# NUCLEAR MEDICINE: POLICY CONTEXT FOR DIFFERENCES BETWEEN EUROPE AND THE UNITED STATES

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# NUCLEAR MEDICINE: POLICY CONTEXT FOR DIFFERENCES BETWEEN EUROPE AND THE UNITED STATES

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| | |
|---|---|
| ABMS | American Board of Medical Specialties |
| ACGME | Accreditation Council for Graduate Medical Education |
| ACR | American College of Radiology |
| EANM | European Association of Nuclear Medicine |
| EU | European Union |
| FDA | Food and Drug Administration |
| LEU | Low Enriched Uranium |
| PET | Positron Emission Tomography |
| SNM | Society of Nuclear Medicine |
| US | Unites States |

# SUMMARY

The World Health Organization published in 2004 a bulletin addressing the gap between research, technology, and its implementation in the health systems of different countries (Haines, Kuruvilla, & Borchert, 2004). Among the barriers described for the implementation of new knowledge in the medical practice is the lack of connection between research results and policy makers. This happens in different subfields within the medical field. The focus of this project is to analyze the differences in implementation of radionuclide therapy technology between the EU and the US. The hypothesis is that this technology has been implemented in the EU earlier and more often than in the US, and that this variation can be connected to the differences in the policies relevant to nuclear medicine.

Nuclear medicine is a unique field because of the way radioactive material is used to create diagnostic images and treat illnesses (mostly cancer). Although radiation is used every day in radiotherapy and radiology, the main difference between these two fields and nuclear medicine is the type of radiation used. Radiotherapy and radiology use closed sources of radiation, or particle accelerators that produce radiation, while nuclear medicine uses open sources of radiation that are injected into the patient's body. This is an important difference because the accelerators used in radiotherapy and radiology can be turned on and off unlike the open sources of radiation used for nuclear medicine. If not handled properly, open sources of radiation may cause radiation contamination. Additionally, the radioactive material must be supplied on a daily basis. With nuclear medicine is possible to create diagnostic images of the body, and to record bodily functions all the way down to the molecular level. It is also possible to treat certain

illnesses, such as some types of cancer, in a targeted manner. This is possible because the radioactive material is "connected" with a chemical compound (or drug) that carries the radioactive atoms to a desired location in the body; this is called targeted therapy. It is also possible to inject the radioactive material directly into the organ or region of interest. The targeted therapy and injected techniques are two processes that are part of radionuclide therapy technology.

In order to check the status of the implementation of radionuclide therapy I used the practice guidelines published on the websites of the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine (SNM) in the US. Assuming that the practice guidelines are evidence of well-established and implemented techniques in the regions, these documents were evaluated according to their content and publication date. The content analysis was focused on the type of practices described: diagnostic, general, or therapy, as well as the type of radioactive material (or radioactive isotopes) used in such practices. The practice guidelines evaluation was done in Nvivo, a text analysis software. In addition to the analysis of practice guidelines, a bibliometric analysis of four databases (Pubmed, Medline, Biosis, and ISI Web of Science) was conducted in four databases. The keywords used for the search were *("radionuclide therapy" AND case AND report) OR (radioinmunotherapy AND case AND report)*. Case reports are publications that expose the day-to-day practice of physicians, and allow medical personnel to take a detail look into a specific case. The records from these sources were analyzed in Vantage Point, a bibliometric analysis software. From the policy landscape, three main types of policies were studied in relation to the practice of nuclear medicine: first, the education standards for the different professionals involved;

second, the policies related to the approval of radiopharmaceuticals in the different drug administration entities; and finally, the policies concerning the production of radionuclide therapies in the two regions.

The main finding of this project is that Europe and US have different policy approaches that affect, directly or indirectly, the nuclear medicine field. The main differences are in the standards of education for nuclear medicine specialist that is divided between radiologist and nuclear medicine specialists in the US; the production of radioactive material, which is commercially supplied by a very few reactors in the world, none of them in the US; and the drug administration institutions, which have very different approaches approving new drugs. Aditionally, Europe has implemented more radionuclide therapy technologies than US.

From the practice guidelines analysis, it was evident that the US started publishing guidelines for nuclear medicine several years before Europe. The US published its first guideline in 1994, while the EU's first guideline was published in 2000. However, as of July 2013, the European association had published more guidelines with 54 unique ones versus 49 from the US. EU also leads in the number of guidelines in regards to therapy, with 13 versus 2 from the US. Additionally, there is more variety in the radioisotopes used in therapy than the ones in diagnostics, and all the radioisotopes are mentioned in the European guidelines, while the US doesn't have guidelines that mention Lu-177, Re-186, and Y-90 isotopes.

From the bilbiometric analysis it was evident that Europe had published case reports for more time and more frequently than the US regarding radionuclide therapy. The first case report record from Europe was published in 1988, almost a decade before

the first case report in the US. Additionally, the US has only 10 publications that match the keywords while the EU has 37. In conclusion, the EU has more practice guidelines on radionuclide therapies regarding more types of illnesses and more radioisotopes, and Europeans have published more case reports on these therapies, which indicates that the EU has implemented radionuclide therapy technology more fully than has the US.

The differences in the policies and standards in education for Nuclear Medicine may influence this difference, because EU has a more standardized education and a more unified professional field than US. While the EU has a proposed syllabus for nuclear medicine practitioners, medical physicists, and radiopharmacists, in the US the education is neither standardized nor unified. Two different boards can certify physicians specializing in nuclear medicine: the American Board of Radiology and The American Board of Nuclear Medicine. The first one does a Nuclear Radiology certification for which the physicians are not required or allowed to conduct radionuclide therapies, while the American Board of Nuclear Medicine requires more nuclear medicine training and involves diagnostics and therapy. These differences are important in the implementation of radionuclide therapy techniques, because not all the nuclear medicine physicians in the US are trained on this aspect or allowed to practice it. For that reason a fraction of the professionals may not be interested or informed about these techniques, leaving the field of nuclear medicine in the US behind its EU counterpart.

The policies that involve the production of radioisotopes and the market for this good deeply affects the status of the field in both regions. Since most of the radionuclide materials for therapies are produced in nuclear reactors, this is a very complex topic. Nuclear reactors are recognized for their capability to produce nuclear energy and not

frequently associated with medicine. The precautionary approach that some regions apply to this topic may affect the availability of the radioisotopes in local markets. The EU has more nuclear reactors capable of the production of materials for radionuclide therapies, while the production of radioisotopes in the US is less and it focused on research. Therefore, the EU has a more stable and reliable supply of radioisotopes, which allows them to use the technology in everyday practice.

Finally, the drug administration entities seem to differ in the clarity of their procedures for the approval of radiopharmaceuticals. The EU tools for approval are clear and easy to find, which may encourage European researchers to work on new radiopharmaceuticals and to carry their findings to the application level. The European Medicines Agency has a Radiopharmaceutical Drafting Group that supports the creation and approval of radiopharmaceuticals. In addition, one of the practice guidelines from the European Association of Nuclear Medicine (EANM) is about the approval of new drugs. This is not replicated in the US; although the Food and Drug Administration (FDA) has a special group that works with radiation therapies and devices, there are no references to a group that relates to radiopharmaceuticals, or the information is not as easy to find. It also looks like the Society of Nuclear Medicine (SNM) is focusing more on research and approval of Positron Emission Tomography (PET) radiopharmaceuticals than on therapy based ones. This is understandable since the radioactive material for PET images is produced in cyclotrons available at many clinics and hospitals around the world.

In conclusion, nuclear medicine is a very diverse field that is capable of important contributions to medicine. However, the radioactive nature of the material needed for the development of new radionuclide therapies presents a barrier to the development of new

drugs. The availability of the drug and the personnel trained in these matters are the most important factors for the successful use of this technology. Although the US and the EU have been collaborating more and more in the creation of standardized procedures for nuclear medicine, it is evident that the EU has more experience in the day to day application of the technology, and the technology is also more accessible in the EU by the physicians interested in it. A trained and informed group of professionals can raise awareness in the public and influence the policy making by monitoring agencies to create clearer paths for drug approvals, and pushing for laws that approve the research and production of alternatives for radioisotopes production such as Low Enriched Uranium reactors.

# CHAPTER 1- INTRODUCTION

The World Health Organization published in 2004 a bulletin addressing the gap between research, technology, and its implementation in the health systems of different countries (Haines et al., 2004). Among the barriers described in this bulletin is the lack of connection between research results and different policy makers. This disconnect is one of the biggest problems of technology transfer in many different fields, but it is especially important for healthcare due to its potential for improving the quality of people's lives.

The differences in policies that result in different time transfer for implementation of new technologies may affect some medical fields more than others, and the time may depend on the demand for the device/drug, the availability of the resources to make it, and the knowledge of the practitioners and policy makers, among other factors. A field that is potentially affected by local policies is Nuclear Medicine (NM), and particularly the subfield of radionuclide therapies. The radioactive nature of the materials that are needed in this medical field brings to the table more regulatory agencies and policies, both local and international, which may cause a greater variation in the implementation time around the world. NM also requires numerous professionals with very specific and specialized training, as well as specialized technology.

The main objective of this project is to understand how, if at all, the differences in policies affect the time of implementation and the techniques used for radionuclide therapies between the European Union (EU) and United States (US). The hypothesis is that this technology has been implemented in the EU earlier and with more variations than in the US, and that this variation can be explained by the differences in the policies

relevant to nuclear medicine. Differences in policies between the EU and the US have been studied in other fields; however, the specific relation among the various types of policies that surround nuclear medicine and their effects on the implementation of these techniques is not clear. There are three main questions in this project which inform the primary objective: 1) Are radionuclide therapies implemented more in the EU than in the US? 2) What differences are there in the policies relevant to nuclear medicine between the US and the EU? 3) To what extent, if at all, can the differences in policies explain differences in the time of implementation of radionuclide therapies? 4) What other factors might explain these differences in the time of implementation?

Even though the adoption and implementation of new technology is important for the advance of health care systems, in some cases, such as in information and communication technology, there are good reasons for the delay of the implementation; for example, the irreversibility of technology application (Christensen & Remler, 2009). Nevertheless, the same delay in the pharmaceutical and medical devices fields may cost more money and wellbeing to patients due to the lack of access to the newest and most effective treatments and diagnosis procedures (Bell, 1983; Kaplan et al., 2004; Kereiakes & Willerson, 2004). This is especially evident in the differences between US's and the EU countries' health systems. The way these systems are design allow some drugs and devices to be available considerably earlier in the EU countries than in the US because the US requires studies on safety and effectiveness while EU only requires the first (Kaplan et al., 2004). This variation in implementation may be critical for many human lives in the US that need to wait for years for the medical trials to prove effectiveness. At the same time, patients in Europe can be paying the cost of using drugs that are not

effective because the early implementation of drugs is done without the effectiveness test that the US requires.

Nuclear Medicine is an interesting field because of the nature of the field itself. Radiation has been use in medicine since Wilhelm Conrad Röntgen discovered "X-rays" in 1895; this technology was implemented in medicine very fast because it is a very useful diagnostic tool. Today, almost every clinic has an "X-ray" machine in any of its varieties, and many physicians specialize in radiology, which includes the reading of the "X-ray" images. NM is considered as part of the radiology field in the US, but is an independent field in other parts of the world. There are four main reasons why NM is different from radiology. First, the nature of the radiation itself makes the approach different. NM uses "open radiation sources," which use radioactive material in the form of a liquid or pills that are not necessarily contained or encapsulated, and is perceived as more hazardous, requiring more stringent safety routines and practices. Second, depending on the complexity of the procedures done in the nuclear medicine facility, it requires more trained professionals, such as a pharmaceutical chemist to prepare the radioactive materials for use. Third, NM requires a constant supply of radioactive material. Finally, NM has the potential to serve as a diagnostic tool as radiology does, but NM has the potential to do diagnostic images down to the molecular level, and to be use in therapies for cancer and other diseases. Although the implementation of the newest advance in diagnostic nuclear medicine, the positron emission tomography (PET) scan, seems very popular in the US and the EU, the case is not the same for the radionuclide therapies or treatment technologies. NM has been used for radionuclide therapies since 1941 with the use of radioiodine for thyroid cancer. The radionuclide therapy potential is

based on the ability to treat targeted regions and cells in the body by linking the radiation with a molecule that transports it throughout the body, but it has not evolved as fast as other parts of the NM field (A. J. B. McEwan, 2002), and the major advances have not been implemented uniformly between regions.

The word "nuclear" is constantly associated with risk, danger, and fear. It is for this reason that it is necessary to talk about risk perception and the precautionary principle whenever the words nuclear, radiation, or other synonymous terms appear in the discussion. Spencer Weart, an expert in the history of modern physics, describes in the first part of his book *Nuclear Fear* how radiation was, since its discovery, associated with something powerful enough to destroy the earth or to keep it safe, providing a continuous clean energy supply. Many scientists of the time, as well as artists and writers influenced the negative or positive, but powerful, first perceptions that people had about radiation (Weart, 1988).

When radiation was discovered, and with it, its medical applications, people started using radiation as a "magic" formula that could solve many medical problems. The consequences of radiation over exposure and misuse became evident over time, and radiation became associated with health problems such as cancer and mutations. The health effects of uncontrolled exposure to radiation, and tragic events such as the Three Mile Island reactor meltdown in Pennsylvania in 1979, the explosion of the atomic bomb in Hiroshima and Nagasaki in 1945, the meltdown of the reactor in Chernobyl in 1986, the Goiana accident of radiation contamination in Brazil in 1987, and the nuclear disaster in Fukushima in 2011, have shifted, shaped, and transformed the perception of the risk of radiation.

Perception of risk is a topic that has been largely studied by psychologists and social scientists. There are many theories about why people perceive risk the way they do with respect to a technology. The knowledge theory is one of the most common, and it is based in the idea that the perception of risk or safety depends on how much the person knows about the topic. Another very common theory is the personality theory, which associates the risk taker/risk averse qualities of a person with his or her personality characteristics overall. There is also a political theory, which relates controversies, interests, and positions of power with risk perception. Finally, the cultural theory, which seems very powerful, is based on the idea that our perception of risk is deeply embedded among our ideologies, values, and beliefs. Wildavsky and Dake tested these theories to find which one is able to predict the person's risk perception about a technology. They found that cultural biases are the strongest predictor of risk perception (Wildasvsky & Dake, 1990). This is also confirmed by other studies where the difference in risk perception by experts and non-experts in radiation is tested, without finding that knowledge can predict the risk perception (the knowledge theory) because in some cases experts' risk perception is higher than the public's, and in other cases, it is the other way around (Freudenberg & Beyer, 2011; Perko, 2013). Something very important in the risk perception theories is the type of risk under study; characteristics such as observable or not, immediate or delayed effects, and controllable or not, among others, shape the perception of different technologies, and place radiation risk in a position of high uncertainty. The characteristics of radiation as an uncontrollable, fatal, and observable risk place it as one of the most risky perceived technologies (Slovic, 1996).

Several authors have studied the differences between the approach to risk between the EU and the US. Some think that the EU is more precautionary than the US, others think that it is the opposite, and others think that they changed in time with Europe more precautionary before 1970, and then US. Testing these three hypotheses, Wiener and Rogers studied the cases of beef, hormones, blood donations, and mad cow disease and found that the pattern of precaution is more complicated than black or white, and it changes with time and type of risk (Wiener & Rogers, 2002). Later, Hammitt et al. created a database of over 2000 risks, randomly selected 100, and tested the stringency of the regulations in EU and US for these risks in the period from 1970 to 2004. They found that neither region could be called more precautionary than the other (Hammitt, Wiener, Swedlow, Kall, & Zhou, 2005). This is important for this project because neither of the two regions can be defined as more precautionary than the other.

Assuming that the professional associations of NM in the two regions and the practice guidelines that they publish are evidence of the practices in the day to day routine, the official practice guidelines from the Society of Nuclear Medicine (SNM) and the European Associations of Nuclear Medicine (EANM) would be used, and would account for the differences in this field between the US and the EU. I expect to find that radionuclide therapy techniques are implemented in the EU more than in the US. The practice guidelines can be accessed on the websites of the two organizations, and in most cases these are also published in the official journal of each society. In order to compare them they were categorized in date of first publication when available, topic, radioactive material used, and type of procedure. The text analysis software Nvivo was used to code the documents.

In addition to the practice guidelines, a bibliometric study of case reports was used as evidence of implementation of radionuclide therapy techniques in both regions. The databases used for the bibliometric search were PubMed, Medline, Biosis Preview and ISI Web of Knowledge. The key words used in the search were *("radionuclide therapy" AND case AND report) OR (radioinmunotherapy AND case AND report)*. Radioinmunotherapy is a specific type of radionuclide therapy used mainly in patients with non-Hodgkins Lymphoma. I selected case report publications because "[i]n medicine, a case report provides important and detailed information about an individual patient, their symptoms, diagnosis, treatment and the outcome of that treatment. Case reports may arise during routine clinical practice and during clinical research studies" (CaseDatabase, n.d.), which serves as an evidence of implementation of the technology.

It is possible that neither the practice guidelines nor the case reports show the complete picture of the implementation stage of radionuclide therapies in each region. Practice guidelines and case reports take a long time to develop and get published and these times may vary between regions, which will not show the real picture of what is currently happening in the regions. It is also possible that the practitioners don't have an interest in publishing even if they are implementing and have experiences with these technologies. The opposite may happen too; it is possible that there are practice guidelines that nobody uses, or case reports on techniques that are implemented in very specific groups that don't represent the regions. There are more direct methods to measure implementation of a technique, such as surveys of medical centers and staff, statistics with the number of procedures done per region, or interviews with professionals

in the area. However, all these require a more extensive and expensive study, which is out of the scope of this project.

The policies that are going to be analyzed in relation with NM are classified in three groups: professional, radioisotope supply, and drug/medical device policies. The policy search was done on the web, and was focused on regulations and laws that affected NM internationally and in each of the regions. Because there are different levels of regulations and agreements that affect NM, the policies were classified as international, national and local (in the US some policies are applied only at the state level). As a result of differences in the policy fields and their infrequent overlapping (besides in the nuclear medicine case) it is not possible to determine clear causal relations between the differences in policies and the variations in the implementation of the nuclear medicine techniques analyzed here. Additionally there are may differences in policies at different levels; for example, there are some professional certifications that in the US are managed at the state level while in Europe they are managed at the national or even international level. These differences in level, and the connections between regulatory agencies (e.g. nuclear regulations and drug development) make it difficult to create causal connections or assign the differences to a single explanation. However, the differences in the policy context between the regions help to explain the variations in the implementation of some nuclear medicine techniques.

