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THE RADIOPHARMACEUTICAL INDUSTRY'S EFFORT TO MIGRATE TOWARD Mo-99 PRODUCTION UTILIZING LEU

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ABSTRACT

The U.S. and European radiopharmaceutical manufacturers rely on a steady supply of HEU to produce targets for the production of Mo-99, I-131 and other radionuclides. Due to non-proliferation concerns, the future availability of HEU for target production is uncertain. The industry in Europe and North America continue to explore ways that HEU can be replaced by newer technology including the use of LEU targets in conventional reactors, as well as solution reactor designs utilizing LEU. At the conclusion of the RERTR meeting in Vienna in 2004, the IAEA conducted a Consultancy Services Meeting focusing on ways to provide LEU or (n,γ) molybdenum target technology to countries who were considering indigenous production. The nuclear medicine community supports non-proliferation of HEU and its eventual replacement by LEU for the production of radionuclides. We are also committed to ensure a reliable supply of radionuclides used to produce radiopharmaceuticals. The radionuclide production industry is therefore seeking methods to develop and phase in the use of LEU without disrupting the supply of radiopharmaceuticals or causing a financial barrier to their use by nuclear medicine physicians. When feasible and economical methods are developed using LEU, that can assure reliable production of medical radionuclides in such large-scale commercial quantities capable of meeting the growing supply demands of the market, the industry is committed to rapidly converting to use of the new technology.

1. Introduction

The nuclear medicine industry today is responsible for delivering high quality radiopharmaceuticals to physicians throughout the world. The radiopharmaceuticals are used to diagnose heart disease, assess brain function, detect and stage cancer, assess complications from AIDS, and diagnose many organ functions. Therapeutic radiopharmaceuticals are used to treat a variety of cancers, both solid tumors, such as thyroid cancer, and blood borne cancers, such as non-Hodgkin's lymphoma. Medical radionuclides are also used in life science research, drug development, medical equipment calibration, AIDS research and many other cutting edge biomedical areas. Molybdenum-99 (Mo-99) and its daughter, Technetium-99m (Tc-99m) are used in more than 80% of the nuclear

medicine studies preformed around the world. It is estimated that more than 45 million[1] nuclear medicine procedures are performed each year in the world.

The nuclear medicine industry continues to show double-digit annual growth representing increasing demand for nuclear medicine procedures. This market has steadily increased through the 1980's and 1990's, and shows no sign of slowing down. The diagnostic market has consistently grown at 8-15% per year[2], while the therapeutic market has grown at an annual rate of more than 15% for the last several years[3]. This growth has been fueled by a combination of innovative new products, as well as an aging population in which cancer and heart disease are prevalent. Many more clinical trials are still underway utilizing Mo-99 and its daughter, Tc-99m, and Iodine-131 (I-131). These clinical trials will hopefully lead to additional new products to detect and fight heart disease and cancer.

The nuclear medicine community is sensitive to the concerns of the non-proliferation community, regarding the use targets made of highly enriched uranium (HEU), but is equally concerned about a stable, reliable supply of critical radioactive raw materials that are used to produce the finished radiopharmaceuticals. The industry believes that it is necessary to continue efforts on an alternative low enriched uranium (LEU) target technology, without creating an operational or financial problem to the nuclear medicine physicians and their patients. Once a feasible and economical, large-scale commercial LEU solution is found, the industry will move toward rapid adoption of the new technology.

2. Discussion

Regulatory Issues

The principal means of producing Mo-99, I-131 and other medical radionuclides is currently using HEU targets to produce fission products. These fission products are then purified through a series of chromatographic steps to remove unwanted radionuclides. Mo-99 is typically supplied to nuclear medicine departments and nuclear pharmacies in a Tc-99m generator. These generators are eluted with normal saline solution, which washes Tc-99m from a chromatography column. These generators supplied in the United States and Europe have undergone extensive development work to assure purity and reproducibility. These products are licensed by drug regulatory authorities such as the U.S. Food & Drug Administration (FDA) and the European Medicines Agency (EMEA). The production of the radioactive raw material used to manufacture radiopharmaceuticals is controlled by a series of well documented steps, referred to as a Drug Master File (DMF). The DMF is locked into the drug regulatory approval process. Any change to the process requires a new DMF and an amendment to the drug approval. Before a new material from a different process is used, it must undergo a review of the DMF in tandem with a review of the radiopharmaceutical process[4].

