The Transport of Radiopharmaceuticals in the United States

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Among all the various uses of radioactive materials for peaceful purposes, the creation and use of radiopharmaceuticals to diagnose and treat medical ailments has probably brought the greatest benefit to humanity. The use of radionuclides in medicine has mushroomed over the past 20 years, as has the number of nuclides and procedures which are now routinely used in hospitals and clinics around the globe. Parallel to the growth in the use of radiopharmaceuticals has been the growth in shipments of these nuclides and their compounds to the locations where they are used.

Growth in Transport of Radiopharmaceuticals

According to a study "Transport of Radioactive Material in the United States: A Review of Current Status" [1], completed in the year 2002 by the U. S. Department of Transportation's (USDOT's) John A. Volpe National Transportation Systems Center (the Volpe Center) for the United States Nuclear Regulatory Commission (USNRC), approximately 17.1 million shipments of radiopharmaceuticals for diagnosis and therapy (including return shipments to the manufacturer of packages containing residual radionuclides) were made in the U. S. in 1999, and another 160,000 shipments of radionuclides were made for the purpose of medical research. The total number of shipments of radionuclides for medical purposes in 1999 was thus approximately 17.3 million; this constituted about 96% of the total number of radioactive material shipments, which had been found to be approximately 18.0 million.

In this study, which extrapolated from data provided voluntarily by a portion of the industry, and therefore has some notable uncertainties, the term "shipment" is used interchangeably with the word "package," a practice which contributes to those uncertainties. It is also true, however, that of the various categories of radioactive material studied, the data for radiopharmaceuticals are believed to be among the most complete. In addition, arguments will be given later to show that the difference between the number of "shipments" and the number of "packages" is expected to be small.

The data on shipments of radiopharmaceuticals was provided to the Volpe Center by the Council on Radionuclides and Radiopharmaceuticals (CORAR). CORAR is a U. S. -based non-profit association of United States and Canadian companies that manufacture, develop, and distribute radiopharmaceuticals, radionuclides, and radiochemicals used primarily in medicine and in research in the life sciences. CORAR claims that over 98% of nuclear medicine procedures performed in the United States are performed with products manufactured by CORAR members.

The data on radiopharmaceutical shipments are believed to cover essentially 100% of the market, most of the shipments having been by CORAR members. (However, to protect members' commercial interests, no breakdown by products or companies was given, and the details of the raw data were not made available in the Volpe report.) These data cover shipments from manufacturers to hospitals, from manufacturers to central radiopharmacies, from central radiopharmacies to hospitals, and return shipments of residual radiopharmaceuticals from hospitals to the manufacturers. They do not include hospital-to-hospital or hospital-to-clinic shipments, nor do they include shipments of radiochemicals for research purposes.

Apparently CORAR did not feel that it would be prudent to release details concerning radiochemicals used in research, most likely due to competitive concerns of member companies. However, they provided estimates of the range of research radionuclide shipments by category. The total number of such shipments in the U. S. in 1999 was estimated to be in a range from about 160,000 to 500,000. The lower bound has been used above and in the discussion which follows. The activities in individual packages of research radionuclides tend to be small, and the majority of these shipments qualify as limited quantity shipments in excepted packages.

In an earlier study, also called “Transport of Radioactive Material in the United States” [2], performed by the company SRI for Sandia National Laboratory, it was estimated that approximately 2.8 million packages of radioactive material were shipped in the U. S. in 1985, of which about 1.26 million, or 45%, were shipments of radiopharmaceuticals or radionuclides destined for medical research. The results of the two studies have been summarized in the following table:

<table>
<tr><th colspan="6">Estimated Number of Packages Shipped</th></tr>
<tr><td></td><td colspan="2">1985</td><td colspan="3">1999</td></tr>
<tr><td>All radioactive materials</td><td>2.8 M</td><td>100 %</td><td></td><td>18.0 M</td><td>100 %</td></tr>
<tr><td>Radiopharmaceuticals</td><td rowspan="2">1.26 M</td><td rowspan="2">45 %</td><td>17.1 M</td><td rowspan="2">17.3 M</td><td rowspan="2">96 %</td></tr>
<tr><td>Radionuclides for Medical Research</td><td>0.2 M</td></tr>
</table>