Additionally, during the literature review there was an important observation about the "problems" in communication among nuclear medicine practitioners in the US. It is possible that the variations in implementation of radionuclide therapy techniques are caused by problems in communication and/or network among the practitioners. The flow

of information among NM professionals in the US seems not to be fluid and/or abundant despite efforts of society. This is evident in their publications because research groups are conducting clinical trials that other groups are not aware of, which may result in very slow flow of patients, expenditure of unnecessary resources, and duplicated efforts toward the same goal. Nevertheless, some professionals in this field recognize that there is a policy barrier that doesn't allow them to move forward with clinical trials. They are in favor of FDA approvals for different NM therapy techniques in order to be able to provide the US' patients with the same treatments that the EU's patients have been receiving for a while (M. M. Graham & Menda, 2011).

Chapter 2 of this document contains a scientific background on what Nuclear Medicine is, how radiation and radioactivity have been use in medicine, and why Nuclear Medicine is of special interest. It also summarizes the literature review done for this project, and provides a background for the following chapters. Chapter 3 explains the methods used for the collection of data about the adoption of nuclear medicine, selection of unique practice guidelines, and how they were classified by content. It also presents the results of the bibliometric analysis. Chapter 4 presents the data analysis on adoption, and turns to the possible relationships between features of the policy context and the findings with regard to adoption. Finally, Chapter 5 presents the conclusions of the project. Details of the data and the analysis are presented in the appendices.

# CHAPTER 2 – NUCLEAR MEDICINE BACKGROUND

## *The Basic Science*

There are some basic physics concepts that are useful in order to understand the complex role of nuclear medicine in the medical world and the challenges it faces. First of all, electromagnetic radiation means energy moving through space. There is a broad spectrum of radiation types that are the physics principle for great variety of devices; some everyday examples are the radio, microwave ovens, and light as shown in Figure 1.

Radiation can be classified into two different types: ionizing and non-ionizing radiation. Ionizing radiation refers to radiation that is able to interact with the atom. These interactions may result in the ionization of an atom, which means that the electric charge of an atom changes as a result of the interaction. Atoms tend to be neutral; for this reason if their charge changes, they are going to interact with their environment until they find equilibrium. If ionizing radiation interacts with an atom that is part of a cell, the ionization of this single atom may trigger a huge variety of chemical reactions, which may later become biological responses to the radiation. Examples of these biological responses are death of the cells, and cell mutations.

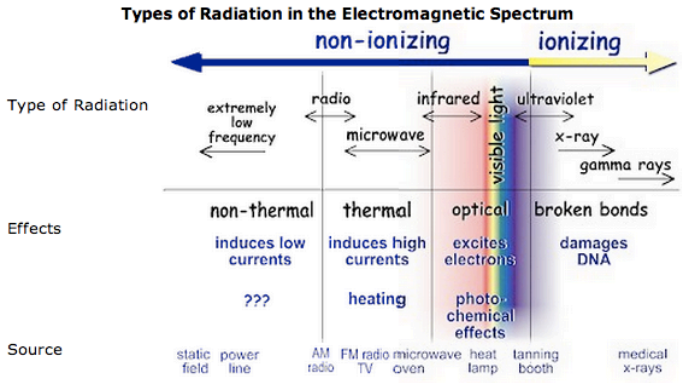


**Figure 1: Types of Radiation in the Electromagnetic Spectrum**

**Source: http://www.epa.gov/rpdweb00/understand/ionize_nonionize.html retrieved May 19 2013.**

Humans can't sense the presence of ionizing radiation; it doesn't have a smell or taste, and for this reason it is necessary to have special devices or detectors. Ionizing radiation detectors are designed in a multitude of ways, but the basic principle is to allow the radiation to interact with the material and to record a trace that can be then interpreted, such as an electric charge or an image. A detector can create an image and reconstruct the path of the radiation, count how much radiation has passed through it, or alert us to the presence of radiation. These different types of detectors are used every day in medicine, the first one for imaging construction, the second one for control of workers exposure to radiation, and the third to control the amount of radiation in the environment for safety reasons.

We are all exposed to ionizing radiation due to cosmic rays and naturally occurring unstable atoms in the earth, but we didn't know it until in 1896 when Henry Becquerel discovered radioactivity when working with uranium salts. Radioactivity is the emission of ionizing radiation by unstable atoms or radioisotopes. Atoms are usually unstable when their nucleus is so large that it needs to release the extra energy by emitting ionizing radiation. There are three types of ionizing radiation that can be emitted by this process: alpha (**α**), beta (**β**) and gamma (**γ**). The main difference between these types of radiation is the presence and amount of mass, the distance that the ionizing radiation can travel through matter, and the amount of energy that it leaves in its trajectory. Alpha radiation is massive and can't go through a sheet of paper, but it can deposit a high amount of energy, creating a lot of ionization in a short distance. Beta radiation has the same mass as an electron (less than alpha radiation) and it could travel through a sheet of paper, but it would be stopped by a few centimeters of plastic or

millimeters of metal. Finally, gamma radiation doesn't have mass and can travel long distances, produces more spread ionizations, and it is very difficult to stop; in order to block gamma radiation it is necessary to use high-density materials such as lead. These characteristics are very important when contemplating the practical uses of ionizing radiation.

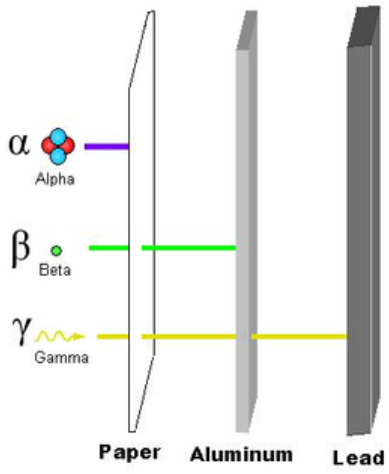


**Figure 2: Radiation Particles**

**Source: http://meteorology.lyndonstate.edu/classes/CMS/index.php/particles Retrieved April 20, 2013**

Radioactive material is a collection of many radioactive atoms. Radioactive materials have very important characteristics besides the type of radiation they emit and the energy of the radiation. Once an atom has emitted the extra energy it has in the form of radiation, it will not do it again, or it will emit a different type of radiation if the atom is too big and has a lot of extra energy. The atom that emits radiation is often known as the parent and the resulting atom is a daughter atom. Figure 3 shows the decay scheme of Carbon 14, which is known as an isotope used to date archeological elements; Carbon 14 is the parent in this case, and Nitrogen 14 is the daughter. Nitrogen 14 is stable, but in some cases the daughter atom is still radioactive and becomes the parent of another atom.

Each of the radioactive atoms emits radioactivity spontaneously. Radioactive material is usually characterized by its activity, which is the amount of ionizing radiation emitted per second, and varies from sample to sample of the material. Besides activity, the half life of a radioactive isotope is a characteristic quantity that is constant for each material, and is defined as the time it would take it to decay to half its activity.

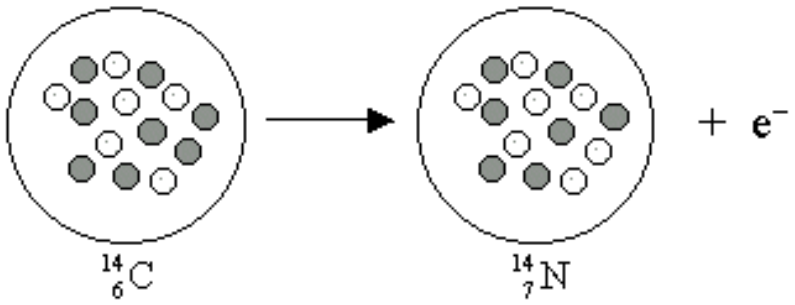


**Figure 3: Carbon 14 decay**

**Source http://cwx.prenhall.com/bookbind/pubbooks/walker2/chapter32/custom1/deluxe-content.html retrieved May 5, 2013**

There are some radioactive atoms that can be found in nature, but most of the materials that are used in industry and medicine are by-products of nuclear reactors or can be produced by cyclotrons or particle accelerators. Besides the radiation emission of unstable atoms, humans have developed different ways to produce radiation. This ionizing radiation is known as X-rays and is the product of accelerating electrons against a target. The physics of X-rays is the same as that of gamma radiation. X-rays discovered in 1895 by William Rögnten.

The use of ionizing radiation for peaceful purposes is allowed and should be done while trying to keep the exposure to the radiation "as low as reasonably achievable," which is known as the ALARA principle. In order to reduce the exposure there are three variables that can be modified: time, distance and shielding. The time of exposure should

be reduced to its minimum, the distance from the radiation source should be maximized, and proper shielding should exist between the source and the people.

Because the misuse of radiation and radioactive materials can lead to terrible consequences, in 1953 president Eisenhower presented the "Atoms for Peace" speech in front of the 470th Plenary Meeting of the United Nations General Assembly and with it gave the basis for the creation of the International Atomic Energy Agency in 1957, whose main objective is "… to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world. It shall ensure, so far as it is able, that assistance provided by it or at its request or under its supervision or control is not used in such a way as to further any military purpose" ("The Statute of the IAEA," n.d.). By February 2013, 159 countries were part of the IAEA, and these countries join forces to develop peaceful uses of radiation and allow IAEA to do inspections to facilities that use radioactive material in their countries. As a result of its work, IAEA produces different publications and creates standards of practice in medicine, industry and nuclear energy.

### *The Use of Radiation in Medicine*

The use of radiation in medicine happened almost immediately after the discovery of this phenomenon in nature. It is commonly known that the first radiography ever taken was the hand of William Rögnten's wife. Since the discovery of radioactivity and X-rays, radiation has been used in different medical fields, where it plays a very important role.

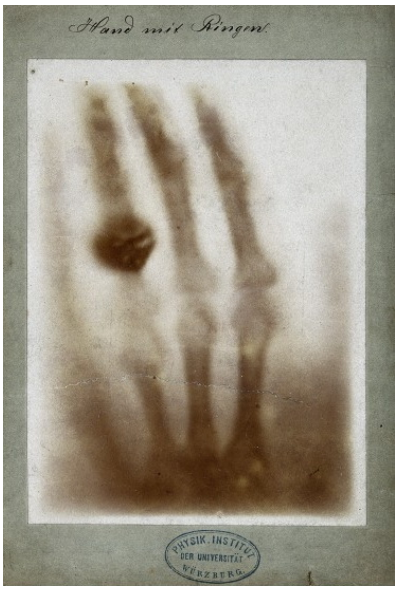


**Figure 4 First radiography**

**Source http://commons.wikimedia.org/wiki/File:First_medical_X-ray_by_Wilhelm_R%C3%B6ntgen_of_his_wife_Anna_Bertha_Ludwig's_hand_-_18951222.jpg.**

**May 5, 2013**

## *Radiology*

Radiology is a very important, well established and still controversial branch of medicine. Its main objective is to create diagnostic images. It uses X-rays to create images of anatomical parts. Almost every hospital has a radiology department, and it is there where you can find the X-ray machines, CT scanners, and other imaging devices that are not radioactive radiation related such as magnetic resonance and ultrasound.

In radiology, radiation is used to create images of the body by placing the anatomic part between the radiation source and the detector. Because of the way radiation interacts with different types of matter, the detector senses different characteristics of the material in between. Bone and soft tissue have different properties; bone can stop X-ray while soft tissue can't. This creates the image of our bones in the detectors; figure 4 is an image of the first radiography ever taken, by William Rögnten. Of course the

applicability of this tool in medicine was very obvious and since then has advanced from the two-dimensional plain images of the Rögnten's X-ray machine, to the CT possibility of having very specific images of thin transversal sections of the body. Figure 5 shows the scheme of how an X-ray machine or CT scan works, and figure 6 shows a transversal section of someone's thorax taken by a CT scanner, in the lower right corner is a planar front image that locates the transversal cut in the lower part of the lungs.

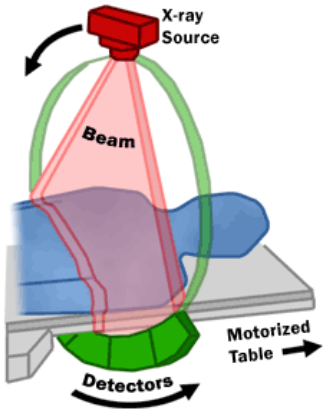


**Figure 5 Scheme of how a X-ray machine or a CT scan works**

**Source: http://www.fda.gov/radiation-emittingproducts/radiationemittingproductsandprocedures/medicalimaging/medicalx-rays/ucm115318.htm. May 5, 2013**

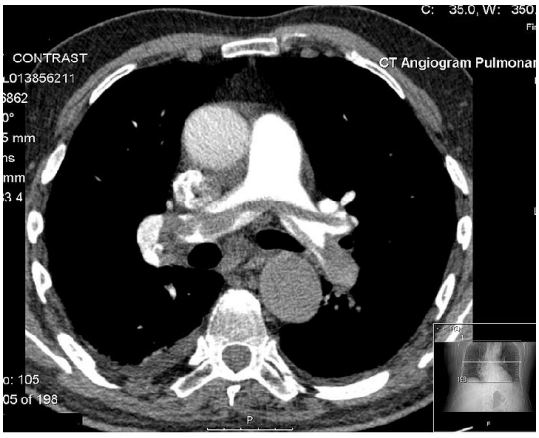


**Figure 6 CT scan image of an abdominal cross section**

**Source: http://en.wikipedia.org/wiki/File:SADDLE_PE.JPG. May 5, 2013**

The physicians that work in this field are in charge of the production of diagnostic images that are then use by specialist in other areas. The ionizing radiation in this department is well controlled and very safe, since is produced by machines that can be turned on and off. Additionally, the devices that produce radiation have plenty of safety configurations, and usually, depending on their power, are located in shield rooms with safety devices like locked doors, where only the patient remains during the procedure.

The labor force of a radiology department is composed of the radiologist, the technicians, and depending on the complexity of the machines they use and the location, an engineer or a medical physicist who frequently visits and checks the department, the machines and the procedures.

### *Radiotherapy*

The radiotherapy branch of medicine uses radiation to treat cancer. In general, the ionizing radiation source is a powerful X-ray machine, and the patient is located at the end of the trajectory of the radiation. With this arrangement there is no detector; the patient is where the radiation needs to arrive in order to create ionization and kill the cancer cells. The first machines used for radiotherapy were discs of radioactive material with high energy and long half-lives, which were shielded by a lot of lead in a shield room. This technology is not longer preferred because the radioactive material doesn't have an on/off switch, and there are other complications like disposal of the radioactive material and loss of control over the radioactive source. This is different from an accelerator that produces radiation in the form of X-rays because once the machine is off, there is not radiation in the environment.

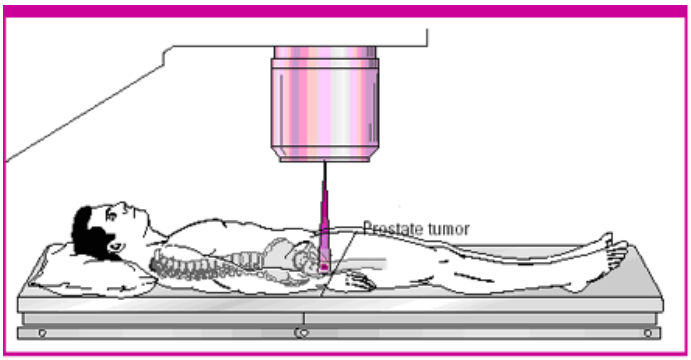


**Figure 7 Scheme of how radiotherapy works**

**Source: http://www.patienthealthinternational.com/prostate-cancer/questio...py?itemId=1620398&nav=yes. May 10, 2013**

The labor force in radiotherapy includes physicians, who usually have a specialization in oncology and a sub specialization in radiotherapy, and the technicians. For radiotherapy purposes it is necessary to have a medical physicist working full time in the service. The reason why more trained personnel is needed in radiotherapy compared with radiology is to calculate the doses and arrange the machine's trajectories over the human body, so the patients receive the energy they need to kill the cancer cells in the exact location where they need it without hurting other organs.

There is another therapy called brachytherapy, which places sealed sources of radiation in the organs with cancer; it is often used for prostate and cervical cancer. The radiation source varies, and depending the country these treatments are considered part of radiotherapy or nuclear medicine. The fact that the radiation is in a sealed source is very important, and allows the physicians to do very localized "radiotherapies."

## *Nuclear Medicine*

Nuclear Medicine is the branch of medicine that uses unsealed radiation sources for the diagnosis and treatment of different pathologies. Unlike the other branches of medicine where radiation is used, nuclear medicine puts the radiation in the patient,

radiation travels through the body, and the images are from outside the patient in the detector.

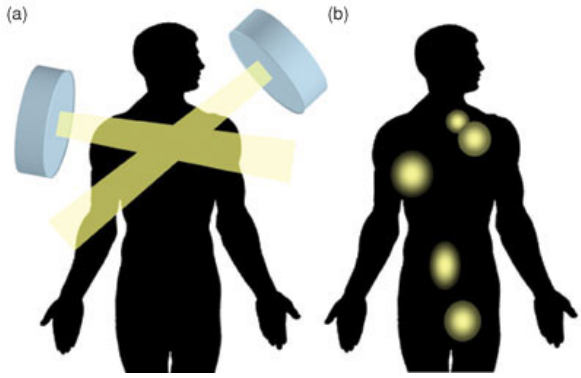


**Figure 8 (a) In radiotherapy and X-ray, the radiation is outside the patient. (b) In Nuclear Medicine the radiation is inside the patient and is used to treat or to detect outside to create the diagnostic images.**

**Source: https://www.llnl.gov/str/JulAug03/gifs/Hartmann1.jpg. Retrieved May 10, 2013**

With these techniques it is possible to create images of the inside of the body without surgery. Additionally, nuclear medicine techniques allow the creation of images of the functionality of organs. For example, in making images of the heart or kidneys, when the patients are injected with the radioactive material, images taken at different times recreate the dynamics of what is happening inside the body. This technique reveals how the blood is flowing in organs and how the organs are functioning. Figure 9 shows a typical sequence of images from thyroid uptake. Because the images of nuclear medicine can be blurry, new machines are able to fuse CT scan images with nuclear medicine images for a better localization of the radiation. The newest advance in imaging in nuclear medicine is the Positron Emission Tomography (PET); it works with the same basics of radiation, but it uses very specific types of radionuclides with very short lives and high energies.

