<th>Radionuclides</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic-77</td>
<td>• In cancer therapy</td>
</tr>
<tr>
<td>Copper-67</td>
<td>• In cancer therapy and to label antibodies for cancer therapy</td>
</tr>
<tr>
<td>Palladium-103</td>
<td>• In the treatment of prostate cancer</td>
</tr>
<tr>
<td>Platinum-195m</td>
<td>• In pharmacokinetic studies of antitumor agents</td>
</tr>
<tr>
<td>Scandium-47</td>
<td>• In the therapy of cancer</td>
</tr>
<tr>
<td>Silver-111</td>
<td>• In cancer therapy</td>
</tr>
<tr>
<td>Tin-117m</td>
<td>• For palliative treatment of bone cancer pain</td>
</tr>
<tr>
<td>Actinium-255/ Bismut 213</td>
<td>• Generator for alpha therapy</td>
</tr>
<tr>
<td>Actinium-255/ Radium-223</td>
<td>• Generator for alpha therapy</td>
</tr>
</tbody>
</table>

**Especially the use of alpha emitters is currently attracting great interest in biomedical research and is expected to rise in the coming years**
EANM-Statement on Supply of Radioisotopes for Medical Use – Supply of Molybdenum-99 in Europe

Shortage of radionuclide, in particular of Molybdenum-99/Technetium-99m, has become a chronic problem since 2007. After severe supply deficits in most European countries, during several weeks in 2008, we actually face again a critical situation. Since the Canadian reactor is none-operational since May 15, 2009 and will be down at least until beginning of autumn, there will be only two operational reactors during almost the entire period from June to October. This has led already to a critical situation, although at this moment no significant shortages have been reported in Europe. However, the situation is extremely fragile, as the Petten reactor is scheduled for repair for a longer period beginning from January 2010 and as unforeseeable defect at the two operational reactors must be considered to occur any time.

If reliable and continuous availability of the by far most relevant radionuclide is not guaranteed, this will severely affect established diagnostic (and therapeutic) workflows in many disease groups like cancer, traumatology, heart and rheumatic diseases. This situation may stimulate attempts to shift toward other modalities and workflows. However, for the foreseeable future substitution of established nuclear medicine methods with Technetium-99m will not be possible due to inherent physiological / biochemical reasons or due to lack of financial resources (equipment for Positron Emission Tomography that could replace a certain part of established Technetium-99m based procedures).

The EANM has given recommendations to their members and national societies how to deal with some of acute problems in case of shortages. There is, however, a need to work on medium-term solutions. In our view, before new facilities for radionuclide supply can be realized, some measures should be taken under coordination of the European Union, such as

- further improvement in cooperation of suppliers concerning scheduling of maintenance.
- international cooperation to achieve standardisation of irradiation targets and transport systems.
- increasing flexibility by transport regulations across the EU member states.
- upgrading of existing reactors to enable them for Molybdenum-99 production to increase activity output.

Vienna, June 12, 2009

Prof. Dr. Wolfram Knapp
President of the EANM
Report on the Mo99 Global Supply
June 2009

I. Current Supply

Today in the global market, 6 licensed reactors, HFR Petten (NL) - BR2 Mol (B) - OSIRIS Saclay (F) – NRU Chalk River (CN) – SAFARI-1 Pelindaba (RSA) – OPAL Lucas Heights (Aus), provide the raw materials to 4 companies, Covidien (NL) – IRE (B) - NTP (RSA) - MDS Nordion (CN), to extract the Mo99, which is then supplied to Tc99m generator manufacturers for distribution to nuclear medicine centres or radio pharmacies.

- **NRU** usually supplies 30 to 40% of global demand for Mo99. NRU was shutdown on May 15 because of a small leak of heavy water. It is expected that the reactor will remain in safe shutdown state for at least three months.
- **HFR**, capacity 30-40% of global demand (supplies approx. 70% European demand), has a technical problem and must gain authorization to operate each cycle (approximately 1 month) and will be down 5-6 months for repair from early 2010.
- **Osiris**, capacity 8% of global demand, needs to shut down 4 months in 2009 & 5 months in 2010 for maintenance and safety upgrades in order to comply with its renewed license until 2015.
- **SAFARI-1** has closer to 15% of the global demand.
- **BR2**, has a capacity of 15% of the global demand,
- **OPAL**: capacity 5% of the global demand.\(^3\)

\(^3\)The Opal reactor currently utilizes 2 of 12 irradiation slots for LEU irradiation and is seeking final regulatory approval for 2 irradiations a week that will (at current yields) allow supply of Australian domestic needs

\(^2\)The current LEU Moly plant (awaiting regulatory approval) has a capacity to produce (with appropriate management of the irradiation) approximately 1.5 to 2X twice the Australian market requirement on a 6 day Curie basis – but this will take some time for reproducibility value engineering processes to be completed (3-4 months).