Conclusions which may be drawn from these data, to the extent that each study may be considered to give an accurate picture of the situation at the time, are that over the 14-year period from 1985 to 1999:

1. The total number of shipments grew by a factor of more than 6.
2. The total number of shipments of radiopharmaceuticals and radionuclides for medical research grew by a factor of almost 14.
3. The percentage of radioactive material shipments due to radiopharmaceuticals and radionuclides for medical research grew from 45% to 96%.

The explanation for these somewhat unexpected results appears to be relatively straightforward. CORAR noted that the growth in the variety of approved radiopharmaceutical procedures, as well as in the number of patients to which they are applied, can account for a significant portion of the increase. They also noted that this effect is compounded by a radical reconfiguration of the delivery system which has resulted from the proliferation of central, i.e., independent (not part of any specific medical facility) radiopharmacies, and the tendency of these independent radiopharmacies, instead of the hospital radiopharmacies, to prepare (and ship) individual patient doses.

CORAR provided the Volpe Center with data from internal marketing studies, in which they estimated that in 1978 there were approximately 10 independent radiopharmacies in the United States, delivering about 5% of an estimated 6.2 million doses per year. In 1985 they found that there were about 153 independent radiopharmacies, delivering about 30% of the total of 7.2 million doses prepared that year. In 1991there were 167 independent radiopharmacies delivering 64% of the doses, and in 2000 there were 299 independent radiopharmacies, delivering 74% of all doses. Most of the shipments made by the independent radiopharmacies are single-dose shipments; hence our assertion earlier that differences between the numbers of packages and the numbers of shipments should be “relatively” small. (In the 1985 report it was found that there were approximately 1.42 packages per shipment, although this number represents all shipments from NRC and Agreement State licensees, and not just radiopharmaceuticals. However the large increase in shipments of individual doses will have lowered this ratio appreciably.) Thus I shall continue under the assumption that we can use the terms “shipment” and “package” interchangeably.

Additional data were provided which broke out the numbers of packages by label category, by mode and by radionuclide. The numbers given in the Volpe report are shown in the following tables.

CORAR indicated that of the estimated 17.1 million packages of radiopharmaceuticals shipped in the U. S. in 1999, 8.7 million were outgoing shipments, and 8.4 million were return shipments of the packages containing some residual of the originally shipped radionuclides. Among outgoing shipments of radiopharmaceuticals, about 0.02% were limited quantities shipped in excepted packages, around 7.0 million, or 41%, of the packages carried Radioactive White I labels, 1.6 million, or 9%, had Radioactive Yellow II labels, and 0.1 million, or 1%, carried Radioactive Yellow III labels. Thus the great majority of radiopharmaceutical shipments are in category White I. A breakdown of the 8.4 million returned packages by category was not given, but presumably the majority of these were "empty packages" or limited quantities shipped as excepted packages.

Radiopharmaceutical Packages Shipped in 1999, by Category		
Category	**Estimated Number of Packages**	**Percent**
Limited quantity	2,704	0.02
Radioactive White I	6,985,596	40.76
Radioactive Yellow II	1,613,533	9.41
Radioactive Yellow III	140,972	0.82
Returned packages	8,395,951	48.99
Total	17,138,756	100

A breakout by modes indicates that about 16.8 million packages (98%) were transported by ground transportation (specifically, by highway), and only about 330,000 by air. It is stated in the 1985 report that 77.4% of all radioactive material packages were transported by highway. Again, however, this refers to all radioactive materials shipped by USNRC and USNRC Agreement State licensees, and not just radiopharmaceuticals. Nevertheless, the accelerated growth of independent radiopharmacies, and the tendency of these to ship individual doses, will necessarily have increased the fraction of packages transported by highway containing radiopharmaceuticals .