Radiopharmaceutical production is controlled by a well documented process submitted to the Regulatory authority in a New Drug Application (NDA). The NDA undergoes a great deal of scrutiny by the same regulatory authorities that review the DMF. The DMF is required to employ a more detailed set of control mechanisms called current Good Manufacturing practices (cGMPs), which are in place to assure drug purity. Each NDA is tied to a series of specific DMFs for the raw materials. Once a new process to produce Mo-99 utilizing LEU is developed, the DMF will have to be developed. Each Tc-99m generator manufacturer that holds a NDA that wishes to use the new DMF for the LEU produced Mo-99 will have to amend their NDA. In order to do this, the manufacturer has to perform a series of analytical tests to assure the new material will perform identically to the original DMF approved with the NDA. This process is illustrated in Figure 1 below.

In order for a manufacturer to submit a request to get material from a new DMF approved by the regulatory authorities, three qualification production runs must be done using the new Mo-99. In each of these qualification runs, the LEU-produced Mo-99 first has to be tested to assure the specifications of the radionuclide are within the acceptable range for a series of parameters. These parameters include pH, concentration, radiochemical purity and radionuclidic purity.

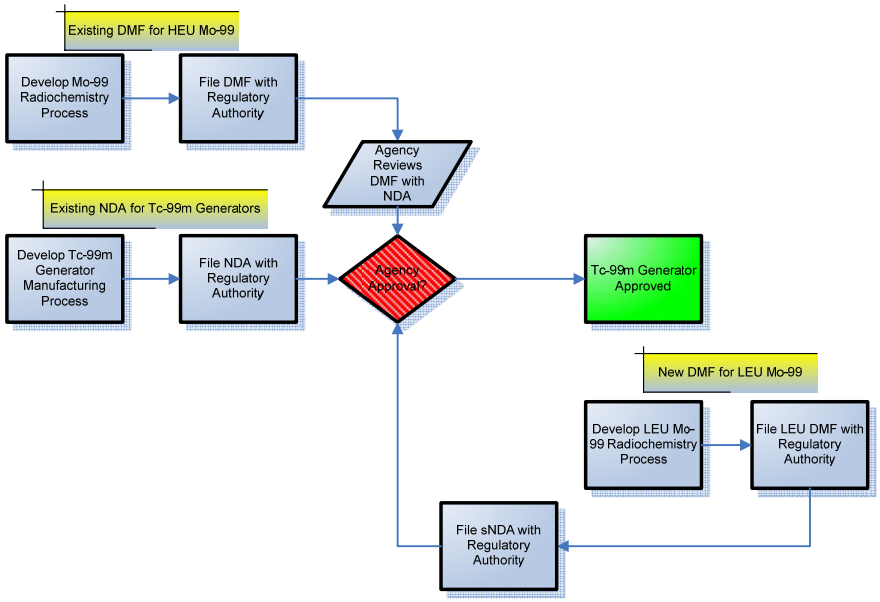

Figure 1. FDA Regulatory Process

Once the material is deemed acceptable, the Mo-99 is then loaded into Tc-99m generators using the previously approved process. The generators produced in each of these qualification runs must then be tested for each of the finished

product specifications in the manufacturers NDA. All of the test data from these three qualification runs must be collected, summarized then submitted to the regulatory authorities as a Supplement to the original NDA (sNDA). The regulatory authorities then review the submitted data and make a judgment as to whether the new Mo-99 appears to work as well as the original Mo-99. Assuming the radiochemistry process for LEU-produced Mo-99 is properly developed, there is no reason to believe the LEU-produced Mo-99 will perform any differently in the Tc-99m generator as the HEU-produced Mo-99.

The costs to qualify a new source of Mo-99 are significant. The costs include developing the protocols for the three qualification runs, the cost of testing the raw material, the production costs of manufacturing the generators in the three qualification runs that must represent typical full production batch sizes, the cost of the materials to produce these generators, the cost of testing the generator themselves in the three production runs, and the cost of compiling and writing the sNDA application. An estimate for the cost of qualifying an LEU-produced Mo-99 source is at least $250,000. Each manufacturer that has a generator and their own NDA will have to go through this process in order to qualify the LEU-produced Mo-99.

In the Fall of 2004 the International Atomic Energy Agency (IAEA) held a Consultancy Services Meeting[5] in Vienna to discuss production of Mo-99 using LEU. Many Mo-99 manufacturers attended including large producers in Canada and Europe. The objectives of this CRP were:

1. To develop and deliver education, awareness, training and coaching workshops to provide sufficient information to enable a recipient to make a knowledgeable decision on the technical, regulatory and economic implications of establishing Small Scale Molybdenum 99 Production using the Available Technology.