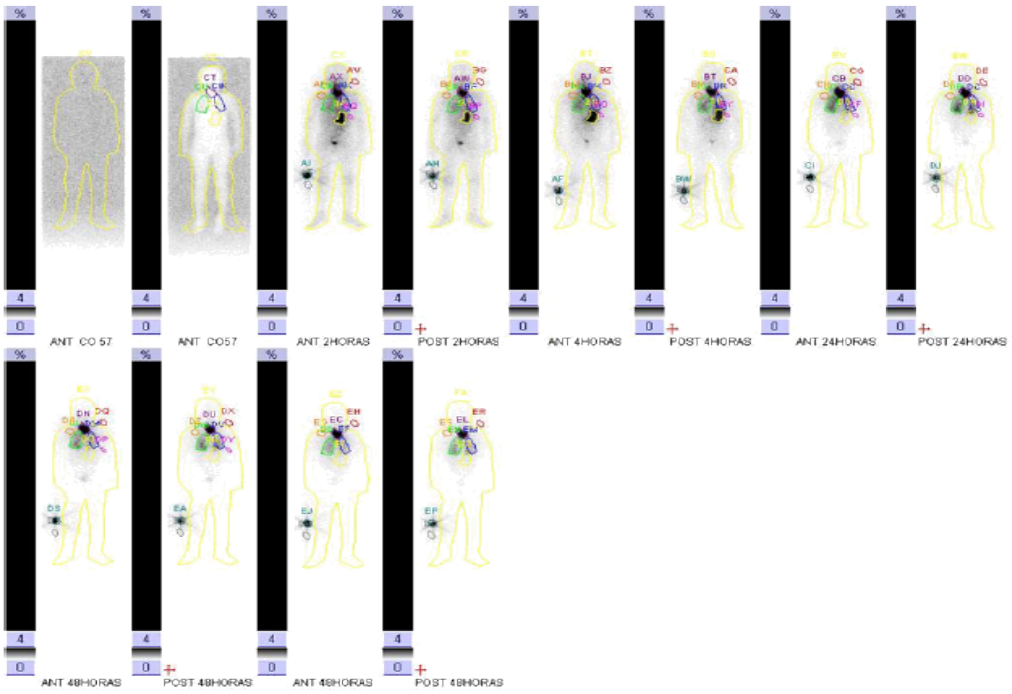


**Figure 9 Sequence of Images of a Thyroid Uptake**
**Source: Personal file**

Nuclear medicine is particularly interesting and complex because it is the only field in whitch open radioactive sources are used; this increases the risk of an accident and the possibility of a contamination, plus creates the need to deal with radioactive waste and mobile sources of radiation. Contrary to the machines used in radiology and radiotherapy, the radioactive material in nuclear medicine can't be turned on and off. The radioactive materials used in nuclear medicine tend to have very short half-lives, from minutes to days, and to emit different types of radiation depending on the purpose of the procedure. For diagnostic images, the intention is to have ionizing radiation that can travel long distances so it doesn't get trapped in the body, so they use gamma radiation. In case of cancer or other treatment the idea is to trap the radiation in the specific location of the body to kill the cells; in these cases the idea is to use radioactive materials that emit alpha or beta, and gammas at the same time. The combination of these radiation types is

ideal, so the radioactive material can do the treatment and be detected outside the body at the same time.

## Labor Force in Nuclear Medicine

The labor force in a nuclear medicine department varies depending on the size and the complexity of the procedures available. The general setup of a nuclear medicine department is based on the nuclear medicine specialized physician and a technician. However, a nuclear medicine department with state-of-the-art technology needs a radiopharmacist or radiopharmaceutical chemist, and a medical physicist.

A radiopharmacist or radiopharmaceutical chemist is in charge of the preparation of the radiopharmaceuticals, which are the chemical compounds that are linked to the radioactive material so the radiation targets a specific part of the body. Although some of the radiopharmaceuticals used in nuclear medicine come ready to use, most of them come in kits and need to be prepared in the workplace. The preparation of these compounds needs to be done in a very specialized environment to control for contaminants, both in the drugs and from the drugs.

Because of the complexity of nuclear medicine, it is ideal to have a medical physicist as part of the department. A medical physicist would assure the safety of procedures and the environment and develop internal dosimetry protocols for the treatments, like the medical physicist in radiotherapy.

The professionals working in nuclear medicine today come from different backgrounds and in many cases end up in these jobs by chance and with little training. For that reason the IAEA published the Nuclear Medicine Resource Manual, which forms the basis for a standard formation of human resources in nuclear medicine. (IAEA, 2006)

Nuclear Medicine Supplies

Nuclear medicine needs two basic supplies besides the labor force. Nuclear medicine needs the equipment usually known as gammacameras to detect the radiation and the radioactive material. Gammacameras are long-lasting and only need calibration and maintenance and there are different suppliers, unlike to the radioactive material.

The most common material use in nuclear medicine is Techntium-99m; it is used in the majority of diagnostic images. It is the ideal radioisotope because it has a half life of 6 hours and emits only gamma rays. Tecnetium-99m is produced as the disintegration of molybdenum 99, which is produced in nuclear reactor facilities. Due to the complexity of molybdenum production, only seven reactors supply 90% of the molybdenum used in the world. The US's supply of this material depends almost 100% on a single reactor located in Canada; the other reactors are located in Europe and South Africa (OECD (NEA), 2010).

For the PET scans it is necessary to have a cyclotron in the hospital or close by in order to produce the radioactive materials. Although the machinery is more expensive for these exams, once the cyclotron is established it can provide radioactive material for all the hospitals nearby. The innovation of this technology is not only the convenience of the in situ production of radioactive material, but that PET allows one to see very small clusters of cancer cells before they can be seen using the other more conventional diagnostic techniques. The reason why this technique is so potent is that the image comes from the molecular activity of the cancer cells instead of their physical characteristics. This is the latest advance in NM and it has received a lot of attention, not only because of its diagnostic power, but because the radioactive material can be produced on site, and the isotopes have very short lives; the most common, Fluor 18, has a half-life of less than

2 hours. However, the energies of these isotopes are very high and they need to be handled with a lot of caution. Table 1 shows the most common used radioisotopes in NM, their main use and how are they produced.

**Table 1: Isotopes Commonly Used in Nuclear Medicine**

| Isotope | Type of Use | Production |
|---|---|---|
| I-124/I-123 | Diagnostic | Cyclotron |
| I-131 | Diagnostic/ Therapy | Nuclear Reactor |
| In-111 | Diagnostic | Nuclear Reactor |
| Lu-177 | Therapy | Nuclear Reactor |
| P-32 | Diagnostic/Therapy | Nuclear Reactor |
| Re-186/Re-188 | Therapy | Cyclotron/Nuclear Reactor(Daugther of W-188) |
| Sm-153 | Therapy | Nuclear Reactor |
| Sr-89 | Therapy | Nuclear Reactor |
| Tc-99m | Diagnostic | Nuclear Reactor (Daughter of Mo 99) |
| Y-90 | Therapy | Nuclear Reactor |
| F-18 | Diagnostic | Cyclotron |

In conclusion, NM is not a new field, but thanks to advances in technology and innovation it has evolved to a point where it is possible to take molecular images of the human body and to treat illnesses in a targeted way with radionuclide therapies. Despite the great possibilities of NM, it is a more complicated field than other medical fields, even other fields that also use radiation. The manipulation of open sources of radiation and the production of these radioactive materials make this field a very unique one.

## *Social and Policy Studies of Nuclear Medicine*

There are many journals that focus on social or policy studies of medicine and/or science and technology. However, there are very few papers and documents that focus specifically on the field of nuclear medicine. The most significant document on policy and nuclear medicine in the US is “Advancing Nuclear Medicine Through Innovation” by the National Academy of Sciences (NAS) in 2007. The document is the result of a

request from the Department of Energy (DOE) and the National Institutes of Health (NIH) to analyze the field of nuclear medicine and to provide areas of significant future research for the DOE's Medical Applications and Sciences Program (MEDICINE, 2007 p3)a. This is the most comprehensive and formal document that addresses the different challenges that NM faces.

One of the main findings of this NAS publication is the lack of professional scientists dedicated to NM in the US (chapter 8). Part of this conclusion came from a survey by The Center For Health Workforce Studies (http://chws.albany.edu/). The survey was done in 2006, and found that up to that time "[a]s few as 1,500 practitioners, nuclear medicine scientists constitute a very small segment of the health workforce in the United States—and a tiny component of the entire labor force. Their small numbers are not indicative of their importance to both the health care system and the larger economy." (Wing, Langelier, & De, 2007).

With respect to what constitutes the workforce of nuclear medicine or what is a professional scientist dedicated to nuclear medicine, the IAEA published in 2006 the "Resources for Nuclear Medicine." With this document the IAEA provides guidance to what an ideal NM service should have in terms of human resources, technology and facilities. In the second chapter of this document they profile the education and training that the different roles in the NM workforce should have. Probably the most important role in the nuclear medicine department is the one of the nuclear physician, who depending on the location could have very different training and responsibilities. There are different publications that discuss how NM is taught in different regions and how the programs have evolved (Eudaldo & Olsen, 2008; M. M. Graham & Metter, 2007; Lass &

Scheffler, 2003; Pascual, Dondi, Paez, Kashyap, & Nunez-Miller, 2013; Silberstein, 2000; Sternberg, 1964). These and other publications on this topic are discussed in chapter 4 as part of the education policy data. In the US there are different paths to become a Nuclear Medicine specialist, there is a professional position for nuclear radiologists (who can only do NM diagnostic images, not therapies), and there are two different boards that can certify nuclear physicians (Ziessman, 2012). In Europe this distinction in nuclear medicine does not apply.

From the professional practice topic there are some interesting papers that discuss the role of the radiologist and nuclear medicine physician in the medical field. Diagnostic images are usually read or interpreted by a radiologist or a nuclear physician, but a diagnostic image is usually done at the request of a different specialist (for example a cardiologist, endocrinologist or orthopedist). This participation from different specialties to diagnose has opened the debate about the boundaries of radiology: should radiologists read images that are going to influence other specialties or should the specialist (not radiologist) read the diagnostic of their own specialty? (Burri, 2008). Of course, radiologists have a very specific training that allows them to interpret images and produce diagnostics of high quality; at the same time their work requires a high level of communication with physicians in other specialties. (Sorrell & Reeves, 1997; Sunshine, Bansal, & Evens, 1993).

There are two main technical reasons why radiology and nuclear medicine imaging are still their own field. One is that they use radiation for many of the images they produce; for this reason they need very specific technology that produces radiation and safety features for protection (Burri, 2008). The other one is the training: it is not

possible to know all the radiology and all the other specialty (Sorrell & Reeves, 1997). In the case specific to nuclear medicine there was a debate on who should deliver the I-131 therapy for thyroid: the endocrinologist or the nuclear physician (Baskin, 1997). In this case "deliver the therapy" means give the patient a capsule full of I-131, which can be done by any of the specialists. More important is all the manipulation of the radioactive material and the radioactive patients, which varies greatly around the world (Al-Shakhrah, 2008).

Stefanoyiannis et al analyzed the differences in education for medical physics in the field of NM, comparing a number of certifications and educational programs in 25 European, 2 North American and 2 Australasian countries. They conclude that "a common policy on matters concerning education and training as well as the practice of the medical physicist profession is generally followed, despite the presence of a few differences" (Stefanoyiannis et al., 2012).

In the nuclear medicine field it is easier to find comments about policy and implementation in the "experts' opinion" section, the editorial, or the "news" section of the nuclear medicine related journals than in policy journals. These comments have been present for long time and in a constant manner. They are usually focusing on what is the future of the field (Atcher, 2008; Ell, 1993; Farquhar, Stryer, & Slutsky, 2002; A. J. B. McEwan, 2002; A. J. McEwan, 2008; Pappas, 2008), calling for policy participation (Cannon, 2007), or giving important news for the field, such as problems with the radioactive supply (Knight, 2009; Webster, 2009) or the creation of an international database of nuclear medicine (IAEA-NUMBAD, 2009). There are also policy comments

in the conclusion of technology or science research papers related to the field such as the ones made by Graham and Menda (M. M. Graham & Menda, 2011), who state that

> *"Current research funding, particularly from the National Institutes of Health, overemphasizes the importance of novelty in research projects. This emphasis has the effect, in the radiopeptide area, of fostering the development of numerous new agents but does not provide the infrastructure for the translational effort to bring the agents to approval. The regulatory requirements in the United States also restrict access to several radionuclides peptides that are being used as clinical tools in a growing number of institutions across Europe."*

The challenges that radiopharmaceuticals face as a result of the regulatory approach used in the US is also mentioned in the "Advancing Nuclear Medicine through Innovation" document of 2007. The second finding they mention is precisely that

> *"There are three primary impediments to the efficient entry of promising new radiopharmaceutical tracer compounds into clinical feasibility studies: (1) complex U.S. Food and Drug Administration (FDA) toxicologic and other regulatory requirements (i.e., lack of regulatory pathways specifically for both diagnostic and therapeutic radiopharmaceuticals that take into account the unique properties of these agents); (2) lack of specific guidelines from the FDA for good manufacturing practice for PET radiodiagnostics and other radiopharmaceuticals; and (3) lack of a consensus for standardized image acquisition in nuclear medicine imaging procedures and harmonization of protocols appropriate for multi-institutional clinical trials"*

One important observation from the commentaries on the US journals is the "problems" in communications among practitioners in the nuclear medicine field. There are some examples in which the different practitioners seem to be lack of information about clinical trials and other processes going on in their areas of expertise. This is important because this would affect the implementation of a new technique, although I didn't measure or follow up this issue in order to assess its real implications.

Although various radiopharmaceuticals were labeled as “Orphan Drugs” (drugs develop for rare medical conditions) in the 1990’s (Swanson, 1996), including some that can be used for cancer therapies, there are very few papers that mention or make reference to this fact (just five from a search of "Orphan Drug" And "Nuclear Medicine" in PubMed, and one when using “Radiopharmaceutical” instead of “Nuclear Medicine”, but there are 1084 results for “Orphan Drug” alone). This is interesting since there are many incentives, programs and regulation specific paths for orphan drugs’ research and approval; however, this doesn’t seem to be an important factor in the literature review.

It is possible to find references and complaints about the difficulties that NM has faced with the FDA (Callahan, 1996; Komoda, Suzuki, Yanagisawa, & Inoue, 2009; Pacific, 1998; Rotman, Laven, & Levine, 1996). The paper by Decristoforo and Schwarz, published in 2011 titled “Radiopharmacy: regulation and legislations in relation to human applications” is one of the few that developed this topic. Their main focus in is radiopharmaceuticals for PET, but the some of the regulations may be shared with the radiopharmaceuticals for therapy. This paper compares the differences in frameworks between the US and Europe specifically for PET radiopharmaceuticals, finding that in both regions the regulatory framework is increasing and that the

> *“[r]egulatory authorities need to be aware of the unique characteristics of PET RPs [Radiopharmaceuticals], including the short half-life and need for single-dose patient preparations, to allow incorporation of rapid scientific advances in the field. Activities of professional organizations may assist in finding appropriate solutions for this highly specialized field, but it remains with the regulators to support these efforts to allow the true potential of PET to develop for use in molecular imaging and drug development which will benefit the community at large” (Decristoforo & Schwarz, 2011)*

There are few papers that analyze the state of the field in different aspects and/or regions. They usually compare the statistics of the field by counting the number of nuclear medicine departments or services in a region and the type of technologies used, mainly based on the implementation of diagnostic tools like PET (not treatment therapies) (Dondi et al., 2011; Lass, 2005). One paper focused on nuclear medicine technology and policy, but is published in German (Lerch & Jigalin, 2005). In the conclusions they show that medical technology is limited in this nuclear medicine journal; as a reason they mention the divergence of the development in medical technology and in the industry locations as well as discrepancies between the policies and the promotion of nuclear medicine techniques in Germany. The IAEA created a Nuclear Medicine Database (NUMDAB) to collect information on nuclear medicine practice around the world (IAEA-NUMBAD, 2009), but the project is based on self report and by May 2013 there were only 2 NM centers reported in USA, and none in France, Germany, and Belgium (http://nucmedicine.iaea.org/).

### *Radioactive Material for Medical Use*

The third finding of the "Advancing Nuclear Medicine Through Innovation" is that there is an inadequate domestic supply of medical radionuclides in the US. They suggested that "[t]here is no domestic source for most of the medical radionuclides used in day-to-day nuclear medicine practice. Furthermore, the lack of a dedicated domestic accelerator and reactor facilities for year-round uninterrupted production of medical radionuclides for research is discouraging the development and evaluation of new radiopharmaceuticals."

This is not the first document that the National Academy of Science has published about this topic. In 1995 they published "Isotopes for Medicine and the Life Sciences" (Adelstein & Manning, 1995), and in 1996 "Radiation in Medicine: A Need for Regulatory Reform"(Gottfried & Penn, 1996), both focused on the big applications and benefits that the applications of radioactive isotopes have in the life sciences, and the barriers it faced.

More recently in 2012, the National Academy of Science published a book called "Assuring a future U.S.-Based Nuclear and Radiochemistry Expertise" where they reiterate, "… isotope availability is an important factor for the field. The lack of an adequate national supply of medical radioisotopes, especially 99 Mo, creates a reliance on foreign sources. Fluctuation in foreign supply streams creates an uncertain future for 99m Tc radiopharmaceuticals. Development of a national facility for long-lived isotope production would reduce the foreign dependence and create more demand for radiochemists."

From other publications the Journal of Nuclear Medicine published a three part special about the future of nuclear medicine, where the first part focused on radioisotopes' availability ("Research Radionuclide Availability in North America," 1997), and some other publications called attention to this problem, emphasizing the fact that 99m-Tc supply in the US comes from a single reactor in Canada, and every time this reactor has had a problem the complete field of NM in the US has to stop (Einstein, 2009; Ruth, 2009).

Europe counts more reactors and facilities that produce radioactive isotopes, and therefore is not affected as badly as the US when the Canadian reactor stops, and there

are more university and experimental reactors running in general in the EU. The European Association of Nuclear Medicine published in 2008 "The medical use of radiopharmaceuticals up to 2025" where they show an expected increase in the use of some radio pharmaceutics, and an increase in other nuclear medicine techniques. (Group, 2008).

Part of the problem in the production of radioactive isotopes comes from nuclear reactor waste. It is for that reason that many researchers have tried to develop new forms of production, one is the construction of Low Enriched Uranium Reactors (LEU) (Fallout, Canada, & Shutdown, 2008; OECD (NEA), 2010; Technology, 2008; Williams & Ruff, 2008). Canada has also incentivized the research for options to produce radioactive materials, especially for the production of technetium because they know they supply a big part of the market with a single reactor, which is old enough to be retired. As part of the Canadian efforts some projects have been focused on the production of Tc-99m in Cyclotrons, one of them resulting in a PhD thesis (Gagnon, 2012).