Radiopharmaceutical Packages Shipped in 1999, by Mode		
Mode	**Estimated Number of Packages**	**Percent**
Ground	16,806,996	98.06
Air	331,760	1.94
Total	17,138,756	100

The total activity contained in these packages was about 48 thousand TBq, of which about 31.3 thousand TBq (65%) were due to molybdenum-99, and 12.9 thousand TBq (27%) to technetium-99m. Appreciably smaller amounts were due to shipments of xenon-133 (1200 TBq or 2.6%); thallium-201 (1000 TBq or 2.1%); iodine-131(490 TBq or 1.0%); and less than 1.0% for each of phosphorus-32, gallium-67, iodine-125, iodine 123, indium-111, and various other unnamed nuclides. In the table which follows, activities in TBq have been rounded to whole numbers for ease of reading.

Radiopharmaceutical Packages Shipped in 1999, by Activity		
Radionuclide	**Activity in TBq**	**Percent**
Mo-99	31,314	65.18
Tc-99m	12,889	26.83
Xe-133	1,231	2.56
Tl-201	1,006	2.09
I-131	488	1.02
P-32	402	0.84
Ga-67	122	0.25
I-125	53	0.11
I-123	48	0.10
In-111	32	0.07
All others	457	0.95
Total	48,042	100

The total activities of various (medical and life sciences) research-related radionuclides shipped in the U. S. in 1999 were indicated by CORAR to fall in the following ranges: 10 to 30 TBq (tritium); 1 to 3 TBq (carbon-14); 3 to 10 TBq (phosphorous-32); 0.3 to 1 TBq (phosphorous-33); 1 to 3 TBq (sulphur-35); 0.3 to 1 TBq (iodine-125); and 0.3 to 1 TBq (all other research-related radionuclides). These give a total activity of all research-related radionuclides shipped in 1999 which falls in a range from 16 to 49 TBq.

Expectations for the Future

A market research company, Bio-Tech Systems, Inc., has produced several recent reports on the future of the use of various diagnostic and therapeutic techniques involving the use of radiopharmaceuticals, and projects very strong growth within the next few years.

In 2003 there were a total of 650,000 procedures in the U. S. involving positron emission tomography (PET), an increase of 48% over the previous year. The number of PET procedures is expected to increase another 35% in 2004, and to increase to about 2.1 million procedures, or 3.2 times the 2003 number, in the year 2008. PET has been used primarily to study cancerous tumors, but cardiology applications are increasing, and PET is now being used more and more for the diagnosis and evaluation of Alzheimer's disease. A prominent radiopharmaceutical product used in PET studies has been fluoro-deoxy-glucose (FDG), which utilizes the positron emitter F-18, the half life of which is about 110 minutes. [3]

There is also a strong surge in the use of therapeutic nuclides to target specific cancers and cancerous organs. Total therapeutic sales in the U. S. were $57 million in 2002; this is expected to grow to $3.8 billion (a factor of 67) by 2008. This is due primarily to the rapid progress in the development of targeted therapies for various cancers. [4]

Radiation Doses Due to Highway Transport of Radiopharmaceuticals

Radiopharmaceuticals are generally gamma or beta-gamma emitters, and as such, even though packages containing them are usually shipped with at least some shielding, the packages are usually accompanied by a measurable external radiation field.

A long-standing concern in the United States has been the difficulty in obtaining reliable data concerning the radiation doses received by transport workers who ship or carry packages of relatively small quantities of radioactive material. This is especially true of packages containing radiopharmaceuticals, since these are believed to be the most likely to be the source of appreciable accumulated dose over the working year.

In a survey of seven highway carriers performed in 1980 for the USNRC [5], where the carriers transported mostly radiopharmaceuticals, a wide range of worker doses was observed. It was found that some carriers had employees receiving estimated annual doses greater than 5 mSv/y (the recommended maximum radiation exposure to a non-radiation worker at that time), and there were even a few who were probably receiving up to and over the legal limit of 50 mSv/y for a radiation worker. This was due partly to work practices which were not always focused on keeping doses as low as reasonably achievable. Nevertheless, it was obvious that even with good work practices, such as minimizing time spent near the packages, meeting proper separation distance and total vehicle TI requirements, etc., it was likely that employees of carriers that transport radiopharmaceutical packages will receive larger doses than workers handling other types of radioactive material packages, precisely because of the small size and large number of such packages, and the fact that the outgoing packages are divided up to be shipped to many different consignees.

