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TORRANCE, CALIFORNIA 90509

Nov. 27, 1990

John E. Glenn, Ph.D.
U.S. Nuclear Regulatory Commission
11555 Rockville Pike
Rockville, MD 20852

Dear John:

As we discussed, I have extensively considered the Immediately Effective Interim Final Rule (FR 55(164): 23 Aug 90, pp. 34513-34518) and the existing portions of Parts 30 and 35 to which it refers. You requested that I consider interpretations that would be desirable and you also requested information about types and frequency of package insert departures.

With my usual brevity (!), I have endeavored to comply. (you certainly won't be able to say that I held back any information!)

I have recommended and described numerous interpretations of Parts 30, 32, and 35 as well as the Interim Rule in order to make the Interim Rule accomplish that which I believe is necessary. Unfortunately, I do not think that this will really be sufficient to solve the problem and I have added the concept of a substitution. I have included a "Surrogate Survey" to substitute for the three-year recordkeeping requirement. I believe the Surrogate Survey to be more complete and more accurate than NRC could attain with the recordkeeping scheme described in the Interim Rule.

If NRC will accept the recommended interpretations and the Surrogate Survey, we can consider significantly shortening the duration of the Interim Rule and addressing the issue in the Petition, which was to remove the package insert entirely as the "gold standard" by which NRC is trying to make us practice medicine and pharmacy. I think that this report should convince you that this has been an unsuccessful NRC effort for good reason, and that the Interim Rule will probably create more problems than it solves.

Gold standards are created by expert consensus, not by regulation or legislation. You probably remember the story about the State Legislature that set the value of π at exactly 3.14. Scientists and mathematicians could not accept it, of course, and it was repealed. Well, the experts in nuclear medicine and nuclear pharmacy are telling you that they reject NRC's false "gold standard" of medical and pharmacy practice, and it is time you repealed Package Inserts.

The nicest thing I can say about the Interim Rule is that it completely misses the point. (I say less nice things about it as this report goes on, but I want to lead you into this gently.)

The appended manuscript is divided into several sections which I believe will be of use to you. Section I deals with background information essential to

the understanding of this issue in general and with the wording and background of the Interim Rule in particular. Section II. covers my actual recommendations. Section III, The Surrogate Survey, covers virtually all the package insert departures or classes of departures that are used each year in the entire United States, and the approximate numbers of each departure. These totals are for the entire country, and do not distinguish between NRC and Agreement State licensees. There is also a section written by Dennis Hoogland, Ph.D., describing common nuclear pharmacy package insert departures. This was compiled for FDA and was received by Dr. Temple (and by Mr. Cunningham) in April, 1990. No one at FDA or NRC has conveyed a single negative comment about any of these departures in the seven months since the report was received. Most of the other departures discussed in Section III. have been discussed in the ACNP-SNM Petition or have been discussed separately in letters sent by members to Mr. Cunningham or Mr. McElroy, and to Dr. Temple at FDA. No negative comment concerning any of these departures has been conveyed to us, and 7 mos. to 2½ years have elapsed since description of these departures were received by both agencies.

I sincerely hope you will give my recommendations careful consideration, as we would all like this Interim Rule to do as little damage as possible. We are also anxious to settle this issue so that we may get on with the major issues of the Petition which have not been addressed as yet despite the fact that the Petition has been at NRC for over 17 months.

Sincerely,

Carol

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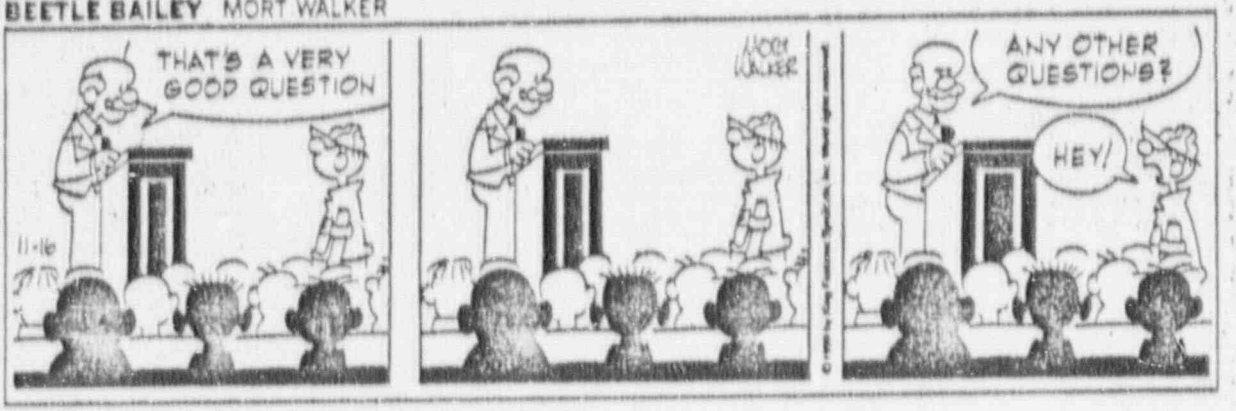