### *Technologies: Effectiveness and Cost-Benefit Analysis*

There are several reviews of new techniques and technologies in NM, and its advantages. To begin with, there are a few studies focused on the differences in implementation of new technologies. From these studies it is easy to identify that there are many differences on the level of adoption of a technology not only at the international level but at the national level too. In the paper prepared by the Health Science Center at Toronto University, it's shown how the same technology for breast cancer management, the sentinel lymph node biopsy for breast cancer, was adopted unevenly through the country. This procedure uses radioactive material to detect the presence of cancer cells

during surgery and in most standard procedures involves the presence of a nuclear medicine physician. With this in mind it was concluded that the factors that had the biggest influence in the adoption were the communication with other professionals that are part of the treatment, the number of cases in which they can apply these techniques, and the administration's support for the implementation (Wright, Gagliardi, Fraser, & Quan, 2011). To draw those conclusions, different type of professionals that were using or were accessible to use the technology were interviewed.

From a technical point of view, there are few studies in the implementation of nuclear medicine technologies, mainly at the national level. The Canadian study on breast cancer (Wright et al., 2011) mentioned before, and the US study on PET/ CT technology (Coleman et al., 2005) have in common the important role that inter professional collaboration and the professional guideline development plays in the development of a field.

There are also several technical reviews that show the effectiveness and challenges of some of the latest developments in nuclear medicine therapies for cancer also known as radionuclide therapies. This is a topic that has promised results since the beginning of the century, evolving from the perspectives of the technology in the field (Breeman et al., 2001; de Jong, Kwekkeboom, Valkema, & Krenning, 2003) to more technical details of the same techniques (Ambrosini, Fani, Fanti, Forrer, & Maecke, 2011; Cremonesi, Ferrari, Bodei, Tosi, & Paganelli, 2006).

The publications by the International Atomic Energy Agency (IAEA) are important for this field since it is the organization that coordinates the world effort for the correct use of radioactive material. As part of its goals IAEA has the promotion and the

right use of radiation. IAEA has a division for human health and a program of action for cancer therapy (PACT), both related to nuclear medicine. As part of their work they have carried out different research projects to assess the efficacy and validity of nuclear medicine compounds for therapy (IAEA, 2007), guides for the research and implementation of new radiopharmaceuticals (IAEA, 2009), and the creation of a world database to asses the status of the field in the world (IAEA-NUMBAD, 2009), among other publications concerned with the quality control, safety and efficacy of more traditional nuclear medicine procedures. IAEA also supports research on different technical aspects of the technologies that would make a certain technique or innovation available for implementation in developing countries, like the in-house preparation of radiopharmaceuticals used for treatment and diagnosis in nuclear medicine (Padhy & Dondi, 2008).

There are some groups that have made studies of the implementation of techniques in medicine at the international level, none of them related with nuclear medicine. The group of medicine of Tokyo University has compared the guidelines for hepatocellular carcinoma around the world and with their results they were able to conclude that the differences in the guides can be attributed to "various etiological factors, high-risk patients, health systems, health resources, medical technology, treatment choices and income levels in different countries," and that the level of implementation in each region depends on what entity is writing the guidelines (Song, 2012). The other common type of articles that compare international implementation of health technologies focus mainly on differences between developed and developing countries in adoption of new technologies. In these cases some focus on the public health

policies, intellectual property rights when licensing to international companies, and international collaborations for the health technology transfer (Salicrup & Fedorková, 2006).

### *Risk Perception and Radiation*

When talking about risk perception and radiation, there are many publications and books that address this topic. However, they focus mainly on topics such as nuclear power plants, nuclear waste or nuclear weapons. Slovic did one of the most important works reviewing the literature on the risk perception of radiation. Among his findings is the fact that the perception of risk from radiation varies depending on the sources of radiation; for example, medical sources of radiation are perceived as less risky than other sources. He points out that none of the papers he reviewed includes nuclear medicine in the list of radiation applications in medicine. He also states that "[i]n 20 years of research on perception and acceptance of technological risks, there has been remarkably little attention given to the medical use of radiation-quite a contrast to the hundreds or more studies of nuclear power and nuclear waste" (Slovic, 1996).

Although many things have changed since Slovic published his paper in 1996, there are still very few publications that look at the relation of risk perception and NM. However, the NCRP Report No. 160, *Ionizing Radiation Exposure of the Population of the United States,* published in 2009, established that Americans are unnecessarily overexposed to medical radiation. That may explain why many of the publications that talk about nuclear medicine and risk perception are focused on the design and content of the informed consent that physicians need to explain to their patients before a procedure,

and the fact that some doctors don't know about this risks and order more diagnostic images than what is necessary (Freudenberg, Müller, & Bockisch, 2009; Picano, 2000)

There are no publications that compare the difference in approaches to NM between the EU and the US. However, the EU commission clearly states, "The precautionary principle … aims at ensuring a higher level of environmental protection through preventative decision-taking in the case of risk. However, in practice, the scope of this principle is far wider and also covers consumer policy, European legislation concerning food and human, animal and plant health" (European Comission, 2000).

In conclusion, the research in nuclear medicine is well documented; thanks to IAEA there are some worldwide standards in nuclear medicine. However, there are differences in the time of implementation of some techniques, mostly in radionuclide therapy that need to be explored since they can potentially affect patients in the regions where its implementation is slow. It is important to keep in mind the differences on risk perception that this topic brings to the table since radiation and its medical applications is more acceptable, but in order to do NM it is necessary to run nuclear plants that are seen as more risky.

# CHAPTER 3 – METHODS AND DATA

Nuclear medicine is different from all other medical fields. Chapter two explains in detail what are the physics principles behind the NM images and treatments. The second part of chapter two shows the wide spectrum of publications that relate NM and policy. However, the questions that motivate this project are not answered there. This chapter gives a detailed explanation of the data that I collected to answer the question, how and why the documents were selected, and how they were analyzed.

## *Data*

The data was collected from websites from professional organizations and regulatory agencies. It consists of documents, publications, and laws publicly available. The dependent variable consists of the practice guidelines and case reports that allow investigating the hypothesis that Europe implements radionuclide therapies before and at higher levels than the US. The independent variable consists of the policies that may affect NM, and its relationship with the technology.

## *Dependent Variable*

The dependent variable is the time and quantity of implementation of radionuclide therapy technologies. In order to answer the first question (Are radionuclide therapies implemented more in EU than US?) I assumed that the practice guidelines from the professional societies as well as the case reports account for the day-to-day practice in NM.

### The Practice Guidelines

The definition of clinical practice guidelines has changed with time, but the most recent definition is “statements that include recommendations intended to optimize

patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" (R. Graham, Mancher, & Wolman, 2011). This definition is commonly accepted, and supports the assumption of a practice guideline as evidence of implementation. The use of practice guidelines had increased since the 1980s for different reasons, and one of the main reasons for this is the need for standardizations in the medical field (Pickett, Waterstram-Rich, & Turner, 2000). The efforts for standardization are evident in the EU publication of "Recommendation of the Council of Europe on Guidelines Methodology" (MINISTERS EUROPE COUNCIL OF COMMITTEE, 2001), the US National Guideline Clearinghouse (http://www.guideline.gov), and the different international efforts such as the Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument (http://www.agreetrust.org/), and the Guidelines International Network (http://www.g-i-n.net/). Therefore, in order to check for the differences in the NM field between the EU and the US I analyzed the practice guidelines available on the websites of the (American) Society of Nuclear Medicine and Molecular Imaging (SNMMI), whish are published in the practice section of its website (http://interactive.snm.org/index.cfm?PageID=772), and the European Association of Nuclear Medicine (EANM), which are published in the publications section of its website (http://www.eanm.org/publications/guidelines/index.php?navId=37). The last day in which these sites were checked was July 1, 2013. The details of the analysis are later in the chapter.

In order to use the practice guidelines published on the websites of the professional societies as the standard of practice in each region and compare their content

at different levels to analyze the implementation of radionuclide therapy techniques in the EU and the US, each document was downloaded from the website and then classified based on different criteria. For the analysis I only use unique guidelines that were approved by the respective society and published on the website.

The SNM has publisheded 53 procedures, divided in 14 categories while EANM has 61 in 17 categories. The categories are listed in Table 2, and although they don't match perfectly they can be compared (for a complete list of the Practice guidelines refer to Appendix A). Some guidelines files listed by SMN are duplicated on its website. For example the guide on "Pediatric dose consensus guidelines." Additionally, SMN has 9 guidelines in collaboration with the American College of Radiology (ACR), and 8 of them are also in collaboration with the Society for Pediatric Radiology (SPR). However, there are other SNM-only guidelines on the website that describe the same procedures as some of the collaboration guidelines. From these 9 collaborative guidelines, two are there repeated "ACR–SNM–SPR PRACTICE GUIDELINE FOR THE PERFORMANCE OF PARATHYROID SCINTIGRAPHY, 2009" and "SNM Practice Guideline for Parathyroid Scintigraphy, 2011." From these two I selected the SNM-only one to code because is the most recent. There are four other guidelines from the collaborative group that are very similar to the other SNM-only guidelines, for example "SNM Practice Guideline for Lung Scintigraphy, 2011" from SNM only and "ACR–SNM–SPR PRACTICE GUIDELINE FOR THE PERFORMANCE OF PULMONARY SCINTIGRAPHY IN ADULTS AND CHILDREN, 2009." Because the guidelines were not exactly the same, I kept these four for the coding phase.

**Table 2: Number of guidelines in SNM and EANM websites and their classifications**

| SNM | Number of documents | EANM | Number of documents |
|---|---|---|---|
| Cardiac | 2 | Cardiology | 3 |
| Endocrine | 4 | Parathyroid | 1 |
| Infection | 3 | Inflammation/Infection | 2 |
| Neurology | 4 | Neuroimaging | 5 |
| Oncology | 8 | Oncology | 13 |
| Musculoskeletal | 2 | Radionuclide Therapy | 9 |
| | | Dosimetry | 3 |
| Pediatric | 5 | Paediatrics | 10 |
| Pulmonary | 1 | Pulmonary Embolism | 2 |
| Gastrointestinal | 3 | | |
| General | 5 | Radiopharmacy | 2 |
| | | Drug Development | 1 |
| | | Physics | 2 |
| | | Technologist Guidelines | 5 |
| Collaborative Guidelines | 10 | | |
| | | EANM:SNMMI Guidelines | 1 |
| Retired Guidelines | 3 | | |
| EANM Guidelines | 3 | SNMMI Guidelines - endorsement by EANM | 2 |
| | | Joint Guidelines | 1 |

The EANM have one duplicate practice guideline, the "Guidelines for standard and diuretic renogram in children" which is posted twice, with two different files, one 2011 and the other one 2000. In this case I kept only the most recent file for coding because the aim is to have only unique documents. EANM has multiple guidelines in collaboration with other European societies, but the practice guidelines are not duplicated on their website.

Besides guidelines, the EANM has listed three papers that are not practice guidelines. Two of them, "Curriculum for education and training of Medical Physicists in

Nuclear Medicine" and "Integration of FDG-PET/CT into external beam radiation therapy planning" are kept for the coding because they clearly state that EANM has endorse them and/or are product of a EANM work. The third file is "PET in radiotherapy planning: Particularly exquisite test or pending and experimental tool?" which is a compilation of reviews of the topic, but do not present statements from the EANM. For this reason it is not used in the Nvivo coding. EANM also listed the Power Point presentation of the "Procedure Guideline for Tumor Imaging with 18F-FDG PET/CT" guideline, which is not used for the coding.

There is one guideline that was developed in collaboration between EANM and SNM and is the "SNM/EANM Guideline for Guideline Development 6.0" in 2012. As its name indicates, this guideline set the methodology for the creation and approval of guidelines in the field of nuclear medicine; it also states that for non-collaborative guidelines the approval doesn't need to come from both societies. The goal of this guideline is to have multiple collaborations and endorse guidelines in the future. Because this guideline was developed in collaboration, it was counted as a document for both societies in the Nvivo coding.

There is a guideline in EANM website listed as a joint guideline developed with SNM and IAEA, but it is not published yet in the SNM website. The name of the guideline is "The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumors (2013)." Because the guideline is not listed in the SNM website and it was published in the European Journal of Nuclear Medicine, it was coded as an EANM practice guideline only.

One of the most important limitations of the data is the existence of the already mentioned joint guidelines, and the guidelines endorsed between the regions. For the joint guidelines, there is no doubt about them belonging to both regions' data sets; however, I took a different approach with the endorsed guidelines. The reason to do this is the lack of clarity about the European guidelines validation by the FDA in the US. Not all the physicians can practice them, which indicates low implementation. There are three guidelines from EANM endorsed by SNM and two from SNM endorsed by EANM; these guidelines are listed in Table 3. These guidelines were only coded to their original societies for the Nvivo coding.

**Table 3: Endorsed Guidelines**

| **Guidelines from EANM endorsed by SNM** | **Guidelines by SNM endorsed by EANM** |
|---|---|
| $^{131}$I-meta-iodobenzylguanidine ($^{131}$I-mIBG) therapy (2008) | Breast scintigraphy with breast specific gamma cameras 1.0 (2010) |
| $^{131}$I/$^{123}$I- Metaiodobenzylguanidine (MIBG) scintigraphy (2010) | Sodium 18F-fluoride with PET/CT bone scans (2010) |
| Radioimmunotherapy for B-cell lymphoma with 90Y-radiolabelled itribumomab tiuxetan (Zevalin)(2006) | |

EANM has a section for technician "guidelines," but these are more like pamphlets of information and are not assigned to a particular procedure; for this reason they were not taken into account for the Nvivo coding.

Finally, both societies have "retired" or outdated guidelines published on the website. The EAMN disclaimer says: **"**Authoritative source: Dr. Richard Wolf, LL.M. Partner (legal advisor) Please note that this guideline has not been updated since 2003 and, therefore, may not reflect the current knowledge and practice in the field of oncology. EANM is providing this guideline on an 'as is' basis for general information purposes only and does not accept any responsibility for the accuracy, completeness,

currency, relevance, reliability or suitability of the information contained therein." The SNM disclaimer says "Please note the below guidelines have been retired and thus not updated since their last approval. Therefore, these guidelines may not reflect current knowledge and practice in the field of nuclear medicine. SNMMI is providing these guidelines on an 'as is' basis for general information purposes only and does not accept any responsibility for accuracy, completeness, currency, relevance, reliability or suitability of the information contained therein." In both cases the guidelines were used in the Nvivo analysis. From the total of 115 documents, only 12 were not part of the analysis in Nvivo. The findings and analysis of the data are presented in chapter 4.

## Bibliometric Analysis of Case Reports

In addition to the practice guidelines a bibliometric analysis was conducted with publications that contain the keywords *("radionuclide therapy" AND case AND report) OR (radioinmunotherapy AND case AND report)* in PubMed, Medline, Biosis Preview, and ISI Web of Knwledge databases. This query was intended to find case reports that contained the words "radionuclide therapy" or "radioinmunotherapy." The term "radioinmunotherapy" refers to a specific type of radionuclide therapy in which the radioactive material is linked with antibodies, and is mainly used for non-Hodgkins lymphoma.

Based on the definition of case reports, these are also assumed to be evidence of implementation of a technique since they are detailed reports of the practice, and would not exist if the technique were not being used. There were 61 publications from PubMed, 16 from Medline, 23 from Biosis Preview and 46 from ISI Web of Knowledge. After cleaning the data for duplicates only 103 publications remain.

I assume that the practice guidelines are published because the technologies and techniques in those guidelines are widely used in the regions, and that all the practitioners have incentives to work with them and to publish case reports. Nevertheless, it is possible that the practice guidelines don't represent a spectrum of the techniques that are used in the day to day practice because it take time to publish them or because some techniques may not be in the interest of those who published the guidelines. Additionally, practitioners may not have interest in publishing their case reports or may be disseminating their knowledge and evidence of implementation in a different form, such as conferences. A more direct way to measure the implementation of a technique is by surveys and interviews of medical centers, medical staff, and records of procedures, but it is not possible to use them for this specific project due to funding and time. Therefore, this project and the variables measured here were selected because the data sources are publicly available and provide a view of what is officially happening in terms of the technologies implemented and supported by the professional societies in the field.

### *Independent Variable*

The independent variable of this study is the policies of the two regions. The risk of using radiation and the consequences of its uncontrolled use caused the creation of many of the regulatory frameworks that we use today. All of them are based in the "as low as reasonable achievable" (ALARA) principle, which means that ionizing radiation doses should be as low as possible for the public and workers while using the properties of radiation for the desired application. Specific practices, and especially accidents with radiation, have motivated most of the regulatory and policy changes related with radiation. However, the ALARA principle and the medical application of radiation are

traditionally very regulated and accidents in these fields have not created any recent focal events that could promote specific policies. It is possible that the use of new techniques and technologies promotes the creation of new regulation and policies in nuclear medicine. A good example of this is the situation of PET and the development of new radiopharmaceuticals for diagnostic use that can be manufactured in the hospital. Nevertheless, the case of radionuclide therapies is different because the materials come from very traditional regulated sources, and variations of the technique have been used for more than 50 years. The possibility of nuclear medicine techniques influencing the policy changes in the policies related to nuclear medicine, as well as the different levels of regulation, make it difficult to elaborate a solid causal relation, but it allows one to place the implementation of radionuclide therapy techniques in a policy context that may elucidate the state of the implementation. This section presents the different types of policies and regulations that surround NM. The types of regulations explored are related to radiation regulations, health regulations, and education regulations, in international, European Union and United States arenas.

## The Policies Involved in Nuclear Medicine

In order to account for the differences in when particular treatments were introduced in the field, I checked the policies from the two regions that affect the nuclear medicine field. Because of the nature of the field, there are more regulatory bodies that affect the practice of NM than other medical fields. Besides the normal health policies and drugs I researched the procedures for implementing new radiopharmaceuticals and the classification of radiopharmaceutical drugs in the different regions, because these policies will directly impact the availability of new drugs.

The policies and regulations related to radiation and radiation protection shows how precautionary the different regions are with respect to the uses of radioactive materials. If the policies are strict and/ or complicated I expect to find that the region implements the technology more slowly than others. There is also the fact that different agencies can be in charge of the same topics; for example, environmental agencies and energy agencies can regulate about radiation protection matters that can overlap, and may or may not coincide in the same region, creating an overregulation on the same topic, which add to the issues for the nuclear medicine practitioners in order to move on.

