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PETITION RULE PRM 35-9
(54 FR 38239)

Dec. 8, 1989

Samuel Chilk
Secretary of The Commission
U.S. Nuclear Regulatory Commission
Docketing and Service Branch
Docket #PRM-35-9
11555 Rockville Pike
Rockville, MD 20852

Dear Mr. Chilk:

On 5 June 89, the Society of Nuclear Medicine and the American College of Nuclear Physicians submitted to NRC a PETITION FOR RULEMAKING TO AMEND 10 CFR PART 35 TO CORRECT REGULATORY INCOMPATIBILITY AND PERMIT THE TRADITIONAL PRACTICE OF NUCLEAR MEDICINE AND NUCLEAR PHARMACY. The purpose of this letter of support is to present other material that was not developed in the original Petition but appears at this time to merit discussion.

The core of the Petition involves the right of a nuclear physician to prescribe radiopharmaceuticals as he sees fit and the right of a nuclear pharmacist to prepare radiopharmaceuticals as he sees fit in order to fill a prescription for a specific patient. In April of 1987, when the revised regulations for 10 CFR Part 35 were published, it became evident that NRC had essentially annihilated the practice of nuclear pharmacy and had begun to severely limit the practice of nuclear medicine. NRC then put itself into the role of making medical and pharmaceutical decisions. As NRC has proceeded to interpret the new regulations in a stricter and tighter manner, the difficulties arising from this stance have become painfully apparent. NRC has no physicians, nuclear physicians, pharmacists, or nuclear pharmacists, and NRC's medical and pharmaceutical judgments are often either not of appropriate professional quality or are not made in a timely manner. Most important is that I do not think NRC should be making these decisions at all. The function of NRC in my mind remains in its traditional roles of setting and enforcing standards in radiation safety, storage, disposal, handling, etc. of byproduct material.

I believe that it is essential for NRC to review its mandate, because I feel NRC has strayed far afield of Congressional intent. I therefore quote the Atomic Energy Act of 1954, Section 104. Medical Therapy and Research and Development:

"SEC. 104. MEDICAL THERAPY AND RESEARCH AND DEVELOPMENT. -

a. The Commission is authorized to issue licenses to persons applying therefor for utilization facilities for use in medical therapy. In issuing such licenses the Commission is directed to permit the widest amount of effective medical therapy possible with the amount of special nuclear material available for such purposes and to impose the minimum amount of regulation consistent with its obligations under this Act to promote the common defense and security and to protect the health and safety of public.

b. As provided for in subsection 102b. or 102c, or where specifically authorized by law, the Commission is authorized to issue li-

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censes under this subsection to persons applying therefor for utilization and production facilities for industrial and commercial purposes. In issuing licenses under this subsection, the Commission shall impose the minimum amount of such regulations and terms of license as will permit the Commission to fulfill its oblications under this Act.

c. The Commission is authorized to issue licenses to persons applying therefor for utilization and production facilities useful in the conduct of research and development activities of the types specified in section 31 and which are not facilities of the type specified in subsection 104b. The Commission is directed to impose only such minimum amount of regulation of the licensee as the Commission finds will permit the Commission to fulfill its obligations under this Act to promote the common defense and security and to protect the health and safety of the public and will permit the conduct of widespread and diverse research and development.

d. No license under this section may be given to any person for activities which are not under or within the jurisdiction of the United States, except for the export of production or utilization facilities under terms of an agreement for cooperation arranged pursuant to section 123 or except under the provisions of section 109. No license may be issued to any corporation or other entity if the Commission knows or has reason to believe it is owned, controlled, or dominated by an alien, a foreign corporation, or a foreign government. In any event, no license may be issued to any person within the United States if, in the opinion of the Commission, the issuance of a license to such person would be inimical to the common defense and security or to the health and safety of the public.

(42 U.S.C. 2134)"

In Section (a), the Commission is urged to "impose the minimum amount of regulation consistent with its obligations under this Act to promote the common defense and security and to protect the health and safety of the public". In Section (b), "the Commission shall impose the minimum amount of such regulations and terms of license as will permit the Commission to fulfill its obligations under this Act". In Section (c), "The Commission is directed to impose only such minimum amount of regulation of the licensee as the Commission finds will permit the Commission to fulfill its obligations under the Act to promote the common defense and security and to protect the health and safety of the public and will permit the conduct of widespread and diverse research and development."