RECOMMENDATIONS CONCERNING THE INTERPRETATION OF THE INTERIM RULE AND THE EXISTING PORTIONS OF PARTS 30 AND 35 TO WHICH IT REFERS

Prepared by

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November, 1990

SECTION I.

BACKGROUND AND INFORMATION

The Congress of the United States relegated the practices of medicine and pharmacy to the States to govern. This has never changed throughout the history of this country. Each State has laws and regulations pertaining to the practice of medicine and to the practice of pharmacy. Each State has a Board of Medicine and a Board of Pharmacy to decide issues and review professional conduct. Licensure in a State is determined by the Board. Peer review is the essence of all professional decisions made by the Boards. Guidance for the State Boards comes from National Boards in every medical and pharmacy specialty. Professional consensus is the very backbone of medicine and pharmacy because these professions do not and by their nature cannot have detailed, prescriptive rules. Patient problems are exceedingly complex, with confounding variables that are often unidentifiable and at best, changing and only occasionally quantifiable. The standard of medical and pharmaceutical practice is an elusive moving target, judged by qualified professionals on a case by case basis. There are no prescriptive regulations in any State for pediatrics, orthopedics, obstetrics/gynecology, general surgery, urology, internal medicine, or psychiatry; there are none for hospital pharmacy, clinical pharmacy,or retail pharmacy. It does not make any sense to attempt to make any for Co-60 therapy, brachytherapy, nuclear medicine, or nuclear pharmacy, either.

I believe that NRC has made two erroneous decisions that are the basis of our current problems. The first mistake was for NRC to distort Section 104 (Appendix I) of the Atomic Energy Act and decide to regulate the actual practices of medicine and pharmacy despite a warning in the law to avoid this action. I do not accept NRC's attempt to preempt States rights or to overturn State Law and do not believe that NRC has any legal authority to dictate the practices of medicine or pharmacy. NRC's mandate is radiation protection of the public and of workers. Radiation protection of the patient is the responsibility of medical professionals, and the responsibility for patient radiation safety guidelines was specifically given to DHHS in 1981 (see Appendix II) in 42USC10001-10008.

The Federal Government has passed numerous laws that impact on the practices of medicine and pharmacy, but none that dictate it. For example, in 1938 the Food, Drug, and Cosmetic Act was passed, and the present form of the FDA was established. The FDA regulates new drug research and drug manufacturers. It is specifically forbidden to regulate the practices of medicine and pharmacy. Mor[illegible]t is the States that

decide that which constitutes the practices of medicine and pharmacy and not FDA.[1] The USP promulgates drug standards, but does not dictate the practice of pharmacy. OHTA controls technology assessment for reimbursement, and HCFA sets the rates. EPA regulates toxic effluents. However, none of these agencies regulates actual medical or pharmacy practice, although they influence it. JCAHO can suspend or revoke accreditation of hospitals and healthcare organizations because of generally bad practices, or they can insist that specific failings be improved before certification, but they cannot prevent certain practices of medicine and pharmacy. They can only prevent reimbursement by government agencies. And, unlike NRC, all JCAHO inspectors are experienced healthcare professionals.