2. To assist the recipient in the development activities to research, test, and evaluate the Available Technology and in determining the implications of the options to access Available Technology, build their own technology, or purchase alternate LEU or (n,γ) molybdenum target technology.

A CRP workshop was also discussed as a venue in which to exchange information concerning the production of Mo-99 for use by the nuclear medicine community. Such a workshop would assist smaller countries in setting up their own operation to produce Mo-99. The first CRP workshop was held in Argentina in May 2005.

Market Background

There are at least six reactors around the world that are producing significant quantities of Mo-99 for the manufacture and distribution of Tc-99m generators. The largest markets, in descending order are the North America, Europe, Japan, South America and Asia. Figure 2 below summarizes[6] many of the largest

Reactor	Country	Producer	Days/Year	Fuel	Target	% of World Mo-99
NRU	Canada	MDS Nordion/AECL	315	LEU	HEU	40
HFR	Holland	Tyco Healthcare/NRG	290	HEU*	HEU	30
BR2	Belgium	Tyco Healthcare/IRE	115	HEU	HEU	9
OSIRIS	France	IRE	220	LEU	HEU	3
FRJ-2	Germany	IRE	210	LEU	HEU	3
SAFARI	S. Africa	NTP	315	HEU**	HEU	10
HIFAR	Australia	ANSTO		HEU*	LEU	<5
RA-3	Argentina	CNEA	230	LEU	LEU	<5

* Scheduled to finish conversion to LEU in 2006
** Conversion to LEU is planned

Figure 2. World's Major Mo-99 producers

reactors currently producing Mo-99. It includes data on each reactor and estimates of the Mo-99 capacity, the duty factor in days of operation per year, the fuel type, and the type of target. The NRU is currently using LEU fuel. The HFR in Petten is scheduled to complete their conversion to LEU fuel in 2006, and the new MAPLE reactors in Canada will use LEU fuel. The main issue has become the use of HEU versus LEU for the targets.

The Energy Policy Art of 2005

U.S. President Bush signed The Energy Policy Act of 2005 (The Act) into law on August 8, 2005. The law has provisions for the export of HEU, and incentives to encourage the development of LEU technology. The Act has been criticized by some entities in the nonproliferation community for weakening controls on the export of HEU. The nuclear medicine industry in the U.S. is a strong supporter of the Act because it was seen as a way to assure the continued export of HEU for use in targets that produce Mo-99 and other medical radionuclide production. The U.S. industry believes LEU Mo-99 production technology needs additional work before it will be available for large-scale commercial production. This additional work can only be successfully implemented through cooperation with the producers.

Argonne National Laboratory has been working on an LEU target for the production of Mo-99 and other medical radionuclides. Although significant progress has been made, it will take a great deal more work for the current Mo-99 producers to use this target design in the existing reactor configurations. It is imperative to consider the broad spectrum of isotope production using LEU targets. The definition of LEU target technology must therefore also include the

target processing facilities and waste management processes of each producer. While there may be to some extent a common overall technology, each producer and facility will be unique in implementation. According to a recent General Accounting Office (GAO) report, any new target technology is still at least 2 to 3 years away from being tested for large-scale commercial use. The nuclear medicine industry remains committed to continue to work with DOE through Argonne National Laboratory on developing an alternative technology to HEU targets. Cooperation and coordination among all key stakeholders is essential to balance concerns of the nuclear medicine and non-proliferation communities.

The Act also contains a provision to foster development of new technology utilizing LEU. The Act requires the U.S. National Academy of Sciences (NAS) to make routine assessments of the current LEU technology. When they judge the LEU technology to be economically and technically feasible, the HEU export provisions in the Act disappear. When an LEU technology does become feasible, it will not only make LEU-produced Mo-99 a viable alternative, it will also make HEU more difficult to obtain. This creates an incentive for the current Mo-99 producers to encourage the LEU-produced Mo-99 efforts, and to embrace it once the technology matures to a point it is economically and technically feasible.

Alternative Reactor Designs

Work on alternate reactor technology has been underway for a number of years. One of the most promising technologies is the aqueous or solution reactor concept. Rather than inserting a conventional fission target in the reactor core, a solution reactor has the Mo-99 production taking place in the fuel solution. To extract the Mo-99 and other medical radionuclides, the fuel solution is removed from the reactor, and it is processed through a series of sorbent columns to remove the unwanted radionuclides, leaving the usable nuclides. Successful solution reactors have been in operation since the early 1960's. Figure 3 below lists[7] of some of the successful solution reactors and partial data on those reactors.