I believe the Act to be clear and appropriate. I think we can dispense with any issues related to the common defense and security and get right to consideration of the protection of the health and safety of the public. This protection has traditionally been accomplished by setting and enforcing

radiation safety standards. The recent trend of NRC to attempt to take over medical and pharmaceutical decision-making is not only against the intent of the Act but itself represents a threat to the health and safety of the public,not its protection. No member of NRC is licensed to make medical or pharmaceutical decisions in any State in the United States. For the sake of protection of the health and safety of the public, only licensed professionals are permitted this privilege. Therein lies the regulatory incompatability we wish to correct. NRC has set up regulations that presumably permit it to practice medicine and pharmacy and at the same time prohibit licensed professionals from doing so. I believe this stance must be revised.

Although the practices of medicine and pharmacy were not given to NRC by Congress, these functions are mandated to other State, Federal, private, and institutional organizations. State Boards of Medical Quality Assurance and State Boards of Pharmacy govern all aspects of the professional practice of medicine and pharmacy. The Food and Drug Administration (FDA) regulates pharmaceuticals made by manufacturers. The United States Pharmacopeia (USP) sets drug standards for physicians, pharmacists, and manufacturers. The Joint Commission on Accreditation of Health Care Organizations (JCAHO) inspects and accredits medical institutions. These institutions have Quality Assurance, Risk Management, Pharmacy and Therapeutics, and Radiation Safety Committees; if the institution is involved in research it has an Institutional Review Board and perhaps a Radioactive Drug Research Committee, both of which operate under the Code of Federal Regulations. In addition, there are professional standard-setting organizations such as the Society of Nuclear Medicine, the American College of Nuclear Physicians, the American Pharmaceutical Association, and the American College of Radiology. I wish to assure NRC that nuclear medicine and nuclear pharmacy are in no imminent danger of going unregulated if NRC decides to let us have our professions back.

Perhaps one of the most compelling arguments in favor of granting the Petition is to explore what happens or would happen if we obeyed the present regulations and policies.

I. VOLATILITY OF NaI-131

One interesting example relates to NaI-131 for thyroid use. A well known centralized nuclear pharmacy purchases NDA-approved NaI-131 from a manufacturer in Europe. The drug, unfortunately, is not adequately stablized and sodium thiosulfate must be added to the product to suppress I_2-131 generation which immediately goes off into the air when the vial is opened (allowing the patient to sip the contents). Unfortunately, the addition of sodium thiosulfate constitutes the practice of pharmacy which none of the nuclear pharmacies in NRC States and some Agreement States are licensed to perform. As a result, huge quantities of I_2-131 go off into the air as I discovered when I had to report a thyroid burden in my technologist who administered 200 mCi NaI-131 to a patient with metastatic thyroid carcinoma. Volatile I_2-131 represented 16% of the total activity. Complaints came in from all over the country, and at the 1988 SNM annual meeting there was even a careful scientific study presented to demonstrate this problem. FDA was informed, but after an initial flurry of paper and a great deal of posturing, absolutely

nothing was actually done, and the problem continued. Finally, one of the company leaders sent out a directive to all his nuclear pharmacies to add sodium thiosulfate and stabilize the NaI-131, even though doing so make them in violation of their license conditions. It is interesting that another nuclear pharmacy, which purchased adequately stabilized but radiochemical NaI-131 (no approved NDA), was crucified this past Spring by NRC for practicing pharmacy against his license and not using an IND or NDA drug. This practice is perfectly acceptable to FDA, but NRC insisted at first that it was against FDA regulations. When told that the uptake capsules were made according to the U.S.P., one NRC representative asked if the radiochemical preparation was sterile. He did not even know that there is no requirement of sterility for oral drugs, anymore than there is for MacDonald's hamburgers! Later NRC realized their mistaken understanding of FDA regulations, but fined the nuclear pharmacist anyway for violating his license. If he had bought the European product and not stabilized it, he would have been perfectly legal according to NRC, even though large quantities of I2-131 gas would have been released. To cap off this absurdity, both this nuclear pharmacist and the large commercial chain use non-IND, non-NDA capsules and filler for their products. No NDA-approved filler and capsules even exist! This is one example of why we need to put the practice of nuclear pharmacy back into the hands of nuclear pharmacists.