The second serious mistake NRC has made is its relentless quest for the perfect procedure manual and the perfect and all-encompassing set of prescriptive rules with which to regulate the practices of medicine and pharmacy. NRC may as well search for the Holy Grail, the Fountain of Youth, or Second Law Violations. This elusive goal is theoretically impossible because of the nature of the process. It may be appropriate and possible to write all-encompassing procedure manuals for nuclear submarines and nuclear reactors, but it is inappropriate and impossible to do so for the raising of children, establishing a positive lifetime relationship with your spouse, painting masterpieces, composing fine music, or the practices of medicine and pharmacy. NRC often gives the excuse that prescriptive regulation is its "style", and that its staff is not capable of evaluating medical and pharmaceutical judgment and needs this prescriptive regulatory

1 Although this function was temporarily given to AEC from 1963-1975 for byproduct drugs, the FDA lifted the exemption and the change is documented in the Federal Register (Appendix III). It is discussed in a chapter written in 1975 and published in 1976 by Earl Myers of FDA and Richard Cunningham of NRC (Appendix IV.). The regulations concerning nuclear pharmacy, promised in the 1975 Federal Register article, were never written. Instead FDA published its 1984 Guidelines for Nuclear Pharmacy (Appendix V; also appended to the ACNP/SNM Petition). It is still very much in effect. When FDA took back the regulation of radioactive drug research from AEC some new FDA regulations were needed to accomplish this. These regulations, 21 CFR 361.1, are in Appendix VI.

approach. That may well be true but it is also irrelevent. NRC should change its style and its medically unqualified staff should not be practicing medicine and pharmacy without a license in the first place. Seeking a convenient crutch for its staff to clutch, NRC chose a false god indeed, the package insert. In a remarkable stroke of regulatory arrogance, NRC imposed as the standard of medical and pharmacy practice an informational and non-binding document from an agency that cannot even regulate the practices of medicine and pharmacy in the first place, FDA. Package inserts are oversimplified, limited in scope, occasionally internally inconsistent, virtually always out of date, and are not the "manufacturers instructions". They are FDA's instructions to the manufacturer and there are often profound disagreements between FDA and manufacturers about package insert contents. If Congress in its wisdom has denied FDA the right to enforce the package insert, it is difficult indeed to imagine that it would grant the non-medical professionals at NRC this privilege. If NRC felt consumed by the need to regulate the practices of medicine and pharmacy, it should have gone for clues to those who do so, the States. In doing so, NRC would have found that no cozy cookbook is available. By insisting on using a "gold standard" as wretched as the package insert, NRC has jeopardized patient care in a variety of ways, some of which were covered in the ACNP/SNM Petition.

When NRC's behavior became even more inappropriate after the Petition was received than beforehand, several ACNP/SNM members spoke with NRC about a "Gentleman's Agreement" to remain in effect until the Petition was put into effect. The initial agreement, which was not very satisfactory but which was at least usable, deteriorated almost beyond recognition into the Interim Rule. Thrust onto the Nuclear Medicine/Pharmacy community without a period of public comment or an explanation of its meaning, NRC's excuse has been to blame FDA for the Rule's obnoxious content and to thus far refrain from explaining its meaning, in part at least from basic lack of comprehension of our field. Blaming FDA is not convincing. If FDA informed NRC that reactors were determined to be "devices" and would in the future be regulated by the Center for Devices and Radiologic Health, would NRC obediently comply? What if the real reason NRC chose to craft such an inappropriate rule?

Let us take a frank look at the regulatory morass NRC created with its April, 1987 rulemaking and the plethora of interpretations of 35.200(b) that followed. Today we

prepare about 10,000,000 radiopharmaceutical doses a year. At least 5,000,000 of them depart from a strict interpretation of the package insert an average of twice, for a total of 9-10 million departures per year. NRC's present interpretation of 35.200(b) and 35.300 (last sentence) has become nothing more than Draconian nonsense. The Petition had a simple cure for this problem, namely, the removal of 35.200(b) and the last sentence of 35.300. Can the convoluted, insulting, and (I believe) illegal Interim Final Rule give us the "regulatory relief" NRC had sincerely promised? It is marginally possible, but it will take a great deal of cooperation by NRC on the question of interpretation and substitution to accomplish this.