\(^3\)Any scale up to use the additional capacity (the balance of the slots in OPAL) will require global teaming to develop a new larger scale Moly plant to process the output from Opal. On a conservative basis this production would initially be of the order of 5% of global
Global capacity will run, at best, between 60 and 80% until end 2010, if all repairs are effective and no other breakdown happens due to the workload imposed on the remaining installations. Without NRU and HFR, the global capacity will be critical around 30% of global demand.

II. Future Needs

The medical applications for Mo99-derived radiopharmaceuticals are increasing with the advent of new molecules in diagnostic imaging and therapy.

The need for Tc99m in imaging will remain stable if not grow as functional imaging, with SPECT as the most common and cost effective method. It will rapidly grow in the emerging markets, such as China and India where nuclear medicine is currently non-existing. This will be compensated by a more productive usage of Tc99, low dose imaging and patient planning, and the further growth of PET imaging.

Due to cost, product distribution and required infrastructure, in the foreseen future PET equipment (less than 3000 cameras) will not be able to replace the 22,000 existing SPECT cameras.

III. Solutions: Action plans & Proposal

AIPES priority is safety first,

1. Short term – 2009/10

- AIPES to continue coordinating the maintenance schedule of reactors at a global level.
- AIPES to help its members, within its own legal frame, in refining and improving product delivery forecasting at customer site to facilitate patient scheduling and optimize Tc99 usage.
- Usage of cyclotron derived radiopharmaceuticals as Tc99m replacement with SPECT cameras such as Thallium for cardiac examinations, Ga67 for oncology, I123 for Neurologic exams.
- EU should use a fast track process for well-known NaF18 drug (metastasis detection)
- EU and its member states to facilitate the exchange, delivery, administration and reimbursement of products from other supplier/sources already approved in one of the OECD countries.

2. Mid Term – 2010/2015

IAEA and AIPES to finalise audit and start-up plans of potential additional medical reactors for Mo99 target production by Q4 2009. Currently identified are Maria in Otwock Swierk Poland, FRM II in Munich Germany, NPP Traveni reactor in Romania and an EVAMP type facility in Egypt. Russia has expressed interest for developing Mo production and extraction.

supply, rising to levels currently available from, for example, the SAFARI reactor in South Africa (of the order of 10%) and then to a full supply basis as outlined by Ian.

4) 1 and 2 above are ANSTO Board approved strategies.
5) Point 3 is the subject of early and informal discussions with a wide range of stakeholders
6) ANSTO would welcome engagement with the EU on this matter.
7) A mutually acceptable investment model and agreed process to accelerate the utilization of OPALs full potential (point 3) is not yet in place and ANSTO would like to progress such thinking with interested groups.
The support of the EU and member states is required to facilitate the transportation of the medical nuclear products and a priority procedure for the regulatory approval of the required manufacturing variations to include these new suppliers and their products into the existing TcGenerators licences.

The support of the EU is required for starting up the Mo99 plant in Egypt, both from a political and commercial, as well as from a technical point of view.

These new suppliers will not only provide 25% of global capacity in back-up, but will also improve the output of the production for regional usage by limiting transportation time and product decay.

3. Long Term – 2015 and onwards

Each global region, at least Europe and North America, will need to have its source of Mo99 to improve output, optimize transportation and provide global back-up.

For Europe this means at least 2-3 recent sources of Mo99 capable of providing up to 80% of the European, Middle East and African needs for the next 20-30 years.

These sources can be research reactors, cyclotrons or other alternative sources.

Many projects are currently on the drawing board but the EU, as leader, and its member states need to urgently evaluate together with the industry and potential commercial partners the preferred solutions and locations and take the key decisions necessary for the wellbeing of the European healthcare. They need to be executed and operational by end 2015 when all the current reactor licenses expire, knowing that their extension is very limited.

Another approach would be the global management of the Mo99 production on a worldwide basis, as raised during the OECD workshop.

The Executive Committee of AIPES

16 June 2009
Annex 4

Extract from "Lessons learned from the shutdown of the Chalk River reactor"

(A report submitted in May 2008 to the Canadian Minister of Health by an Ad Hoc Health Experts Working Group on Medical Isotopes)

Conclusions and summary of recommendations

The ad hoc group recognizes the role of Health Canada as a regulator in setting standards, establishing guidelines and supporting research and as a leader in protecting the health of Canadians. The minister and his staff demonstrated that Health Canada was a valued partner to the nuclear medicine community and to the patients and their families who suffered during the crisis. The ad hoc group believes that it is essential to use the momentum from the crisis to create a robust, integrated and effective system for the management of medical isotopes in Canada and internationally. To this end, we are confident that the recommendations contained in this paper, when taken together, will address seven critical areas requiring both immediate and long-term action.