Regulation of the production of radioisotopes is also a very important part of the regulatory policies that doesn't apply to other medical fields. In this case the regulatory bodies are lokely to be the same as the ones regulating nuclear power plants, because many of the radionuclides used in NM are produced in these types of facilities. The other option for radioactive material production is the cyclotron, which is mainly used in PET imaging. As mentioned before, there are very few plants that produce this type of material, and they are mainly managed by the local governments, which assume the risks and costs of the power plants. The existence or not of regulation for the production of radioactive material for medical use, and the characteristics of the regulations is very important for the development of the NM field in the two regions, because without constant and secure availability of radioisotopes there is no certainty for the future of the field. The supply-demand problem has been one of the most emblematic of the NM field after the shortage of material that NM facilities have gone through in the recent past.

Additionally, I investigated the differences in the education programs for medical doctors with NM specialization, and the credentials and certifications needed for practice

in the different regions, because the regulations on the NM specialist profession would account for differences in the field between different regions. The efforts to standardize practices are not only limited by the differences in practice guidelines, but by the qualifications that different professionals need in order to work. Different educational paths may bring professionals to the same certifications, but that doesn't guarantee their knowledge to be similar. The strength professional qualifications would also reflect the level of knowledge transfer that is needed to practice. For example, a regulation that makes professionals renew their credentials through specific examinations is more likely to keep professionals in the field up to date on techniques and knowledge than a lack of regulation or credentials.

## *Radiation Regulation*

### International

Radiation regulation is a very complex topic that is usually divided among nuclear energy, peaceful applications of radiation, and nuclear weapons. Most of the regulations regarding radiation fall under these three topics. The projects and applications that are radiation related have a lot of intervention from the government and from international organizations, due to the risk and cost involved in these topics. There are two important international organizations that focus their studies on safe limits of radiation dosis, and set the standards that shape national and local regulations around the world are the International Commission on Radiological Protection (ICRP) and the International Commission on Radiation Units and Measurements (ICRU). Based on the recommendation of these two agencies, different regulatory bodies establish limits on the

amount of radiation that the public, the health practitioners, and children should receive under different situations.

The International Atomic Energy Agency (IAEA) is one of the most active and important agencies regulating radiation in the world. In order to assure that the use of radioactive material is limited to pacific and safe uses, the IAEA conducts inspections in countries with nuclear reactors and important nuclear facilities. Additionally, the IAEA has a special division for human health applications of radiation. In this division they realize different projects related to nuclear medicine that result in publications that are publicly available through their website (http://www-naweb.iaea.org/nahu/NM/publication.html). By March 2013 they had nine technical documents, eleven human health series, one human health report, two training courses, five safety report series, and nine technical report series in NM topics (a list of these documents is provided in Appendix B). These documents create standards and serve as a reference for NM practice around the world. Their documents go from planning a NM center to how to label radiopharmaceuticals. One of the most influential documents of IAEA is the general manual for NM, where they propose a syllabus for all the professions related to NM (IAEA, 2006).

Additionally, the IAEA has tried to develop a database of all the nuclear medicine centers in the world and their practices (http://nucmedicine.iaea.org/default.asp), but U.S centers are not actively participating (by July 7, 2013 only 3 had reported anything), and not all the EU countries are reporting. Furthermore, the IAEA has databases of radioisotopes for medical production (http://www-nds.iaea.org/medical/) and reactors that produce isotopes (http://nucleus.iaea.org/RRDB/Content/Util/IsoTopes.aspx). Based on

this information, there are 15 operational reactors capable of isotope production in the US (listed in Table 3), and 13 in Europe (listed in Table 4).

**Table 4: List of Nuclear Reactors in US Capable of Isotope Production**
**Source: retrieved from http://nucleus.iaea.org/RRDB/Content/Util/IsoTopes.aspx July 1 2013**

| FACILITY NAME | TYPE | LAST UPDATE |
|---|---|---|
| **AFRRI TRIGA** | TRIGA MARK F | 26/05/2011 |
| **ATR** | TANK | 09/04/2013 |
| **MITR-II MASS. INST. TECH.** | TANK | 09/05/2011 |
| **HFIR** | TANK | 22/03/2012 |
| **OSTR, OREGON STATE UNIV.** | TRIGA MARK II | 09/04/2013 |
| **PSBR PENN ST. UNIV.** | TRIGA MARK CONV | 23/12/2010 |
| **RRR REED COLLEGE** | TRIGA MARK I | 09/03/2012 |
| **NSCR TEXAS A&M UNIV.** | TRIGA CONV | 16/08/2012 |
| **GSTR GEOLOGICAL SURVEY** | TRIGA MARK I | 09/04/2013 |
| **UCI, IRVINE** | TRIGA MARK I | 09/04/2013 |
| **UFTR UNIV. FLORIDA** | ARGONAUT | 09/04/2013 |
| **MURR UNIV. OF MISSOURI** | TANK IN POOL | 13/08/2012 |
| **WSUR WASHINGTON ST. UNIV.** | TRIGA CONV | 09/04/2013 |
| **UC DAVIS/MCCLELLAN N. RESEARCH CENTER** | TRIGA MARK II | 09/04/2013 |
| **TRIGA II UNIV. TEXAS** | TRIGA MARK II | 09/04/2013 |

**Table 5: List of Nuclear Reactors with Isotope Production Potential in Europe**
**Source: Retrieved from http://nucleus.iaea.org/RRDB/Content/Util/IsoTopes.aspx July 1, 2013**

| COUNTRY | FACILITY NAME | TYPE | LAST UPDATE |
|---|---|---|---|
| **BELGIUM** | BR-2 | TANK | 14/06/2012 |
| **CZECH REPUBLIC** | LVR-15 REZ | TANK WWR | 09/04/2013 |
| **FINLAND** | FIR-1 | TRIGA MARK II | 09/04/2013 |
| **FRANCE** | OSIRIS | POOL | 14/01/2013 |
| **FRANCE** | HFR | HEAVY WATER | 09/04/2013 |
| **FRANCE** | ORPHEE | POOL | 08/07/2012 |
| **GERMANY** | FRMZ | TRIGA MARK II | 10/10/2010 |
| **GERMANY** | FRM II | POOL | 09/04/2013 |
| **NETHERLANDS** | HOR | POOL | 30/05/2010 |
| **NORWAY** | JEEP II | TANK | 28/06/2013 |
| **POLAND** | MARIA | POOL | 09/04/2013 |
| **PORTUGAL** | RPI | POOL | 09/04/2013 |
| **ROMANIA** | TRIGA II PITESTI - SS CORE | TRIGA DUAL CORE | 09/04/2013 |

Besides the IAEA, the Organization for Economic Co-operation and Development (OECD) countries have created a Nuclear Energy Agency whose mission is

> *"To assist its member countries in maintaining and further developing, through international co-operation, the scientific, technological and legal bases required for a safe, environmentally friendly and economical use of nuclear energy for peaceful purposes. To provide authoritative assessments and to forge common understandings on key issues as input to government decisions on nuclear energy policy and to broaden OECD policy analyses in areas such as energy and sustainable development.* (OECD-NEA, 2013)*"*

One of their work areas is medical radioisotopes; it was established in 2009 with a High-Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR). Their main concern is the dependability of supply of Tc-99m in their countries and the world. As a result they have five publications on the supply of medical radioisotopes, but they are focused on Tc-99m and I-131. They found that the pricing structures of radionuclides do not reflect the cost of the production. Additionally, the lack of coordination between different reactors causes the extra cost of overproduction. These two findings add to the fact that there is not a transparent system to understand the cost and price dynamic of the production of radionuclides, and the role of governments in this chain is not always clear. Moreover, there is not consistency on the policy approach to this issue from the different governments that are affected. This group proposed policies for the participant countries that implicate market reforms such as full cost recovery of production, a shift in government participation, and subsidies for isotope production activities. They also suggest incentives for R&D related to alternative technologies for isotope production such as Low Enriched Uranium reactors (LEU) (OECD-NEA, 2011).

To summarize, ICRP and ICRU are the international intuitions that set standards for maximum levels of exposure to radiation, among other scientific measures. Additionally, the IAEA and NEA from OECD are the two most influential organizations that influence the policies of radiation practices internationally. The work of these organizations is in many cases complementary, and they work together on many projects. Now I am going to explore the organizations that influence NM policies at the regional level in the EU and the US.

## European Union

The European Union has its own agreements in the radiation field. The European Commission, which is the executive body of the European Union, has legislated on nuclear energy topics almost since the creation of the EU. The "Treaty Establishing the European Atomic Energy Community" (Euratom) was signed for the first time in 1957, its principal objectives to promote research and knowledge transfer, to establish safety standards for work with radiation, to ensure the basic needs/ supplies for the development of nuclear energy, and to control the use of nuclear material and assure that it is used for peaceful purposes (EU, 2007).

The Council Directive 97/43 of Euratom legislates on medical radiation exposures and article 6, item 3 says

> *"In radiotherapeutic practices, a medical physics expert shall be closely involved. In standardized therapeutical nuclear medicine practices and in diagnostic nuclear medicine practices, a medical physics expert shall be available. For other radiological practices, a medical physics expert shall be involved, as appropriate, for consultation on optimization including patient dosimetry and quality assurance including quality control, and also to give advice on matters relating to radiation protection concerning medical exposure, as required* (EU President, 1997).

With this statement the Euratom mandates the presence of medical physicists in all the nuclear medicine services that provide therapies. Additionally, in the guidelines of EANM there is a proposed syllabus for Medical Physicists. With these tools, NM services in the EU assure the presence of capable personnel in their facilities. Additionally, different countries of the EU have acknowledged the use of the proposed syllabus by IAEA for the medical practitioners. This syllabus includes the study of radionuclide therapies in the NM specialist education.

EANM also has a guideline for the application of new drugs, that details the legal processes for the acceptance of new drugs, clinical trials, etc. This guideline is especially important for young or foreign researchers that are not used to the system.

## United States

The Nuclear Regulatory Commission (NRC) was established by the Energy Reorganization Act of 1974. This organization manages all the regulations on nuclear power plants, radioactive waste, licenses for manipulation of radioactive material, etc. In these regulations the medicine applications are in Title 10 of the code of Federal Regulation part 35 –Medical use of byproduct material, and part 70-Domestic use of special material.

The NRC shares the regulation of radionuclides used in medicine with the FDA. On the main website of the FDA there is a tab for Radiation-Emitting Products; however, none of the classifications they have is for nuclear medicine applications (last checked July 8, 2013). The path for radiopharmaceutical approval starts with the application for an Investigational New Drug Application (IND), follow by a clinical trial or clinical research study. In the case of therapy, to prove the efficacy of a drug is slower and more

complicated than for a diagnostic procedure, and an application for FDA approval need to include efficacy (Decristoforo & Schwarz, 2011).

The Department of Energy also plays an important role in the nuclear medicine fields because the production of medical isotopes in the US is coordinated by the "National Isotope Development Center" (NIDC). This center also manages the distribution of isotopes in the US. The isotope production site lists nine reactors; the locations of the reactors and the isotopes they produce are shown in Figure 10. The information on these reactors was updated in 2011, and for this reason may not be the same as that on the IAEA website in Table 3.

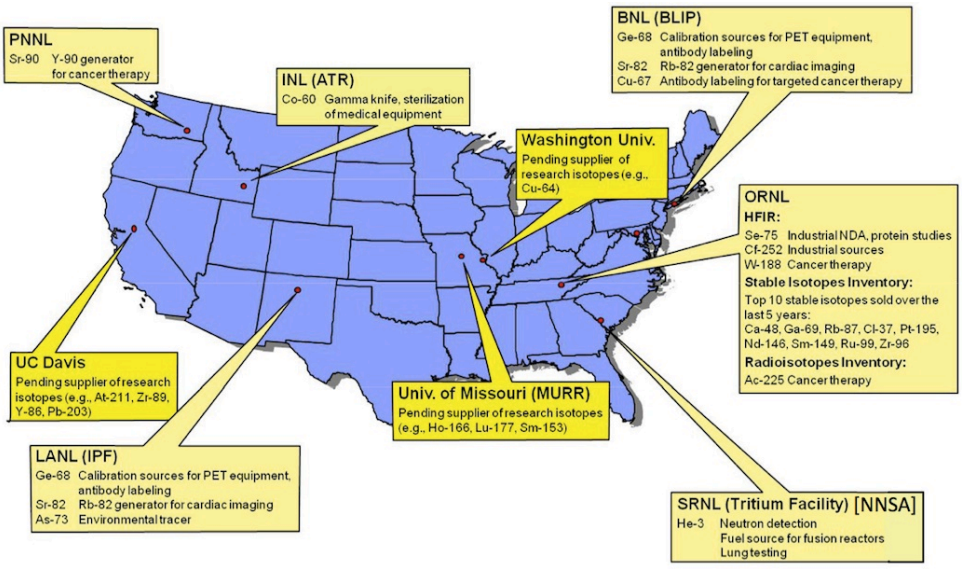


**Figure 10 Isotope production sites**
**Source: Retrieve from http://isotopes.gov/sites/sites.html, June 20, 2013**

From the different documents presented previously in this manuscript it is evident that these nuclear reactors don't supply the US market optimally. For that reason, plus the initiatives of the OECD-NEA, the bill S. 99 (112th): American Medical Isotopes Production Act of 2011, was introduced in January 2011. Sections 3 and 6 of the bill were focused on the domestic production of radionuclides for medicinal use. Section 3

"Directs the Secretary of Energy (DOE) to implement a technology-neutral program to evaluate and support projects for the production in the United States (except in certain circumstances without the use of highly enriched uranium) of significant quantities of molybdenum-99 for medical uses, implemented in cooperation with non-federal entities, whose costs shall be shared in accordance with certain cost sharing requirements of the Energy Policy Act of 2005," and section 6 "Amends the Atomic Energy Act of 1954 to authorize the NRC to issue a license, or grant an amendment to an existing license, for use in the United States of highly enriched uranium as a target for medical isotope production in a nuclear reactor, but only if specified conditions are met, including certification by the Secretary that the federal government is actively supporting development of an alternative medical isotope production target that can be used in that reactor. (*American Medical Isotopes Production Act of 2011 LIBRARY OF CONGRESS SUMMARY*, 2011)" This bill died after it passed the Senate on November 17, 2011.

Besides the challenges in supply of NM materials, professionals working in nuclear medicine face different challenges from the educational policies. First, the physicians have two paths to be certified as nuclear medicine specialists. The Board of Radiology has a specialization in nuclear medicine radiology that only includes diagnostic images, and the Board of Nuclear Medicine has its own certifications that include therapies. There is not a standardized curriculum for these physicians; while some take 3 years of radiology and one of nuclear medicine, others may have four years in nuclear medicine. The definitions of nuclear radiology and nuclear medicine are not clear, and that is why there are some overlapping practice guidelines between the ACR and SNM. The paper by Stefanoyiannis et all (Stefanoyiannis et al., 2012) on the

education of medical physicists also shows that different states regulate the presence of medical physicists in nuclear medicine facilities differently. This is also evident in Figure 11 from the website of the American Association of Medical Physicist (AAPM), where they list the state regulations and licensures for medical physicists in the US. Additionally, by 2011 there were only two postgraduate programs on radiopharmacy in the US while the EU has many of these programs already established for years (Decristoforo & Schwarz, 2011) .

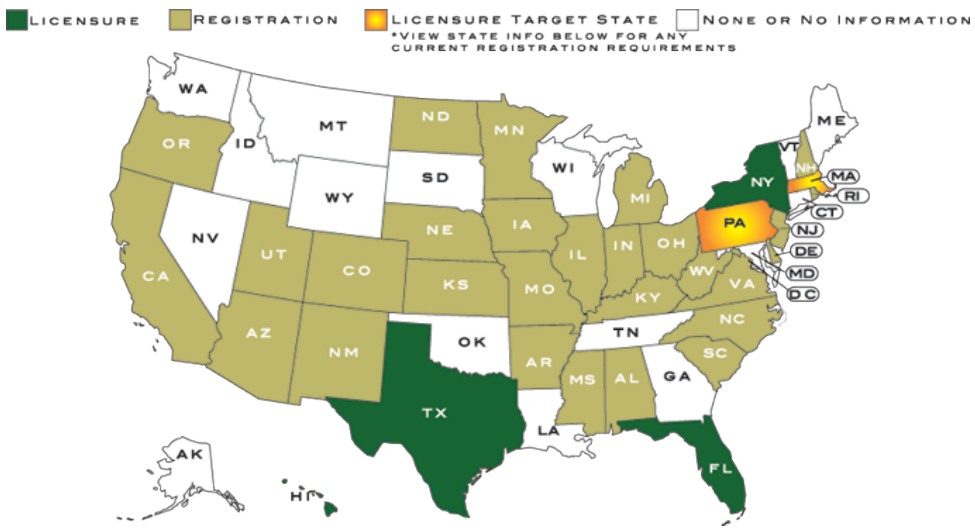


**Figure 11 Medical Physicist Regulations and Licensures by State**
**Source: Retrieve from http://www.aapm.org/government_affairs/licensure/default.asp July 15, 2013**

## *Methods of Analysis and Limitations*

The analysis of the practice guidelines was facilitated by using the text analysis software Nvivo, which supports qualitative research by allowing the search of words in multiple documents at the same time, coding entire documents or parts of documents for different classifications, running the frequency of words in and among documents, and many other functions.

In order to find when the techniques were implemented first, the initial objective was to identify when the guidelines were first published. The first classification used with the practice guidelines was time. Because many of the guidelines have been reviewed and/or have different iterations, I also classified them per version. In order to do this I searched for older versions in the official journals of the societies. However, I found that not all the guidelines were published in the society journals, and in some case the files for a guideline are not the same as on journal and in the website, although the content may be almost identical.

The guidelines were also compared by topic, using the classification that the websites provide, and then paired one to one to see if they had analogous guidelines in the other region. They were further classified as diagnostic, therapy or general, based on the intended purpose of the procedure. Classified as general or miscellaneous were guidelines such as the guideline for guideline development, practice of good reports in dosimetry, or the ones about preparation of medication and radiopharmacy. This classification makes visible distinctions between the different uses of nuclear medicine between regions.

Finally, using the features of Nvivo, I searched for names of different radionuclides across the guidelines. For example, the radionuclide Technetium 99m was searched as *Tc-99m or 99m-Tc or 99m-Technetium*, and coded under the same category every time it appeared in a guideline. This allowed me to evaluate when the radionuclide technologies introduced in the guidelines were published, what radionuclides are used in the regions, and how they are being used for diagnostic and therapy purposes.

For the bibliometric analysis I used the bibliometric software Vantage Point (VP). After downloading the records from the different databases, I merged the records in VP, then cleaned the list of titles to assure that the records were not duplicated. Sometimes, the same titles had different uses of capital letters or periods, which was easy to fix with a "clean list" query already provided by the software. After that, I merged the duplicate data so it retained the different information provided from the different databases. Then I merged the fields of country and country of affiliation to assure all the records had this field. The same procedure was done with the year. These were the only two fields of interest since the information I needed was region and date of publication. I cleaned the names of countries for different spellings such as *The Netherlands* and *Netherlands.* Then I proceeded with the analysis and results, which are presented in the following chapter.