II. ADDITION OF ASCORBIC ACID

Another example of regulatory inappropriateness concerns the fact that NRC-licensed nuclear pharmacists and nuclear physicians are not permitted to add ascorbic acid to Tc-99m-methyl diphosphonate and Tc-99m-DTPA. The ascorbic acid is an antioxidant and keeps the reduced Tc on the desired molecule instead of allowing it to oxidize spontaneously and become unbound. This makes for a better quality radiopharmaceutical. The addition of ascorbic acid constitutes the forbidden practice of pharmacy. No matter that the drug is better --- it is not permitted. When this practice was explained to NRC staff, some did not even realize that ascorbic acid is Vitamin C. Anyone can walk into a supermarket and buy a bottle of 500 mg Vitamin C tablets and pop as many as he likes to prevent an incipient cold (if one believes Linus Pauling). However, the addition of 100 micrograms to a radiopharmaceutical dose caused consternation.

III. ACTIVITY VS. MASS OF TC

An example of regulatory nitpicking ad absurdum concerns the package insert instructions pertaining to the activity of Tc-99m which is to be added to a radiopharmaceutical kit. In fact, a kit can bind a certain mass of Tc whether it be Tc-99m or Tc-99. The package insert, according to FDA, must reflect the worst case, that is, one may assume that the Tc-99m generator was eluted for the first time on the last day before expiration, which of course carries with it a very large amount of Tc-99 relative to Tc-99m. In the case of a commercial nuclear pharmacy which elutes its generators two or three times a day, far more activity may be added than stated on the package insert without saturating the kit contents. A recent violation issued to a nuclear pharmacy because they added twice the activity listed on the package insert was recently shown by both me and an independent NRC scientist to be a few hundred times less than the mass that the kit could accommodate. The manufacturer that made the kit was asked

why an activity number was given instead of a mass number. The reply was that FDA required the package insert to be simple, the instructions were not written with centralized nuclear pharmacies in mind, and that as FDA did not require adherence to the package insert, it did not seem to matter. This last point about the FDA intent of the package insert has been an item of severe contention with NRC since the Petition was submitted. In the second and third addenda to the Petition, sent to Dr. Anthony Tse, we included three published policy statements and one letter from FDA stating that the package insert is informational only, for nuclear pharmacists and physicians, and that deviations in kit reconstitution and product indication and route of administration are certainly permitted. However, the manufacturer cannot be held liable for significant deviations from instructions. These become the responsibility of the pharmacist and physician.

IV. MINORS AND PREGNANT WOMEN

The current regulations and policies have caused some truly strange situations. To my knowledge, no one is taking these two aspects seriously, but it has become illegal to perform nuclear medicine procedures in pregnant women and it is illegal to perform most nuclear medicine procedures in children under eighteen. We could consign these groups to higher radiation, higher risk, or more invasive procedures by turning them over to diagnostic radiology where possible, but this prospect is at present too ridiculous to take seriously. The problem stems from the fact that most package inserts say something like: "This product has not been shown to be safe and effective in children under eighteen or pregnant women." As NRC policy states that we may only employ radiopharmaceuticals for uses that have been shown by FDA to be safe and effective, we are stuck. Although NRC has not issued any violations for this, we have been unable for over a year to obtain a written waiver from these conditions from NRC.