TCI Medical, Inc of Albuquerque, New Mexico has been working with The Kurchatov Institute in Moscow and Argonne National Laboratory in Chicago, Illinois on the development of a LEU solution reactor for the production of Mo-99 and other medical radionuclides. A pilot solution reactor has been running successfully in Moscow since 1981, producing small quantities of Mo-99 from HEU UO_2SO_4 fuel. The current solution reactor being operated at The Kurchatov Institute is running at a power level of 20 kW with HEU fuel. The current design can safely be increased to a power level of 50 kW. At this level the reactor can produce 250 (6-day) Ci per week. Further development work is planned with a multiple-core design that will significantly increase Mo-99 output.

BWXT, formerly Babcock & Wilcox, worked with Oak Ridge on solution reactors in the early 1960's. The SHEBA reactor, built at the Los Alamos National Lab, is a solution reactor used for research in the pulse mode. That design used a

solution of 5% enriched uranyl fluoride. Results from that technology can be used to apply to an LEU uranyl nitrate fuel solution. The reactor fuel, after operation at 100 kW can flow through sorbent filter to remove and purify Mo-99 and other useful radionuclides.

These two commercial efforts to build LEU solution reactors are very promising. In both cases further development work needs to be done before they can become commercially viable. This technology has the potential to meet the incentive milestone for The Act of 2005 as discussed above. If either of those reactor designs can be used to build and successfully operate a Mo-99 production facility, it will trigger a provision in The Act to remove the language easing restrictions on the export of HEU fuel.

Reactor	Country	Location	Enrichment	Power (kWt)	Status
ADIBKA	Germany	Julich			Shutdown
DR-1	Denmark	Riscoe	20%	2.0	Shutdown
Mirene	France				Shutdown
Silene	France	CEA-Valduc	93%	1.0	Operating
Hazel	Great Britain				Shutdown
Purnima II	India			0.1	Shutdown
L-54	Italy			50	Shutdown
STACY	Japan	NUCEF		0.2	Shutdown
TRACY	Japan	NUCEF		10	Shutdown
IIN-3M Hydra	Russia	Moscow	90%	10	Operating
ARGUS	Russia	Moscow	90%	20	Operating
IGRIK	Russia	Snezhinsk	90%	30	Operating
YAGUAR	Russia	Snezhinsk	17-90%	10	Operating
FOTON	Uzbekistan		90%	10	Operating
WBRL	Taiwan			100	Shutdown
PNL-CML	USA	Battelle NW			Shutdown
ARR	USA	Chicago			Shutdown
LIWB	USA	Livermore		0.5	Shutdown
Kinglet	USA	Los Alamos			Shutdown
HYPO	USA	Los Alamos		6	Shutdown
SUPO	USA	Los Alamos		25	Shutdown
L-77	USA Ter.	Puerto Rico		10	Shutdown
KEWB	USA	Santa Susana, CA		50	Shutdown
L-47	USA	Rockwell			Shutdown
L-77	USA	Rockwell		0.01	Shutdown
L-85	USA	Nuclear exam		3000	Shutdown
L-77	USA	UCSB		0.01	Shutdown
L-77	USA	Univ of Nevada		0.01	Shutdown
L-77	USA	Univ of Wyoming		0.01	Shutdown
L-54	USA	Walter Reed-Washington		50	Shutdown
SHEBA	USA	Los Alamos	5%	2.0	Critical assembly

Figure 3. Solution Reactor Designs

3. Summary

CORAR and the medical radionuclide community support non-proliferation of HEU and its eventual replacement by LEU in both fuel and targets. We are also committed to ensure a reliable supply of radionuclides used to produce radiopharmaceuticals. The radionuclide production industry is therefore seeking methods to develop and phase in the use of LEU without disrupting the supply of radiopharmaceuticals or causing a financial barrier to their use by nuclear medicine physicians. These new methods include alternate LEU reactor designs. When feasible and economical methods for using LEU are developed to produce radionuclides on a large-scale commercial basis, the industry is committed to rapidly use the new technology.

4. References

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2) *The U.S. Market for Diagnostic Radiopharmaceuticals,* Report 150, Bio-Tech Systems, Inc.

3) *The U.S. Market for Therapeutic Radiopharmaceuticals*, Report 160, Bio-Tech Systems, Inc.

4) U.S. Food & Drug Administration Regulations found at Title 21 *Code of Federal Regulations*

5) IAEA CSM Report, Vienna, Austria, 2005

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