The analysis of the policies is qualitative, and no special software or text analysis was done. It focused on the relationships that the policies have with NM and how they affect the implementation of radionuclide therapy techniques. This analysis is presented in the following chapter after the results of the practice guidelines and bibliometric analysis, and leads to the conclusions of the project.

Because the data for this project is limited to the information publicly available on the Internet, and the time frame to develop the project is constrained, the analysis is more descriptive than explanatory. It is focused on understanding the state of the art of nuclear medicine as a practice and particularly the use or implementation of radionuclide therapy. The study has produced observations of differences in the policy context that inform the variations in adoption of the practice; full exploration of the causal connections would

require a larger study. The following chapter undertakes an explanation of how the differences in policy are related to the differences in time of implementation.

# CHAPTER 4 – ANALYSIS AND FINDINGS

Up to this point, chapter two explains the details of the science and the variety of publications that mention NM and policy. This chapter also clarifies why NM is different from all other medical fields, and how little has been written about the importance of the field and the policies that surround it. Chapter three describes the data used to test the hypothesis that Europe implements radionuclide therapy technology before and more than the US because of the regions' different policy environments. The data for the dependent variable, time and quantity of implementation, consists of the practice guidelines from the different professional societies and the publications of case reports. The data for the independent variable consists of policies that affect the nuclear medicine field. Chapter three explains in detail how the data was selected and what the plan of analysis is. Now I present the results of the analysis, and the findings.

## *Results*

### Practice Guidelines

After carefully coding the 103 practice guidelines from EANM and SNM in the Nvivo software, and adding additional information such as older versions of the same practice guideline, I proceeded to analyze the data. The first inquiry was the time of implementation of the different nuclear medicine techniques; in order to do it I checked for the date of publication of the different guidelines. Table 5 shows the number of guidelines published each year and the version of each guideline. From the table it is easy to notice that SNM has guidelines with more iterations than the EANM. All the EANM guidelines are first or second versions. Europe has an especially high productivity in 2009-2010. One of the guidelines with version 6 for SNM is the joint "SNM/EANM Guideline for Guideline Development 6.0" which is version 6 for SNM but not for

EANM. The first version was published by SNM in 1996. For this reason it was not counted as an old version for the EANM case. The information about older versions was obtained mainly through the search of the guidelines in the official journals of the associations.

**Table 6: Number of guidelines and versions by year of publication**

| Year | Europe | | | USA | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Version | | Total | Version | | | | | | Total |
| | 1 | 2 | | 1 | 2 | 3 | 4 | 5 | 6 | |
| 1999 | 0 | 0 | **0** | 1 | 1 | 0 | 0 | 0 | 0 | **2** |
| 2000 | 1 | 0 | **1** | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| 2001 | 0 | 0 | **0** | 0 | 0 | 1 | 0 | 0 | 0 | **1** |
| 2002 | 3 | 0 | **3** | 2 | 0 | 1 | 0 | 0 | 0 | **3** |
| 2003 | 4 | 0 | **4** | 0 | 0 | 6 | 0 | 0 | 0 | **6** |
| 2004 | 0 | 0 | **0** | 0 | 1 | 3 | 0 | 0 | 0 | **4** |
| 2005 | 1 | 0 | **1** | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| 2006 | 2 | 0 | **2** | 1 | 0 | 3 | 0 | 0 | 0 | **4** |
| 2007 | 3 | 1 | **4** | 0 | 0 | 0 | 1 | 0 | 0 | **1** |
| 2008 | 4 | 2 | **6** | 0 | 0 | 2 | 0 | 0 | 0 | **2** |
| 2009 | 7 | 4 | **11** | 1 | 0 | 3 | 0 | 4 | 0 | **8** |
| 2010 | 11 | 1 | **12** | 2 | 0 | 0 | 1 | 3 | 1 | **7** |
| 2011 | 2 | 1 | **3** | 1 | 1 | 1 | 0 | 1 | 0 | **4** |
| 2012 | 2 | 0 | **2** | 0 | 1 | 1 | 2 | 0 | 1 | **5** |
| 2013 | 3 | 0 | **3** | 0 | 0 | 0 | 0 | 0 | 0 | **0** |
| Total | 43 | 9 | **52** | 8 | 4 | 21 | 4 | 8 | 2 | **47** |

Based on the year of publications of the first guidelines (version 1), the US clearly moved earlier than the EU in the NM field. Table 7 presents the years in which the guidelines with more than one version were published. This table provides evidence that the SNM started working in practice guidelines at least 6 years before the EANM. There are two cases for each association where the first version of the guideline was not available. 1996 and 1997 seem especially productive for SMN. Having in mind that the SNM was founded in 1954, and the EANM in 1985, it is understandable the delay in the production of practice guidelines by the EANM. Additionally, in 1989 the Agency for

Healthcare and Policy and Research was created in US, and in 1990 the National Academy of Science published "Clinical Practice Guidelines: Directions for a New Program" (Field & Lohr, 1990). These two events incentivized the creation of practice guidelines in the different medical fields, and that may explain the increase in practice guideline production in US in the mid-1990s. In conclusion, the US field began publishing procedures in nuclear medicine before the EU; however, the EU has more practice guidelines today.

**Table 7: Year of first publication of guidelines with more than one version**

| Fist Version | Europe | US |
|---|---|---|
| **1994** | 0 | 1 |
| **1995** | 0 | 4 |
| **1996** | 0 | 11 |
| **1997** | 0 | 10 |
| **1998** | 0 | 5 |
| **1999** | 0 | 3 |
| **2000** | 1 | 0 |
| **2001** | 0 | 1 |
| **2002** | 2 | 1 |
| **2003** | 4 | 1 |
| **Unknown** | 2 | 2 |

Moving towards the content analysis of guidelines, I compared the classifications that each society has for them (Table 1). Although there are many classifications that are comparable or the same, such as cardiology from EANM and cardiac from SNM, there are some that are very different. For example, there are differences in the way the two societies classify oncologic procedures. In the SNM classification they include diagnostic and therapeutic procedures, while the EANM divides these procedures in two; the oncology classification contains all the diagnostic images, and in the radionuclide therapy classification you can find all the therapies, not all of which are cancer related. EANM

also has categories the SNM doesn't have; moreover, SMN doesn't have any guidelines that cover some of those topics; for example, there are not specific guidelines in dosimetry in the SMN, while the dosimetry section of EANM has five practice guidelines; one of them is a heavy math supplement of one of the other guidelines.

Although some of the extra classifications from the EANM are guidelines for doctors, some others are intended for other professionals in the nuclear medicine field, or are for procedures that do not involve direct interaction with the patient, like the physics section and the radiopharmacist section.

In order to check for the differences between the practice guidelines between the two regions, I paired them by procedure, taking into account type of procedure, anatomical specifications and radioactive material use. There are 10 guidelines in SNM that don't have a pair in EANM, but they are all related to diagnostic procedures. There are 28 EANM guidelines that don't have a pair in SNM. These include guidelines for how to introduce a new drug into the EU market, and several guides in dosimetry, but the main difference is in guidelines related with oncology and therapy. This provides evidence that the EU is working in a wider spectrum of topics than the US.

Additionally, I coded each guideline in Nvivo as diagnostic, therapy or general (miscellaneous information). Table 8 shows the results of this counting. SNM has more diagnostic guidelines than EANM, but EANM has five times more practice guidelines in therapy. In the general category, there is one joint guideline that is counted for both regions, but EANM has more guidelines in this aspect. Although in general, EANM has more guidelines, the big difference in guidelines for therapy is interesting, and it gives evidence that the fields are not level for this part of the practice between the regions.

Additionally, SNM has more guidelines in the diagnostic areas, but some of these guidelines come from the collaboration with the ACR, and overlap with other SNM-only guidelines, so this does not necessarily show more technologies adopted by the SNM in the diagnostic part of the practice.

**Table 8: Type of practice guideline procedure by region**

| | Europe | US |
|---|---|---|
| Diagnostic | 32 | 40 |
| General-miscellaneous | 9 | 7 |
| Therapy | 13 | 2 |

The two guidelines from SNM endorsed by EANM listed in Table 2 are diagnostic, and from the three guides from EANM endorsed by SNM, two of them are therapy related, and one is diagnostic. Furthermore, the SNM has the following warning for the endorsed guidelines: *"Applicable in the United States: The radiopharmaceutical(s) used for the diagnostic and therapeutic procedure(s) addressed in this guideline/guidance document is/are not approved by the Food and Drug Administration (FDA) in the United States. Therefore in the United States, these procedures should be performed only by physicians holding an FDA-approved Investigational New Drug (IND) application for the radiopharmaceutical."* This indicates that the practices that they endorse are not routinely procedures for the type of illness for which these procedures are prescribed in Europe. Additionally, the three guidelines were published by EANM in 2006, 2008 and 2010, but they were endorsed by SNM only in 2012.

EANM also has a warning for the SNM guidelines they endorse, which states "*EANM endorses these guidelines. Dosage recommendations should be taken in the context of "good practice "of nuclear medicine and do not substitute for national and*

*international legal or regulatory provisions. The use of administered activities as reported in the EANM dosage card is suggested.*" EANM doesn't have a date for the endorsement of the SNM guidelines that were published in 2010. The warning messages between the two organizations are very different, and provide evidence for the differences in implementation between the regions.

Table 9 describes when the guidelines were published by type of guideline. It is easy to see that the two guidelines for therapy from the SNM were published nine years apart, of difference while the EANM has been publishing therapy guidelines since 2002 in a very regular manner. EANM has a peak in the publication of therapies in 2008 with 4 publications, and a peak in the publication of diagnostic guidelines in 2009, with 11. The publications regarding diagnostic images from the SNM are continuously distributed in time, with a peak in 2009-2010. There is a great difference in the production of therapy guidelines between the two regions, but much less difference in the guidelines for diagnostic images. In the case of the general topics, it seems that it is a more recent preoccupation for EANM, while SNM has had this type of guideline for a longer time. There seems to be an unusual incentive in 2009 for the EANM because the production of diagnostic practice guidelines has a peak.

From this table is also clear that the high level of publication of EANM is not from a single time period, it is something that has been evolving, and the 13 guidelines for radionuclide therapy they have are the collection of knowledge over the years. This is an evidence of more and earlier implementation of radionuclide therapy techniques. For EANM the years of low production of therapy guidelines are years of low production in general, except for 2009. It seems that SNM doesn't have incentives for the production of

therapeutic guidelines. Based on the disclaimers on the endorsed guidelines, this lack of incentive to create their own guidelines is based on the fact that many of the drugs needed for the therapies are not approved, or are still under study by FDA.

**Table 9: Type of practice guideline in time**

| YEAR | EU Therapy | US Therapy | EU General | US General | EU Diagnostic | US Diagnostic |
|---|---|---|---|---|---|---|
| **1999** | 0 | 0 | 0 | 0 | 0 | **2** |
| **2000** | 0 | 0 | 0 | 0 | **2** | 0 |
| **2001** | 0 | 0 | 0 | 0 | 0 | **1** |
| **2002** | **1** | 0 | 0 | **1** | **2** | **2** |
| **2003** | **1** | **1** | 0 | **1** | **3** | **4** |
| **2004** | 0 | 0 | 0 | 0 | 0 | **4** |
| **2005** | 0 | 0 | 0 | 0 | **1** | 0 |
| **2006** | **1** | 0 | 0 | 0 | **1** | **4** |
| **2007** | **1** | 0 | **1** | **1** | **2** | 0 |
| **2008** | **4** | 0 | **1** | 0 | **1** | **2** |
| **2009** | 0 | 0 | 0 | 0 | **11** | **8** |
| **2010** | **2** | 0 | **4** | **2** | **6** | **7** |
| **2011** | **1** | 0 | 0 | **1** | **2** | **3** |
| **2012** | 0 | **1** | **1** | **1** | **1** | **3** |
| **2013** | **2** | 0 | **1** | 0 | 0 | 0 |

Summarizing up to this point, the US was the first to move to publish practice guidelines; however, most of their publications are focused on diagnostic procedures. The EU on the other hand, has been working in radionuclide therapies for a little longer than the US, but it has published a lot more guidelines related to this topic, which suggest that the EU has implemented radionuclide therapy technology more fully. In order to check if the guidelines were not only different in the type of procedure (diagnostic, therapy or general), but in the radionuclide material involved in the procedure, I analyzed the content and the radioisotopes used in the guidelines.

In order to find the radionuclides mentioned in each guideline, the eleven radionuclides of interest were searched among the guidelines with the "word search" function of Nvivo. Each search found where in the documents the radionuclides were mentioned. The selection of the radionuclides of interest was based on the previous exploration of the documents and the query of frequency of words (also run in Nvivo) to find what isotopes were mentioned in general. The search was done by the isotope but not by the radiopharmaceutical product, so it is possible that the regions are using the same isotope with different ligand/molecules for different purposes. Table 10 shows the 11 isotopes used in the searches and the number of practice guidelines in each region that mention each isotope. From the table it is easy to notice that there are three isotopes that are not mentioned in any of the SNM guidelines, while EANM mentions all the isotopes at least once. The only isotope that the SNM mentions in more guidelines than EANM is Tc-99m, the most traditional isotope for nuclear medicine diagnostic images.

**Table 10: Isotopes in EANM and SNM Guidelines**

| Isotope | EU | US |
|---|---|---|
| **I-124/123** | 18 | 8 |
| **I-131** | 20 | 16 |
| **In-111** | 26 | 20 |
| **Lu-177** | 3 | 0 |
| **P-32** | 1 | 1 |
| **Re-186** | 4 | 0 |
| **Sm-153** | 3 | 2 |
| **Sr-89** | 3 | 3 |
| **Tc-99m** | 24 | 31 |
| **Y-90** | 7 | 0 |
| **F-18** | 11 | 6 |

There is not only a diference in the number of guidelines that use radioisotopes, which is expected up to some point because EANM has more guidelines in general than SNM, but the way they use them and refer to them is different. Table 11 shows in what

types of practice guidelines the isotopes are mentioned. The isotopes that are not mentioned in any of the SNM guidelines (Lu-177, Re-186, and Y-90) are mentioned mostly in radionuclide therapy guidelines of the EANM. The isotopes that are more often mentioned in SNM guidelines (Tc-99m, In-111, and I-131) are mainly mentioned in relation to diagnostic images, although I-131 is one of the most comon and traditional isotopes used for thyroid therapies. One of the guidelines for therapy with I-131, "EANM procedure guidelines for 131I-meta-iodobenzylguanidine (131I-mIBG) therapy," is endorsed by SNM and was published for the first time by EANM in 2003, and secondly in 2008, but was endorsed by SNM in 2012. The active ingredient in this therapy is Meta-iodobenzylguanidine, or Iobenguane; Iobenguane was approved by the FDA in 1994, but it is currently discontinued. Meta-iodobenzylguanidine does not appear in the approved drugs dataset of the FDA (FDA, n.d.-a). The lack of clarity in the status of this therapy may create confusion for the new professionals trying to start their careers in this field, and for patients looking for information on these types of resources, and this may contribute to the delay in the time of implementation of radionuclide therapy techniques.

**Table 11: Mention of the different isotopes in the EANM and SNM guidelines**

| | Diagnostic | | Therapy | | General | |
|---|---|---|---|---|---|---|
| | **EU** | **US** | **EU** | **US** | **EU** | **US** |
| F-18 | 10 | 5 | 0 | 1 | 1 | 0 |
| I-124-123 | 11 | 6 | 6 | 1 | 1 | 1 |
| I-131 | 8 | 12 | 8 | 2 | 4 | 3 |
| In-111 | 14 | 17 | 8 | 1 | 4 | 2 |
| Lu-177 | 1 | 0 | 2 | 0 | 0 | 0 |
| P-32 | 0 | 0 | 1 | 1 | 0 | 0 |
| Re-186 | 1 | 0 | 3 | 0 | 0 | 0 |
| Sm-153 | 1 | 0 | 2 | 2 | 0 | 0 |
| Sr-89 | 1 | 1 | 2 | 2 | 0 | 0 |
| Tc-99m | 20 | 29 | 2 | 0 | 2 | 2 |
| Y-90 | 1 | 0 | 5 | 0 | 1 | 0 |

Another example of these differences is in one of the 2011 SNM guidelines that mentions I-123, stating that "…this agent [123I-ioflupane] has **shown efficacy for detecting** degeneration of the dopaminergic nigrostriatal pathway, allowing better separation of patients with essential tremor from those with presynaptic Parkinsonian syndromes, **as well as differentiating** between some causes of parkinsonism." Later in the same document they say that "123I-ioflupane (123I-FP-CIT) is a SPECT tracer, licensed by the European Medicines Agency and available in Europe since 2000. In the United States, 123I-ioflupane was approved by the Food and Drug Administration on January 2011 and is commercially available (22). This guideline covers the indications, technical aspects, interpretation, and reporting of DaT SPECT scans with 123I-ioflupane and considers the work of the European Association of Nuclear Medicine (23)" (Djang et al., 2012). With these statements the SNM acknowledges the benefits of this therapeuthic technique, and the delay in its implementation in the US.

Another good example is the Y-90 iosotpe. Although there are no guidelines from SNM that mention it, they have endorsed one that mentions this isotope. The guideline was published in 2006 by EANM. The summary of the guideline explains the success of these therapies, and the experience that they have had with it. "EMEA [European Medicines Agency] **has approved** 90Y-radiolabelled ibritumomab tiuxetan, Zevalin®, in Europe for the treatment of adult patients with rituximab-relapsed or -refractory CD20+ follicular B- cell non-Hodgkin´s lymphoma (NHL) in January 2004. The number of European nuclear medicine departments using Zevalin® **is continuously increasing, since the therapy is often considered successful**" (Giammarile, Lassmann, Oyen, & Brans, 2004). Based on the disclaimer that SNM uses for the EANM guidelines they

endorse, this procedure hasn't been approved by the FDA. Nevertheless, FDA has approved Zevalin® since 2002, as shown in the database of approved drugs (FDA, n.d.-b). Once again, the information between the guidelines, the disclaimers, and what FDA approves is conflicting.