In a presentation for PATRAM-89 [6], J. M. Shuler analyzed doses to drivers carrying radiopharmaceuticals under USDOT exemption DOT-E 8308, which allows carriers party to the exemption to ignore separation distance requirements and places no limit on the total transport index, so long as they maintain a radiation protection program which includes personal dosimetry monitoring of key personnel, and adherence to an upper limit of 12.5 mSv per quarter for whole body dose equivalent. The average radiation dose to drivers operating under the USDOT exemption was 9.72 mSv per year. He then combined the results of the study of the USDOT exemption holders to results of other studies of dose to drivers for carriers of radiopharmaceuticals not operating under the exemption, to arrive at a somewhat lower annual average of 4.21 mSv for drivers in the larger group.

He also cited data for carriers of other types of radioactive material. Radiation doses to drivers of low level waste averaged 1.14 mSv per year; to drivers of uranium hexafluoride cylinders, 0.55 mSv per year, and to drivers of spent fuel shipments, 0.17 mSv per year. Thus the greatest potential for receiving an appreciable annual radiation dose under normal conditions of transport generally appears to occur for cargo handlers or drivers involved in the transport of radiopharmaceuticals.

Although no comparable analysis of recent results for DOT-E 8308 exemption holders has been made, a qualitative review indicates that doses to cargo handlers and drivers under the exemption are still appreciable. Little or no data are available concerning radiation dose to transport workers carrying radiopharmaceuticals without the benefit of the exemption.

Doses Due to Air Transport of Radiopharmaceuticals

A companion USDOT exemption, DOT-E 7060, exists for the transport of radiopharmaceuticals by air. This exemption allows an airline to transport radioactive material on cargo planes without satisfying the separation distance requirements and without a limit on the total transport index, so long as the airline maintains a radiation protection program which includes personal dosimetry monitoring of key personnel, and adherence to an upper limit of 12.5 mSv per quarter for whole body dose equivalent. .

(It should be noted that neither of the exemptions cited is restricted to the transport of packages containing radiopharmaceuticals; however, since these are the packages most often transported by commercial carriers on a regular basis, the great majority of packages shipped under these exemptions are, in fact, packages carrying radiopharmaceuticals.)

There are presently two parties to exemption DOT-E 7060, with very different types of operations. One is a large-volume carrier using large cargo planes, carrying very large numbers of packages of all kinds in dozens of planes at many different airports. Radioactive material packages are sorted at airport hubs and loaded into unit load devices (ULDs); these are placed in designated locations toward the rear of the plane. Monitoring over several years has indicated that the flight crew, seated at the front of a plane operating under the exemption, receive essentially zero radiation dose from the radioactive cargo. Key personnel throughout the company involved in the transport of radioactive materials, including those involved in exemption flights, wear dosimeters. Of those monitored who receive a measured dose of 10 μSv or more per quarter, the average dose is usually in the range 0.15 - 0.30 mSv per quarter, with a quarterly maximum dose typically on the order of 4 or 5 mSv.

The other party to exemption DOT-E 7060 is a company which advertises time-critical transportation delivery services, including long-distance delivery of radiopharmaceuticals with especially short half lives. These are delivered to most major cities in the U. S. in small planes, the radiopharmaceuticals in Lear jets. Because of the smaller dimensions of the planes and the relatively higher initial radiation levels associated with the shorter-lived radiopharmaceuticals, dose rates to flight crew (pilot and co-pilot) and cargo handlers are appreciable. The flight crew can easily receive 0.2 to 0.3 mSv in a single flight; of those monitored employees - flight crew and cargo handlers - who receive a measured dose of 10 μSv or more per quarter, the average dose is usually in the range 0.30 - 0.40 mSv per quarter, with a quarterly maximum dose typically on the order of 5 to 10 mSv or more.