1. Ensure efficient and effective communication with the medical community and the public.

   1.1 Implement a process to ensure timely disclosure of potentially extended interruption at any point along the supply chain; report serious threats to nuclear medicine facilities.

   1.2 Work with nuclear medicine facilities to ensure accurate communications and the equitable distribution of generators during shortages.

   1.3 Health Canada should work with the CSNM, the CANM and the CMA to develop a real-time communications protocol to ensure that relevant information is distributed to all nuclear medicine facilities.

   1.4 With support from Health Canada, the CANM and the CSNM should develop the capacity to provide real-time notifications to the nuclear medicine community.

2. In decision-making, ensure a balance between the health and safety of the public and the health outcomes of individual patients.

   2.1 The impact on individual patient care must be considered and factored into any decisions that might result in disruptions of the supply of medical isotopes.

3. Assure appropriate physician participation and input into the decision-making process.

   3.1 Ensure that nuclear medicine specialists are actively involved in the decision-making processes at all stages in the supply chain and in all decisions regarding the supply, distribution and use of medical isotopes across Canada and the management of medically significant shortages of isotopes.

   3.2 The federal government should establish a process to ensure early, ongoing and meaningful physician input and involvement in decision-making.

   3.3 The requirement that the monitoring physician at nuclear medicine sites be an RCPSC-certified nuclear medicine specialist should be restored.

4. Minimize the potential for future interruptions in the supply of medically necessary materials and equipment.

   4.1 Strive for a made-in-Canada solution.

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4.2 Plan for the timely replacement of the NRU reactor as a supply of Mo-99.
4.3 Explore potential opportunities to bring new nuclear reactors on line to produce medical isotopes.
4.4 Create formal cooperation agreements among the current reactor facilities in Canada.
4.5 Work with international partners to review global capacity and remove current barriers or obstacles to the international movement of radioisotopes during periods of shortage.
4.6 Diversify generator supply sources, preferably within Canada.
4.7 Secure generators from more than one supplier. This may require that facilities in smaller centres develop regional purchasing strategies.

5. Mitigate the consequences of unpredicted disruptions.
5.1 “Fast track” approval of generator products that may be of use in emergency situations.
5.2 Develop a regulatory and procedural strategy to maximize expired generator productivity.

6. Enhance the capability of suppliers and end users to respond to interruptions in supply.
6.1 Develop guidelines and best practice protocols for
   • triage
   • use of radiopharmaceuticals labeled with alternative isotopes
   • alternative procedures for patient assessment
   • increasing diagnostic and therapeutic slots and extending the workday
   • addressing the backlog.

6.2 Prepare guidelines and implementation plans to mitigate shortfalls, including protocols for the use of alternative radiopharmaceuticals and the use of positron emitting radiopharmaceuticals.
6.3 Develop clinical trial agreements with Health Canada for positron emitting radiopharmaceuticals.

7. Establish a clear and appropriate alignment of authority and accountability for the management of medical radioisotopes.

Recognizing that a number of federal departments and agencies are involved in nuclear safety, the ad hoc group recommends that
7.1 Health Canada, CNSC and AECL collaborate on the development of best practices for the management of medical shortages in collaboration with provincial and territorial partners
7.2 All nuclear medicine facilities require a response plan in case of shortages of medical isotopes
7.3 A systematic and sustainable mechanism to ensure fair and just distribution of medical isotopes during national shortages be created
7.4 Development of alternatives to commonly used radioisotopes be accelerated, i.e., by pre-approving clinical trial applications
7.5 A national contingency plan be developed to ensure that the supply of medical isotopes can be returned to pre-interruption levels as soon as possible after an interruption
7.6 The participation of international stakeholders be facilitated.
Annex 5:

Composition of the internal European Commission ad hoc Interservice Group on Sufficiency in Supply of Radioisotopes for Medical Use

Chairperson: Andrzej RYS  
Director for Public Health and Risk Assessment, Health and Consumers Directorate General

Members:

John F. RYAN  
Health and Consumers Directorate General, Head of the Health Threats Unit

Helmut WALERIUS  
Health and Consumers Directorate General, Health Threats Unit

Albrecht WERNER  
Health and Consumers Directorate General, Health Threats Unit

Marianne TAKKI  
Health and Consumers Directorate General, Health Threats Unit

Silvia HRUBANOVA  
Health and Consumers Directorate General, Health Threats Unit

Philippe JEHENSON  
Research Directorate General, Health Biotechnology Unit

Roberto MAY  
Joint Research Centre Directorate General, Advisor for Nuclear Affairs

Didier HAAS  
Joint Research Centre Directorate General, Head of Unit Work Programme EURATOM

Sabine ATZOR  
Enterprise Directorate General, Pharmaceuticals Unit

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