For example, it is obvious that NRC had no idea of the extent to which package inserts have been necessarily ignored. (It would be interesting to see NRC's estimate of paperwork burden to OMB in this regard.) The data-keeping and tallying requirement would be enormously burdensome. In addition, it is amusing to imagine NRC's (or FDA's) "data analysis" of $1 \times 10^7 \times 3$ years x 40% = 12,000,000 bits of non-uniform data by staff who have virtually no understanding of radiopharmaceutical chemistry. I have therefore decided to use this document to relate a good approximation of the nationwide tally of the litany of departures listed in Section III. This has two advantages. First, it reflects the whole nation, not just NRC licensees. Second, as FDA is blamed for this unpopular record-keeping requirement to begin with, why not give them the information they appear to want in an accurate manner? Licensees will be saved time and expense, and NRC staff will not have to waste taxpayer's money performing an impossible analysis. This should make everyone happy. Therefore please consider Section III the culmination of a three year survey of departures and totals. Now, what does NRC plan to do with it? I suggest NRC have it reviewed by its ACMUI, if anything, and send a copy to FDA if it likes.

Another example of NRC's interpretation flexibility that will be absolutely essential is in the area of patient benefit in the category of "cost effectiveness". Cost effectiveness must be an appropriate reason for a package insert departure. The DHHS has made cost effectiveness the First Law of Medicine in the USA, and NRC needs to internalize this. DHHS wants the cheapest way of doing a satisfactory study. As "He who pays the piper calls the tune", we comply. FDA requires cost effectiveness before they approve a new drug, OHTA requires cost effectiveness for new healthcare technology, and HCFA requires cost effectiveness when they

set the reimbursement levels that dictate federal and most private payor reimbursements. If we cannot do a study for the reimbursement offered, the patient goes without the study. Why doesn't NRC try going to HCFA and ask them to pay the extra cost of new requirements that NRC thinks would be nice but cannot prove valuable or necessary and which we think are scientifically unsubstantiable? The bottom line is that if we have a cheaper way to make a satisfactory drug we will do it, package insert not withstanding.

Still another example of advisable NRC flexibility lies in the licensing options available under 32.72(2)(ii). As discussed in the Petition, the NRC has never permitted a centralized nuclear pharmacy to exercise this option and restricts such licenses to always exclude it. It is interesting that NRC made a regulation permitting an activity and then denied it to every single applicant for approximately 15 years. Why not use it? The stabilization of NaI-131 to prevent dangerous airborne contamination is an excellent example of how to use the license to benefit public health and safety. Nuclear pharmacies prepare about 90,000 of these doses/yr for diagnosis and therapy from NDA-approved material that nevertheless requires stabilization. It is silly to ask physicians or pharmacists to keep track of 90,000 x 3 x 0.4=108,000 departures/3 yrs when all NRC has to do is permit nuclear pharmacies to do this by license amendment. The same is true of the stabilization of Tc-99m-MDP and Tc-99m-DTPA with approximately 1 mg of ascorbic acid (vitamin C) per dose. Nuclear pharmacies then would stabilize about 1,100,000 doses/yr in the United States, which would represent 1,100,000 x 3 x 0.4=1,320,000 items of recordkeeping for NRC licensees over 3 years, which is also silly. This could simply be done by a license amendment as well. Nuclear pharmacies, of course, would not be the only source of this departure. This methodology has been in the literature for many years and is used by other as well. Such amendments would be "interim", until the package inserts were dropped altogether.

NRC may well decide to rescind the Interim Rule and avoid all these problems and give us instead what we asked for in the Petition, namely, the removal of 35.200(b) and the last sentence of 35.300. No one paid any attention to package inserts before 1987 and not many did afterwards and no harm is evident. Although many physicians will deny knowingly deviating from package inserts, most in fact have no idea what is in the package inserts, either. After 100,000,000-150,000,000 administrations of radiopharmaceuticals over the last 53 years without very much regard to package inserts at all, NRC had better find a lot of

radioactive corpses or stop uttering self-righteous threats of mysterious risks to public health and safety which it cannot document. Now that NRC has the information it wants (Section III), it needs to act appropriately and as quickly as possible.

In the event that NRC needs an "Interim Understanding" of the Interim Rule until a final decision is made, please find my specific recommendations in the following section.

SECTION II.

SPECIFIC RECOMMENDATIONS

RECOMMENDATIONS FOR INTERPRETATION OF 10 CFR 35.200(b): A licensee shall elute generators and prepare reagent kits in accordance with the manufacturer's instructions.