V. LYMPHOSCINTIGRAPHY

Another problem with the regulations concerns the fact a nuclear pharmacist cannot always fill the prescription of an appropriately licensed nuclear physician. Not long ago a broad licensee called his centralized nuclear pharmacy and asked the Director what he had for lymphoscintigraphy. (There is not a single product on the market with FDA approval for lymphoscintigraphy, although the procedure has been performed for over 20 years. A colloid with the correct particle size is prepared under practice of pharmacy/medicine law for this purpose.) The Director informed the physician that everything he had involved the practice of pharmacy, which he was forbidden to undertake. The physician, although licensed to prescribe and make the drug, was not set up to do so at the time. The nuclear pharmacist was told by NRC in Washington that he could not do it because it wasn't NRC's problem - it was FDA's problem! NRC would require FDA to "approve" the procedure first, which at this point amounted to an alteration of the reconstitution of an NDA-approved kit. As FDA does not regulate the practice of pharmacy or medicine, and does not require anybody to obey the package insert, this became a wonderful "Catch-22" until an understanding FDA official gave his own personal opinion that it was probably all right. (The procedure answered the surgeon's question, and the following day the patient had surgery for malignant melanoma.) The nuclear pharmacist spent over three hours on the telephone trying to get permission to prepare the radiopharmaceutical. And, he was told by NRC that if he wanted to do it again he would have to undergo the same process.

VI. THERAPEUTIC RADIOPHARMACEUTICALS

Part of the Petition refers to the provisions of 35.300, in which a physician is absolutely tied to the package insert for therapy drugs. He may not use it for any indication not described in the package insert and may not vary the route of administration. This is not the FDA intent, and there have been problems with P-32 sodium phosphate, P-32-chromic phosphate, and I-131-sodium iodide. The use of P-32-sodium phosphate for treatment of essential thrombocytosis was adamantly denied at the regional level and the physician was threatened with maximal penalty for willful commission of a therapy misadministration if he dared treat his patient. NRC in Washington, much more reasonable, labored for 72 hours trying to find a "legal" way to get the patient treated. The patient was treated after a fascinating mental gyration by NRC, but this has to be decided on a case-by-case basis. The use of P-32-chromic phosphate for intrapericardial metastasis had been denied a physician for years; he has finally gotten permission to do one but a Petition submitted to NRC about six months ago to permit this use generally has never been acted upon. Occasionally in treating a patient with I-131-sodium iodide the physician does not wish to administer it orally. The patient may be vomiting or have some problem swallowing. In that case, the radiopharmaceutical may be prepared for IV injection. I do not know of situations where physicians have asked NRC for permission to do this, which is forbidden under 35.300. Would NRC rather have the patient vomit up 150 mCi I-131 all over the room?

VII. ALARA

Let us consider ALARA, both from the point of view of the patient and the radiation worker. Radiation workers are irradiated primarily when preparing radiopharmaceuticals and to a lesser extent when administering them. They are also irradiated by proximity to patients who have received radiopharmaceuticals. The trio of shielding, time, and distance are varied to achieve ALARA. But making up multiple kits at once by pooling contents ("megakitting"), which decreases radiation absorbed dose to the nuclear pharmacist, is forbidden by NRC because it is not described in the package insert. Likewise, using a syringe shield may prolong an intravenous injection, require multiple sticks, and result in significant infiltration and a repeat administration. This is not necessarily ALARA for the worker or for the patient.

The patient gets ALARA several ways, the main ones being the choice of radiopharmaceutical and the choice of administered activity. I am primarily concerned here with the choice of radiopharmaceutical, because many radiopharmaceuticals which require deviations from package insert instructions or have no IND's or NDA's at all are nevertheless drugs of choice and give lower radiation absorbed dose to the patient than drugs that conform to NRC regulations. This is a travesty of ALARA. For example several years ago my laboratory developed a Tc-99m-leukocyte preparation which required a package insert deviation. By substituting a 5 mCi Tc-99m-leukocyte preparation for a 500 μCi In-111-leukocyte preparation, I save, on a yearly basis, 80% of the total "national debt" due to whole body radiation from nuclear medicine misadministrations. That is one procedure in one 500-bed hospital. The NRC is mandating an orders-of-magnitude increase in radiation absorbed dose relative to the amount they wish to save from misadministrations, simply because of unfortunate regulations.

If the definition of a misadministration were to include "administration of a radiopharmaceutical or alternate procedure different from the first choice of the nuclear physician resulting in 50% or higher whole body radiation absorbed dose", the largest perpetrator of misadministrations in the United States would be NRC.