It is seen that in this type of transport of radiopharmaceuticals in small planes, where possibilities for increasing the distance between the cargo and the crew are limited, it is much harder to reduce radiation levels and the doses received by carrier employees. The installation of sufficient shielding, either in the planes or in the packages, would reduce the weight or amount of cargo that could be carried, and appreciably increase the cost of the service and therefore of the product. Flight times are already short, bounded by the speed of the aircraft and the times for takeoff and landing. This is not to say that there is no room for improvement in practices to reduce individual employee doses, such as looking for ways to make procedures more efficient to reduce package handling times, and utilizing self-shielding of the packages. Nevertheless, in this type of operation compliance with regulatory limits, the costs of the service and of the product, and the health benefit to be gained from use of the product, are all very much in play, and it is difficult to achieve a satisfactory balance of these factors.

Summary and Conclusions:

The use in the United States of radiopharmaceuticals for diagnostic and therapeutic purposes has increased dramatically over the past 20 years, and promises to accelerate still more in the near future. Technological advances in PET scanning, more creative means of diagnostic imaging, the expansion of the range of conditions which can be analyzed and treated with the help of radioactive compounds, and an increase in therapies targeted to specific organs, all contribute to this growing field. The growth in the use of radiopharmaceuticals implies a parallel growth in the number of shipments of these materials.

At the same time, because the packages containing radiopharmaceuticals are relatively small, because there are more and more of them, because package shielding often cannot be increased very much without making the packages too heavy to handle, and because it is not always possible to reduce doses by maintaining sufficient distance between the packages and the transport workers or by increasing the shielding between the packages and the transport workers, under normal conditions of transport workers involved in the transport of radiopharmaceuticals tend to receive relatively high radiation doses.

The most obvious measures that can be taken to improve this situation are those that we already know: go back to the fundamental processes and look for ways to improve them. In the radiation protection world these are “time, distance and shielding.” Many technological aids are imaginable, and efforts should be made to incorporate them where possible. Useful aids include the very simple one of paying attention to and improving, where appropriate, the procedures employed by the workers. Perhaps the most important potential aid is that there be some person or persons in every company involved in the transport of radiopharmaceuticals who are constantly reviewing the processes and procedures used, with an eye toward looking for ways to reduce radiation levels and to reduce the amount of time that the employees are in those radiation fields. Regardless of which procedures are judged to be the most effective in reducing employee doses, the employees must be well-trained in following those procedures, and the degree to which they follow those procedures should be periodically evaluated and variances corrected.

In the United States most shippers of radioactive material are licensees of the USNRC or of a USNRC Agreement State and, as such, many of these operate under a radiation protection program as part of their license conditions. However, detailed regulations for limiting radiation doses to transportation workers involved in all aspects of radioactive material transport need to be developed and implemented. This is especially important for carriers, since carriers, including brokers and freight forwarders, do not usually operate under such a license. These regulations must be developed in such a way that the degree of regulation is appropriate to the degree of hazard, and so that such regulations do not impose a crushing financial burden on the companies involved. Within the overall task of establishing workable radiation protection requirements for the transport of radioactive materials, special attention will have to be paid to how such requirements are to be applied to the transport of radiopharmaceuticals.

References:

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[2] "Transport of Radioactive Material in the United States: Results of a Survey to Determine the Magnitude and Characteristics of Domestic, Unclassified Shipments of Radioactive Materials," Contractor Report SAND84-7174, Final Report, April 1985.

[3] Bio-Tech Report #200, "The Market for PET Radiopharmaceuticals & PET Imaging," Bio- Tech Systems, Inc., Copyright 1999-2004, http://biotechsystems.com.

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[5] "Radiation Exposure of Transportation Workers Handling Large Quantities of Radioactive Packages," NUREG/CR-2200, January 1982.

[6] Shuler, J. M., "A Comparison of Yearly Radiation Dose to Drivers from Various Types of Radioactive Materials," PATRAM-89 Symposium, Washington, DC, 1989.