As a final example of the difference between the fields, the guideline published in collaboration among EANM, SNM and IAEA is for neuroendocrine tumor therapy. This guideline is not published on the SNM website, and mentions two of the isotopes that aren't present in other SNM guidelines. The introduction mentions that

> *"[p]eptide receptor radionuclide therapy (PRRNT) is a molecularly targeted radiation therapy involving the systemic administration of a radiolabelled peptide* ***designed to target with high affinity and specificity receptors overexpressed on tumours****. PRRNT employing the radiotagged somatostatin receptor agonists 90Y-DOTATOC([90Y-DOTA0,Tyr3]-octreotide) or 177Lu-DOTATATE ([177Lu-DOTA0,Tyr3,Thr8]-octreotide or [177Lu-DOTA0,Tyr3]-octreotate)* ***have been successfully used for the past 15 years to target metastatic or inoperable neuroendocrine tumours expressing the somatostatin receptor.****"*

Later in the same introduction they mention the regulatory issues with a special section for US.

> *"The radiopharmaceuticals used for the diagnostic and therapeutic procedures addressed in this guidance document are not approved by the Food and Drug Administration (FDA) in the USA. Therefore in the USA these procedures should be performed only by physicians enrolled in an investigational protocol pursuant to a valid Investigational New Drug application or Radioactive Drug Research Committee approval and under the purview of an appropriate institutional review board."*

This particular example is interesting because it is about the same technology mentioned in the paper "Radiopeptide Imaging and Therapy in the United States" by Michael M. Graham and Yusuf Menda in 2011, where they state that

> *"[t]he regulatory requirements in the United States also restrict access to several radionuclide peptides that are being used as clinical tools in a growing number of institutions across Europe. This issue is potentially critical for patients who may benefit from PRRT and need to travel to Europe for this treatment. Future attempts to balance the effort in the field with appropriate clinical trials are important so that at least some of these remarkable agents can be made available to patients in the United States."*

This paper received a response from Peeyush Bhargava and Ebrahim S Delpassand in May, 2012 saying that they have two clinical trials going on in this topic since 2010 in the US. The differences in information, plus the fact that the joint guideline says that this practice has been going on for more than 15 years, shows how the information and knowledge flows are dissimilar within each region and between regions.

While the European guidelines are clear about the approval situation of new drugs, and there are no guidelines for the use of non-approved radiopharmaceuticals, the US case is very different with several guidelines that overlap in topic, and special miscommunications regarding the approval status of the drugs. The communication factor among professionals in a field was a particularly important factor for the Canandian study of breast cancer tehcniques by Wright about technology implementation (Wright et al., 2011). It is difficult to implement new technologies if there is no good communication among professionals. From the results of the therapy guidelines analysis, and the papers review in the topic the communication among professionals may be one of the reasons for variations in the time of implementation of new technologies in the radionuclide therapy field.

Up to here, I have presented the results of the analysis of the practice guidelines of the European and American professional soceties of nuclear medicine in time and content. One of the most important findings is that Europe has published more practice

guidelines that cover different types of radionuclide therapy, although the US started publishing procedures before Europe did. Because Europe has implemented more variations of radionuclide therapies, and having in mind the endoresed guidelines, it is possible to say that the EU has implemented these technologies more fully than the US. In order to confirm and support these results, the next section presents the results of the bibliometric analysis.

## Bibliometric Analysis of Case Reports

The results found in the bibliometric analysis reinforce those previously shown in practice guidelines. Europe has implemented radionuclide therapies before and more than the US. For the bibliometric analysis four databases were consulted: Pubmed, Medline, Biosis Preview, and ISI Web of Knowledge with a total of 103 unique publications. Of these publications, 64 are published in Europe, meaning that the country or country of affiliation of the bilbiometric data is a European Union country. There are 26 publications that are from US, or have some US affiliation. There are 2 publications that are Europe and US affiliated, both from the same authors. Figure 12 shows how the first publication that complies with the keyword search in Europe appeared almost ten years before the first case report from the US. There is also a general increase of these publications since 2000. There are a couple of years when the EU did not publish case reports; however, there are eight years when the US did not publish case reports on radionuclide therapies. In 2002 the US has more publications in a diverse line of topics whithin radionuclide therapy, while the peak year of publications for the EU was 2012, and from the nine EU publications in that year seven were focused in neuroendocrine cancers and peptide receptors, one of the lates techniques in radionuclide therapies.

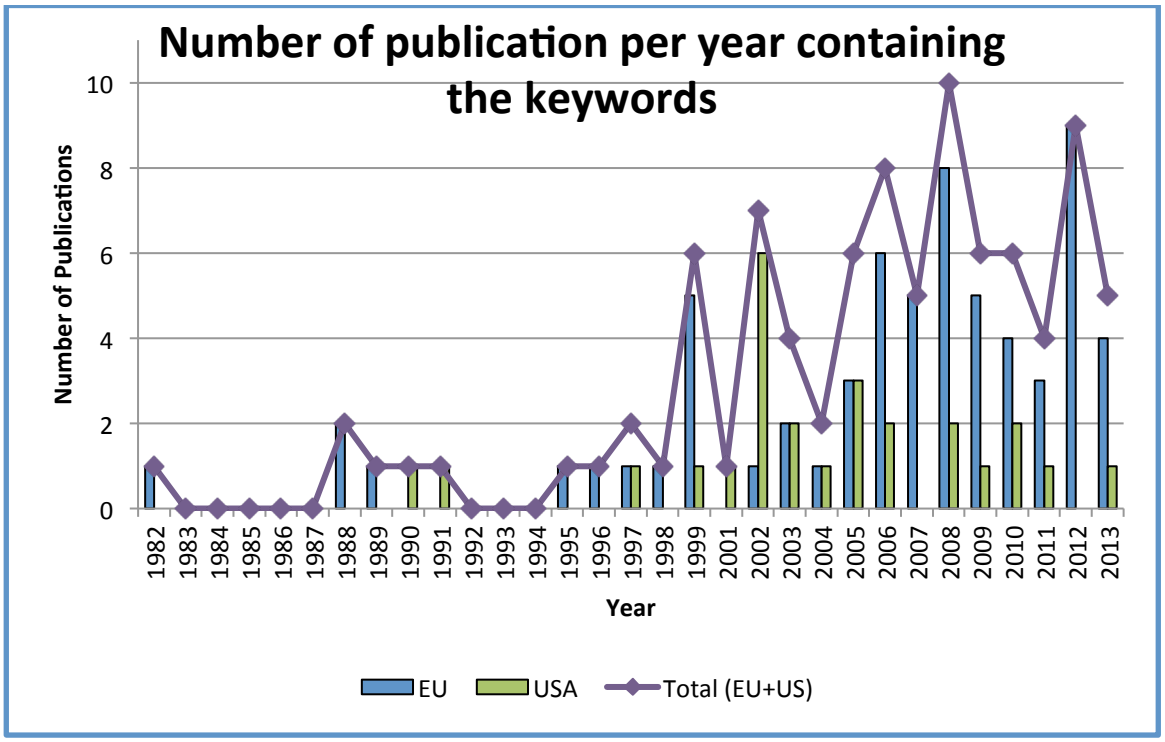


**Figure 12 Bibliometric Results**

It is clear that the time of implementation of radionuclide therapies is different between the US and the EU. The EU has more practice guidelines about these techniques, and more case reports published on radionuclide therapy techniques. Additionally to these differences in implementation of new technologies in radionuclide therapies, there are differences in the policies and regulations on NM that may account for the implementation dissimilarity.

There are three main policy fields whose the differences may impact the difference in time of implementation of radionuclide techolgies in NM. These are the difference in education policies for NM specialists, the production of isotopes for medical use, and the regulations for approval of new radiopharmaceutical drugs. The education policies are important because NM, and specially radionuclide therapies, are technologies that need to be implemented by a highly educated team in different areas such as medicine, physics, and pharmacy. The availability of the primary material for

radionuclide tharapies is also a determinant of the existence of the technology in a region; without a good suppply of radioisotopes there is no posibility of implementation of the technique. Finally, the lack of clarity in the procedures for the approval of radiopharmaceutical drugs delays the time of implementation of the technology and prevents innovation and knowledge transfer in this area. In the last chapter I will analyze in detail how each of these policy fields may affect the implementation of radionuclide therapies, and the implications of these effects.

# CHAPTER 5 – DISCUSSION AND CONCLUSIONS

This project started with the question: Are radionuclide therapies implemented before in the EU than the US? In order to answer that, I assumed that the practice guidelines and publications of radionuclide therapy case reports were evidence of implementation; therefore, I am able to conclude that the EU has implemented radionuclide therapies earlier and more fully than the US. This result was followed by the second question: What differences are there in policies relevant to nuclear medicine between the US and the EU? I was able to identify key international organizations that may affect the policy environment in nuclear medicine as well as key differences in the policy arena between the EU and the US. These key differences are in education, the supply of radioactive materials, and radiopharmaceutical drug approval policies. Now I will discuss the answers to the last two questions of this project: To what extent, if at all, can the differences in policies explain differences in the time of implementation of radionuclide therapies? And what other factors might explain these differences in the time of implementation?

## *The Education Barrier*

First, education is very important in the field of NM because a well-educated staff not only assures the safety of the service, but also is up to date with the field research and techniques. As I showed in chapter 2, NM is a very specialized field of medicine that needs the support of very specialized professionals in physics and chemistry, as well as trained technicians and nurses that need to know about radiation protection in order to have a safe practice. The main difference between training in nuclear medicine in the US and the EU is that physicians who finish the preparation to become NM specialists in the

US don't have all the same background. In US you can be a nuclear radiologist and never have to do a therapy or be a nuclear medicine specialist and work in diagnosis and therapy. The editorial by H. Ziessman in the Journal of Nuclear Medicine in 2012 (Ziessman, 2012) explains the difference between the Nuclear Medicine Residency and the Nuclear Radiology Fellowship. The first one is accredited by the American Board of Nuclear Medicine while the fellowship one is a certification in Nuclear Radiology. Although he mentions that the number of candidates for the residency is an average of 55 vs 5 from the fellowship, the fact that there are two professional organizations competing for students under different requirements is not positive for the field. One of the main differences in the standards between the fellowship and the residency used to be the presence of "radionuclide therapies" in the standards of education; it used to be a requirement for the residency, but not for the fellowship, but since 2012 the fellowship is trying to incorporate the therapies in to the curriculum. The lack of knowledge of some nuclear medicine specialists about radionuclide therapy techniques may explain the increased focus of US professionals on diagnostic techniques and PET, and the late implementation in therapy. The EU, on the other hand, has a proposed syllabus in NM that is intended to privide standardization in the education of physicians, and that contains a broader spectrum of the field including radionuclide therapies (Cuocolo, Milcinski, & Bischof Delaloye, 2008; Prigent, Huic, & Costa, 2012).

In addition to the education of medical practitioners, the education and certifications required in the medical physics and radiopharmacy professions may influence the development of the field of NM. In the EU the presence of a medical physicist is required in order to do a radionuclide therapy. This was established in

EURATOM. In the US the principal focus of the medical physicist is radiotherapy, and regulation is not consistent nationwide, as these certifications vary at the state level. Additionally, there are very few radiopharmacy programs in the US. The lack of these professionals in the NM practices means they don't bring knowledge and innovation, which interferes with the development and implementation of radionuclide therapies in the US.

### *The Market Failure*

The lack of supply of radioactive isotopes, the primary material for radionuclide therapies, interferes with the implementation of this technique. The production of the radioisotopes used in nuclear medicine is done in nuclear reactors, and the supply of these isotopes is often subsidized by governments because of the high cost and risk associated with their production. However, there is not enough research on how this market works, and on less expensive and risky ways to produce radioisotopes. Having in mind that US technetium depends on a Canadian nuclear reactor that may be decommissioned in few years, and that US research reactors produce only small quantities of radioactive material, it is difficult to imagine what the future of this field in the US will be if there is not enough supply. The bill S. 99 (112th): American Medical Isotopes Production Act of 2011 was proposed as a solution to this problem, but died after passing the Senate in 2011. Meanwhile, Canada has invested in R&D to solve the technetium availability problem and as a result a PhD researched and found a way to produced technetium in a cyclotron (Gagnon, 2012), but it may take years until this technology is available, and it doesn't solve the problem of producing radionuclides for therapy. The low reliability of the supply of medical isotopes in the US may have shifted

the interest of NM professionals to PET applications where the isotope production can be controlled easily because they can be produced in hospitals and at the levels that are convenient for each institution. Moreover, the market model works better in this part of the NM practice, because the technology is cheaper (compared with the construction of a nuclear reactor), the risk is lower, and private investors such as clinics are able to participate.

There are more nuclear reactors in the EU that produce radioisotopes for medical use, and the uranium market for energy and isotope production is controlled in order to ensure availability in the participant countries. Additionally, in the EU the different approach that the countries take toward nuclear reactor scenario is less likely to affect the country supply of radioactive material because in a region with a great variety of countries there are also a great variety of approaches to the "nuclear reactor" problem.

The issue of supply of radioactive materials for NM is a complicated issue and deserves a lot of study and attention, and besides the OECD-NEA there are not a lot of efforts to study the medical radioisotope market.

### *The Regulatory Path Complications*

The US not only needs to deal with the lack of supply of radioisotopes for therapeutic use, but with a lack of clarity in the FDA about the path for approval of radionuclide therapies, and this may slow down the implementation of radionuclide therapy technologies in the US. The role of the FDA and its policies on radionuclide therapies is continuously mentioned in the publications about nuclear medicine from the Academies of Science and other academic papers, which often make reference to the lack of clarity about the approval of radiopharmaceuticals.

Contrary to the US, the EU has a unified system of approval for radiopharmaceutical drugs, and the professional society provides a route map for researchers that want to make a drug available in the EU. These types of tools are invaluable for the transfer of technology and knowledge from the lab to the medical center, and they facilitate the implementation of new technologies.

### *Other Possible Explanations*

One thing that caught my attention during the development of this project is that the US professional field showed signals of problems in communication and coordination within the field. This may not only explain the lack of implementation of radionuclide technology, but also account for some of the policy issues, because if there are conflicts among the professionals in the field it is difficult to find the coalitions that would move forward the policies needed for the development of the field. This is evident in the confusing information about clinical trials, approved drugs, paths for drug approval, and overlapping practice guidelines. All these conflicts in information impede the flow of knowledge among practitioners, scientists, and patients.

If there is a lack of communication among professionals, as the one perceived in the literature review, this would not only slow down the implementation of new technologies, but would prevent professionals in NM from coming together as a field to shape the policies that affect them. This is especially evident with the FDA, because it is still complicated to find and understand their policies on radionuclide materials, and in the lack of solutions for the production of radioactive isotopes in US since the bill S. 99 (112th): American Medical Isotopes Production Act of 2011 didn't pass and nothing else has been proposed since then.

The other problem in communication and coordination among professionals is the relationship between Radiology and Nuclear Medicine in the US. Ziessman, in an editorial mentioned above, finishes by saying that

> *"Radiology leadership has never fully accepted nuclear medicine as an independent specialty and considers it a subspecialty of radiology. However, the ACGME and ABMS consider nuclear medicine a primary specialty. It is time for radiology leadership to begin to work together with nuclear medicine to devise the best educational experience to train future nuclear medicine physicians and to certify them."*

With this statement, he recognizes that there is a problem with the two fields trying to complete, and part of the result of that competition may be the lack of implementation of radionuclide therapies in US.

The poor communication among professionals in the field may be playing a bigger role that it appears in my documentation analysis. There are other methods to measure and explore that, which are not part of this project, but which may be of interest for the future.

## *Conclusion*

This project aimed to explain the particularities of nuclear medicine, its role in the medical field, and more specifically the use of radionuclide therapies in nuclear medicine. I found that there are important differences in time and types of implementation of radionuclide therapies between the EU and the US, and this was demonstrated through the date of publication and content of practice guidelines and case report publications. Europe has more practice guidelines in radionuclide therapies and has published them more often, while the US started publishing earlier but has only written two practice guidelines in this field versus 13 by the EU.

The variations in implementation between the regions were then analyzed from the policy aspect and I found three main policy fields that may be affecting the implementation of these techniques in US. First, the variety of standards in nuclear medicine education; second, the unreliable supply of radionuclide material in the US, and third the confusing regulatory path for radiopharmaceuticals for therapies. As an additional explanation, I proposed the poor communication flow among professionals in the nuclear medicine field, which was evident in the documentation analysis but would need to be explored further in the future.

It is important to continue exploring why nuclear medicine therapies are implemented slowly in the US, and to make an effort to standardize education and credentials for the different professionals involved in this field. It is also very important to solve the supply problem of radionuclide materials in the US. Without policies to incentivize the production of radioisotopes for medical use and/or the use of Low Enriched Uranium or other techniques for the production of nuclear medicine supplies, there is going to be a bigger delay in the implementation of radionuclide therapies. Moreover, without policies that confront this problem the whole practice may be at risk, and those most affected will be the patients that benefit from this practice. Finally, a clear path for radionuclide drug approval by FDA will benefit the knowledge transfer process from the lab to the practice in nuclear medicine.

In conclusion, radionuclide therapy is a technology whose implementation is behind in the US compared with the EU, and this is due to problems in the standardization of education, lack of supply of radioactive materials, and confusing regulatory policies in the FDA. If the US does not act in order to solve these problems,

the practice will keep being behind in radionuclide therapy and potentially in other parts of the NM practice as well.