VIII. DEATHS

Now, let us get even more serious. Let us talk about deaths. Death that would be caused by obeying NRC interpretations of its regulations. I have chosen one example, and that is the use of Tc-99m-macroaggregated human serum albumin (MAA) for imaging purposes. This is a scenario of what would happen if we obeyed NRC directives to conform to the package insert. It should be a relief to NRC to know at the outset that no physician I know of has done so. Granting of the Petition should insure that no physician ever will.

The package insert for MAA contains a contraindication. It states that this procedure is contraindicated in patients with severe pulmonary hypertension. The procedure in question is a scan to diagnose blood clots in the pulmonary artery circulation (pulmonary embolus). Approximately 5% of nuclear medicine procedures are lung scans, so we perform about 500,000 lung scans/year. Let us say of these patients, 100,000 have pulmonary hypertension and 10,000 have "severe" pulmonary hypertension. What would happen to those 10,000 patients who could not be scanned with MAA? There are several possibilities. The first is that the patients could undergo pulmonary angiography, an invasive radiologic contrast procedure in which a catheter is threaded up a large peripheral vein to the heart, through the right atrium and right ventricle and out the pulmonary artery into the right and left branches and sub-branches thereof. Contrast material is injected at multiple sites and fluoroscopic images obtained. This is an excellent system for diagnosing pulmonary embolus, but it has several drawbacks. For one thing, the death rate is 25/10,000, but these 25 are mainly the high risk patients, that is, those with severe pulmonary hypertension. The complication rate overall is, 160/10,000 (complications include serious arrhythmias, venous and arterial perforation and hemorrhage, damage to cardiac valves, septal perforation, pneumo/hemo-thorax, etc.). Last but trivial by comparison, the radiation absorbed dose to the lungs (2200 mrem) is 4.4 times as high as that with MAA (500 mrem to the lungs). It would not be unexpected to find an overall death rate in these patients to be 10-20%, and most angiographers would not undertake these procedures if at all possible. Another thing we could do with these high risk patients is treat them with an anticoagulant for presumed pulmonary embolus, without ever proving they have the disease. If the drug used for this purpose, heparin, were harmless, that would be a reasonable possibility. However, the death rate from heparin is 9.5/10,000, and complications (hemorrhage) are common. It is not acceptable to use this drug without ascertaining that the patient has the disease in the first place. That is why standard medical textbooks state that the test of choice for pulmonary embolus in these patients is the lung scan.

Why, then, does the package insert for MAA list this contraindication? Because in the 1960's and early 1970's, three deaths were reported in the United States and one in England from MAA scans, and all patients had severe pulmonary hypertension. Two of those patients were terminally ill and two

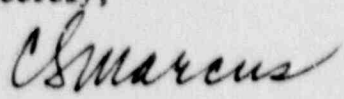
others would not have lived much longer. One had very widespread metastases from breast cancer, two had severe progressive systemic sclerosis, and the fourth was a child with very severe birth defects. In those days, about ten times the number of MAA particles were used to plug pre-capillary arterioles than are used at present, and the products used then are not the products in use now. No one today pays any attention to this contraindication, and in fact few nuclear physicians were even aware that the package insert included it until NRC, by recently issuing two violations of the package insert instructions, made us read the thing. Nuclear medicine physicians are taught to drop the number of administered particles by a factor of ten or twenty for patients with severe pulmonary hypertension or right-to-left intracardiac or intrapulmonary shunts. Nuclear pharmacists are frequently asked to make high specific activity particles (the same administered activity but on the lower number of particles), and this has been standard practice for at least a couple of decades. Suddenly, NRC has decided that this is not permissable because these instructions are not in the manufacturers instructions. It is very difficult for me to believe that NRC really expects us to put our patients at risk with unreduced numbers of particles, not enough activity to perform a good quality study, a stroke (in the case of right to left shunts) or deny this safe and effective study completely and turn the patients over to high risk angiography or a high risk drug (heparin) treatment.

If NRC really expected us to do this, and there were any physicians or pharmacists foolish enough to comply, NRC would have to bear the responsibility for causing deaths. Such publicity would be most unfortunate.

Please let us help you change the regulations. It would be very wise for NRC to grant this Petition.

Thank you for your attention and consideration.

Sincerely,



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