# APPENDIX A: List of Practice Guidelines

| SNM Practice Guidelines | Date Approved |
|---|---|
| **Cardiac** | |
| Procedure Guideline for Myocardial Perfusion Imaging | 9/1/08 |
| Society of Nuclear Medicine Procedure Guideline for Gated Equilibrium Radionuclide Ventriculography | 6/15/02 |
| **Endocrine** | |
| SNM Practice Guideline for Parathyroid Scintigraphy | 9/17/11 |
| Society of Nuclear Medicine Procedure Guideline for Thyroid Scintigraphy | 9/10/06 |
| Society of Nuclear Medicine Procedure Guideline for Scintigraphy for Differentiated Papillary and Follicular Thyroid Cancer | 9/5/06 |
| Society of Nuclear Medicine Procedure Guideline for Thyroid Uptake Measurement | 9/5/06 |
| **Gastrointestinal** | |
| SNM Practice Guideline for Hepatobiliary Scintigraphy | 6/4/10 |
| Procedure Guideline for Adult Solid-Meal Gastric-Emptying Study | 2/8/09 |
| Society of Nuclear Medicine Procedure Guideline for Hepatic and Splenic Imaging | 6/20/03 |
| **General** | |
| SNM/EANM Guideline for Guideline Development 6.0 | 6/8/12 |
| Clinical Performance Standards FOR THE NUCLEAR MEDICINE TECHNOLOGIST (Revision 2011) | 5/11/11 |
| THE SNM PROCEDURE GUIDELINE FOR GENERAL IMAGING 6.0 | 9/12/10 |
| Procedure Guideline for the Use of Radiopharmaceuticals | 2/7/08 |
| Society of Nuclear Medicine Procedure Guideline for Diagnosis of Renovascular Hypertension | 6/20/03 |
| Society of Nuclear Medicine Procedure Guideline for Telenuclear Medicine | 6/15/02 |
| **Infection** | |
| Society of Nuclear Medicine Procedure Guideline for Gallium Scintigraphy in Inflammation | 6/2/04 |
| Society of Nuclear Medicine Procedure Guideline for 99mTc-Exametazime (HMPAO)-Labeled Leukocyte Scintigraphy for Suspected Infection/Inflammation | 6/2/04 |

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| Society of Nuclear Medicine Procedure Guideline for 111In-Leukocyte Scintigraphy for Suspected Infection/Inflammation | 6/2/04 |
| **Musculoskeletal** | |
| SNM Practice Guideline for Sodium 18F-Fluoride PET/CT Bone Scans | 12/2/10 |
| Society of Nuclear Medicine Procedure Guideline for Bone Scintigraphy | 6/20/03 |
| **Neurology** | |
| SNM Practice Guideline for Brain Death Scintigraphy | 6/8/12 |
| SNM Practice Guideline for Dopamine Transporter Imaging with 123I-Ioflupane SPECT | 10/26/11 |
| Society of Nuclear Medicine Procedure Guideline for FDG PET Brain Imaging | 2/8/09 |
| Procedure Guideline for Brain Perfusion SPECT Using 99mTc Radiopharmaceuticals | 2/8/09 |
| **Oncology** | |
| The SNM Practice Guideline for Therapy of Thyroid Disease with 131I | 6/8/12 |
| The SNM Practice Guideline for Somatostatin Receptor Scintigraphy | 7/19/11 |
| SNM Practice Guideline for Breast Scintigraphy with Breast-Specific g-Cameras | 6/4/10 |
| Procedure Guideline for SPECT/CT Imaging | 4/3/06 |
| Procedure Guideline for Tumor Imaging with 18F-FDG PET/CT | 2/11/06 |
| Society of Nuclear Medicine Procedure Guideline for Breast Scintigraphy | 6/2/04 |
| Society of Nuclear Medicine Procedure Guideline for Palliative Treatment of Painful Bone Metastases | 1/25/03 |
| Society of Nuclear Medicine Procedure Guideline for Lymphoscintigraphy and the Use of Intraoperative Gamma Probe for Sentinel Lymph Node Localization in Melanoma of Intermediate Thickness | 6/15/02 |
| **Pediatric** | |
| Pediatric Radiopharmaceutical Administered Doses: 2010 North American Consensus Guidelines | 10/1/10 |
| Procedure Guideline for Diuretic Renography in Children | 9/1/08 |
| Society of Nuclear Medicine Procedure Guideline for Renal Cortical Scintigraphy in Children | 6/20/03 |
| Society of Nuclear Medicine Procedure Guideline for Pediatric Sedation in Nuclear Medicine | 1/25/03 |

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| Society of Nuclear Medicine Procedure Guideline for Radionuclide Cystography in Children | 1/25/03 |
| **Pulmonary** | |
| SNM Practice Guideline for Lung Scintigraphy | 7/19/11 |
| **EANM Guidelines** | |
| EANM procedure guidelines for 131I-meta-iodobenzylguanidine (131I-mIBG) therapy | 9/22/12 |
| 131I/123I-Metaiodobenzylguanidine (mIBG) Scintigraphy – Procedures Guidelines For Tumour Imaging | 3/20/12 |
| EANM procedure guideline of radio-immunotherapy for B-cell lymphoma with 90Y-radiolabeled ibritumomab tiuxetan (Zevalin®) | 3/20/12 |
| **Collaborative Guidelines** | |
| ACR–SNM TECHNICAL STANDARD FOR DIAGNOSTIC PROCEDURES USING RADIOPHARMACEUTICALS | 2011 |
| ACR–SNM–SPR PRACTICE GUIDELINE FOR THE PERFORMANCE OF CARDIAC SCINTIGRAPHY | 2009 |
| ACR–SNM–SPR PRACTICE GUIDELINE FOR THE PERFORMANCE OF GASTROINTESTINAL SCINTIGRAPHY | 2010 |
| ACR–SNM–SPR PRACTICE GUIDELINE FOR THE PERFORMANCE OF SCINTIGRAPHY FOR INFLAMMATION AND INFECTION | 2009 |
| ACR–SNM–SPR PRACTICE GUIDELINE FOR THE PERFORMANCE OF LIVER AND SPLEEN SCINTIGRAPHY | 2010 |
| ACR–SNM–SPR PRACTICE GUIDELINE FOR THE PERFORMANCE OF PARATHYROID SCINTIGRAPHY | 2009 |
| ACR–SNM–SPR PRACTICE GUIDELINE FOR THE PERFORMANCE OF PULMONARY SCINTIGRAPHY IN ADULTS AND CHILDREN | 2009 |
| ACR–SPR–SNM PRACTICE GUIDELINE FOR THE PERFORMANCE OF ADULT AND PEDIATRIC RADIONUCLIDE CYSTOGRAPHY | 2010 |
| ACR–SNM–SPR PRACTICE GUIDELINE FOR THE PERFORMANCE OF THYROID SCINTIGRAPHY AND UPTAKE MEASUREMENTS | 2009 |
| Pediatric Radiopharmaceutical Administered Doses: 2010 North American Consensus Guidelines | 10/26/10 |
| **Retired Guidelines** | |
| Society of Nuclear Medicine Procedure Guideline for Gallium Scintigraphy in the Evaluation of Malignant Disease | 6/23/01 |
| Society of Nuclear Medicine Procedure Guideline for Tumor Imaging Using F-18 FDG | 2/7/99 |

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| Society of Nuclear Medicine Procedure Guideline for Gastrointestinal Bleeding and Meckel's Diverticulum Scintigraphy | 2/7/99 |

| **EANM** | Date Approved |
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| **Cardiology** | |
| Hybrid cardiac imaging: SPECT/CT and PET/CT. A joint position statement by the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of Nuclear Cardiology (ECNC) | 2011 |
| EANM/ESC guidelines for radionuclide imaging of cardiac function | 2008 |
| EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology | 2005 |
| **Dosimetry** | |
| EANM Dosimetry Committee Series on Standard Operational Pı Therapeutic Dosimetry II. Dosimetry prior to radioiodine therap diseases | 2013 |
| EANM Dosimetry Committee Series on Standard Operational Procedures for Pre-Therapeutic Dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases | 2013 |
| EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting | 2010 |
| EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry | 2010 |
| EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry I: blood and bone marrow dosimetry in differentiated thyroid cancer therapy | 2008 |
| **Drug Development** | |
| Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU | 2008 |
| **Inflammation/Infection** | |
| Guidelines for the labelling of leucocytes with 111In-oxine | 2010 |

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| Guidelines for the labelling of leucocytes with 99mTc-HMPAO | 2010 |
| **Neuroimaging** | |
| EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2 | 2009 |
| EANM procedure guidelines for brain neurotransmission SPECT/PET using dopamine D2 receptor ligands, version 2 | 2009 |
| EANM procedure guidelines for brain neurotransmission SPECT using 123I-labelled dopamine transporter ligands,version 2 | 2009 |
| EANM procedure guideline for brain perfusion SPECT using 99mTc-labelled radiopharmaceuticals, version 2 | 2009 |
| EANM Procedure GuidelinesforBrain Tumour Imaging usingLabelled Amino Acid Analogues | 2006 |
| **Oncology** | |
| EANM 2012 guidelines for radionuclide imaging of phaeochromocytoma and paraganglioma | 2012 |
| Integration of FDG-PET/CT into external beam radiation therapy planning | 2012 |
| 111In-pentetreotide scintigraphy: procedure guidelines for tumour imaging | 2010 |
| 131I/123I-Metaiodobenzylguanidine (mIBG) scintigraphy: procedure guidelines for tumour imaging | 2010 |
| Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE | 2010 |
| PET in radiotherapy planning: Particularly exquisite test or pending and experimental tool? | 2010 |
| EANM-EORTC general recommendations for sentinel node diagnostics in melanoma | 2010 |
| Joint practice guidelines for radionuclide lymphoscintigraphy for sentinel node localization in oral/oropharyngeal squamous cell carcinoma | 2009 |

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| FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0 | 2009 |
| FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0-Presentation | 2009 |
| Sentinel node in breast cancer procedural guidelines | 2007 |
| 67GA SCINTIGRAPHY PROCEDURE GUIDELINES FOR TUMOUR IMAGING | 2003 |
| BONE SCINTIGRAPHY PROCEDURES GUIDELINES FOR TUMOUR IMAGING | 2003 |
| BREAST SCINTIGRAPHY PROCEDURE GUIDELINES FOR TUMOUR IMAGING | 2003 |
| **Paediatrics** | |
| Guidelines for standard and diuretic renogram in children | 2011 |
| Guidelines for paediatric bone scanning with 99mTc-labelled radiopharmaceuticals and 18F-fluoride | 2010 |
| GUIDELINES ON 99mTc-DMSA SCINTIGRAPHY IN CHILDREN | 2009 |
| Guidelines for 18F-FDG PET and PET-CT imagingin paediatric oncology | 2008 |
| Guidelines for lung scintigraphy in children | 2007 |
| GUIDELINES FOR DIRECT RADIONUCLIDE CYSTOGRAPHY IN CHILDREN | 2002 |
| GUIDELINE FOR RADIOIODINATED MIBG SCINTIGRAPHY IN CHILDREN | 2002 |
| GUIDELINES FOR GLOMERULAR FILTRATION RATE DETERMINATION IN CHILDREN | 2000 |
| GUIDELINES FOR INDIRECT RADIONUCLIDE CYSTOGRAPHY | 2000 |
| GUIDELINES FOR STANDARD AND DIURETIC RENOGRAM IN CHILDREN | 2000 |
| **Parathyroid** | |
| 2009 EANM parathyroid guidelines | 2009 |
| **Physics** | |
| Acceptance testing for nuclear medicine instrumentation | 2010 |

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| Routine quality control recommendations for nuclear medicine instrumentation | 2010 |
| Curriculum for education and training of Medical Physicists in Nuclear Medicine | 2012 |
| **Pulmonary Embolism** | |
| EANM guidelines for ventilation/perfusion scintigraphy Part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography | 2009 |
| EANM guidelines for ventilation/perfusion scintigraphy Part 2. Algorithms and clinical considerations for diagnosis of pulmonary emboli with V/PSPECT and MDCT | 2009 |
| **Radionuclide Therapy** | |
| EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds | 2011 |
| EANM procedure guidelines for therapy of benign thyroid disease | 2010 |
| EANM procedure guidelines for 131I-meta-iodobenzylguanidine (131I-mIBG) therapy | 2008 |
| EANM procedure guideline for treatment of refractory metastatic bone pain | 2008 |
| Guidelines for radioiodine therapy of differentiated thyroid cancer | 2008 |
| EANM procedure guideline for 32P phosphate treatment of myeloproliferative diseases | 2007 |
| EANM procedure guideline of radio-immunotherapy for B-cell lymphoma with 90Y-radiolabeled ibritumomab tiuxetan (Zevalin®) | 2006 |
| EANM Procedure Guidelines for Radiosynovectomy | 2002 |
| GUIDELINES FOR 131 I - ETHIODISED OIL [LIPIODOL] THERAPY | 2002 |
| **Radiopharmacy** | |
| Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals | 2010 |
| GUIDELINES ON CURRENT GOOD RADIOPHARMACY PRACTICE (CGRPP) IN THE PREPARATION OF RADIOPHARMACEUTICALS | 2007 |

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| **Collaboration in Guidelines** | |
| SNM/EANM Guideline for Guideline Development 6.0* | 2012 |
| **SNMMI Guidelines - endorsement by EANM** | |
| SNM Practice Guideline for Sodium 18F-Fluoride PET/CT Bone Scans | 2010 |
| SNM Practice Guideline for Breast Scintigraphy with Breast-Specific g-Cameras | 2010 |
| **Joint Guidelines** | |
| The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours | 2013 |
| **Technologist Guidelines** | |
| Principles and Practice of PET/CT | 2010 |
| Advanced Performance and Responsibility Guidelines for the Nuclear Medicine Technologist. | 2001 |
| Patient information leaflets. | 2001 |
| Competences for the European Nuclear Medicine Technologist | 1998 |
| WORKING WITH PROTOCOLS | n/a |

# APPENDIX B
# IAEA LIST OF DOCUMENTS FOR NUCLEAR MEDICINE

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| **Human Health Series** |
| **Clinical Translation of Radiolabelled Monoclonal Antibodies and Peptides**<br>Human Health Series No.8 Publication 1416 |
| **Quality Assurance for SPECT Systems**<br>Human Health Series No.6 Publication 1394 |
| **Quality Assurance for PET and PET/CT Systems**<br>Human Health Series No.1 Publication 1393 |
| **Appropriate use of FDG-PET for the Management of Cancer Patients**<br>Human Health Series No.9 Publication 1438 |
| **Planning a Clinical PET Centre**<br>Human Health Series No.11 Publication 1457 |
| **Atlas of Bone Scintigraphy in the Developing Paediatric Skeleton: The Normal Skeleton, Variants and Pitfalls**<br>Human Health Series No.16 Publication 1491 |
| **Quality Assurance Programme for Screen Film Mammography**<br>Human Health Series No.2 Publication 1381 |
| **Comprehensive Clinical Audits of Diagnostic Radiology Practices: A Tool for Quality Improvement**<br>Human Health Series No.4 Publication 1425 |
| **Comprehensive Clinical Audits of Diagnostic Radiology Practices: A Tool for Quality Improvement**<br>Human Health Series No.17 Publication 1482 |
| **Human Health Reports** |
| **Implementation of the International Code of Practice on Dosimetry in Diagnostic Radiology**<br>Technical Reports Series No. 457: Review of Testing Results Publication 1498 |
| **Books and Publications** |
| **IAEA Quality Control Atlas for Scintillation Camera Systems - 2003**<br>Publication 1141 |
| **Nuclear Medicine Resources Manual - 2006** |

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| Publication 1198 |
| **Operational Guidance on Hospital Radiopharmacy A Safe and Effective Approach - 2008**<br>Publication 1342 |
| **Quality Management Audits in Nuclear Medicine Practices - 2008**<br>Publication 1371 |
| **Strategies for Clinical Implementation and Quality Management of PET Tracers - 2009**<br>Publication 1344 |
| **Training Course Series** |
| **Clinical Training of Medical Physicists Specializing In Nuclear Medicine**<br>Training Course Series No. 50 |
| **Competency Based Hospital Radiopharmacy Training**<br>Training Course Series No. 39 |
| **IAEA Technical Documents (TECDOC)** |
| **A Guide to Clinical PET in Oncology: Improving Clinical Management of Cancer Patients**<br>IAEA TECDOC-1605 |
| **Clinical Applications of SPECT/CT: New Hybrid Nuclear Medicine Imaging System**<br>IAEA TECDOC-1597 |
| **Criteria for Palliation of Bone Metastases - Clinical Applications**<br>IAEA TECDOC CD-1549 |
| **Development of Kits for 99mTc Radiopharmaceuticals for Infection Imaging**<br>IAEA TECDOC-1414 |
| **Nuclear Medicine in Thyroid Cancer Management: A Practical Approach**<br>IAEA TECDOC-1608 |
| **Strategy and Methodology for Radioactive Waste Characterization**<br>IAEA TECDOC-1537 |
| **The Role of PET/CT in Radiation Treatment Planning for Cancer Patient Treatment**<br>IAEA TECDOC-1603 |
| **Radioisotope Handling Facilities and Automation of Radioisotope Production**<br>IAEA TECDOC-1430 |
| **Development of Radioimmunometric Assays and Kits for Non-Clinical Applications** |

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| IAEA TECDOC-1498 |
| **Radioisotopes and Radiopharmaceuticals Series** |
| **Technetium-99m Radiopharmaceuticals: Status and Trends**<br>Publication 1405 |
| **Nuclear Security Series** |
| **Security in the Transport of Radioactive Material**<br>IAEA Nuclear Security Series No. 9 Publication 1348 |
| **Security of Radioactive Sources**<br>IAEA Nuclear Security Series No. 11 Publication 1387 |
| **Safety Standards Series** |
| **International Basic Safety Standards for Protection against Ionizing Radiation and for the Safety of Radiation Sources (CD-ROM Edition, 2003)**<br>IAEA Safety Series No. 115/CD Publication 996 |
| **Legal and Governmental Infrastructure for Nuclear, Radiation, Radioactive Waste and Transport Safety**<br>IAEA Safety Standards Series No. GS-R-1 Publication 1093 |
| Governmental, Legal and Regulatory Framework for Safety General - Safety Requirements Part 1.<br>IAEA Safety Standards Series 1100 Subject Classification: 0614-Legal and governmental aspects |
| **Regulatory Control of Radiation Sources**<br>IAEA Safety Guide GS-G-1.5 Publication 1192 |
| **Safety Report Series** |
| **Release of Patients After Radionuclide Therapy**<br>Safety Reports Series No. 63 Publication 1417 |
| **Applying Radiation Safety Standards in Nuclear Medicine**<br>Safety Reports Series No. 40 Publication 1207 |
| **Optimization of Radiation Protection in the Control of Occupational Exposure**<br>Safety Reports Series No. 21 Publication 1118 |
| **Radiation Protection in Newer Medical Imaging Techniques: Cardiac CT** |

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| Safety Reports Series No. 60 Publication 1366 |
| **Radiation Protection in Newer Medical Imaging Techniques: PET/CT**<br>Safety Reports Series No. 58 Publication 1343 |
| **Technical Report Series** |
| **Quality Assurance for Radioactive Measurement in Nuclear Medicine**<br>Technical Reports Series No. 454 |
| **Technetium-99m Radiopharmaceuticals: Manufacture of Kits**<br>Technical Reports Series No. 466 |
| **Comparative Evaluation of Therapeutic Radiopharmaceuticals**<br>Technical Reports Series No. 458 |
| **Labelling of Small Biomolecules using Novel Technetium-99m Cores**<br>Technical Reports Series No. 459 |
| **Therapeutic Radionuclide Generators: 90sr/90y and 188w/188re Generators**<br>Technical Reports Series No. 470 |
| **Cyclotron Produced Radionuclides: Guidelines for Setting up a Facility**<br>Technical Reports Series No. 471 |
| **Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods**<br>Technical Reports Series No. 468 |
| **Cyclotron Produced Radionuclides: Principles and Practice**<br>Technical Reports Series No. 465 |

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