1. "In accordance with" means "in agreement with", not "word for word mindless obedience". The package insert directs the user to make a safe and effective product, and if one does that he is "in accordance with" the package insert. This allows for some measure of variability and encompasses Good Pharmacy Practice. This more liberal interpretation was actually stated by NRC to be the intent of the April, 1987 Rule in the first place, but was eroded over time into the unworkable situation we have facing us today. This semantic, artificial problem may easily be relegated to non-problem status by going back to the original NRC intent of interpretation.

2. Kit preparation does not include how many hours have elapsed from nuclear pharmacy to nuclear medicine department and how many more hours elapse until the dose is actually administered. Kit preparation does not include anything about quality control - if it is done at all, how it is done, or when it is done before or after dose administration. Therefore, time considerations, Q/C, and any other aspects of the package insert that are not directly about preparation should not be considered under 35.200(b).

   FDA has begun to add items under "Kit Preparation" instructions that have nothing to do with kit preparation, just to get NRC to enforce FDA's will. NRC has seemed perfectly willing to be used by FDA in this manner. We hope that NRC will no longer allow itself to be abused this way and will no longer abuse nuclear medicine/pharmacy professionals with FDA's insidious little mischief either.

RECOMMENDATIONS FOR USE OF 10 CFR 32.72(2)(ii)

1. Consult with licensees who manufacture and distribute radiopharmaceuticals in order to add license conditions that obviously facilitate safety (patient, worker, or member of the public) and efficacy. Examples are the stabilization of NaI-131 and the addition of ascorbic acid as an antioxidant to DTPA and MDP kits.

RECOMMENDATIONS FOR INTERPRETATION OF 35.200(c)(1) and 35.300(b)(1): Permissible benefit categories.

1. The wording of the conditions under which a physician may decide to depart from package insert instructions is devious and contemptible. It can mean anything or nothing, and is so poorly crafted that I will not waste time dwelling on it but will instead list appropriate reasons for departures which will be necessary for NRC to accept in order for this Rule to cover necessary departures and be of any value to us:

The nuclear physician should have an appropriate degree of expectation that the departure will yield a result that has

a) lower morbidity or mortality than an available alternative

b) higher sensitivity or specificity than an available alternative

c) higher resolution than an available alternative

d) the advantage of timeliness in diagnosis or treatment compared to an available alternative

e) lower radiation absorbed dose to the patient than an available alternative

f) cost effectiveness superior to an available alternative

g) a chance of helping the patient when equivalent or superior procedures are unavailable because of location, lack of appropriate personnel, or lack of necessary instrumentation or resources

h) minimized patient inconvenience, unpleasantness, pain or fear

i) a rather low probability of benefit but may preclude the need for a dangerous procedure, use of a dangerous drug, or use of a relatively expensive diagnostic alternative procedure

j) a high probability of satisfying the primary care or requesting physician who does not wish his patient to undergo an alternative procedure

k) a higher degree of worker safety than an available alternative

l) a higher degree of public safety than an available alternative

m) advantages representing a combination of the above reasons.

The licensed nuclear physician does not know what the package insert says and orders that which he believes is appropriate, only to find out later that it was a departure.

Whether or not the preparation is a departure depends on the brand of kit one uses. A physician may order an ordinary dose but the brand the pharmacist used necessitated a departure prescription.

Other reasonable reasons.

RECOMMENDATIONS FOR DOCUMENTATION OF PRESCRIBED DEPARTURES AND NUMBERS OF DEPARTURES IN EACH CATEGORY

The record-keeping requirement of the Interim Rules is fatally flawed because it is virtually impossible to comply with as written under present NRC interpretation of 35.200(b). In the original verbal negotiations with the NRC we agreed to prescriptions for departures, but not to tallying totals in each category. The agreement for prescriptions for departures was silly but we could comply with it. Nuclear physicians know how to use their drugs, but they do not know or care to know or care about what FDA has forced the manufacturer to put in a package insert. Therefore, SNM/ACNP and the nuclear pharmacies were going to put together a "megalist" of departure "prescriptions" and distribute it to nuclear physicians who would sign them as fast as they could, send copies to their nuclear pharmacies, put a copy in their procedure manuals and forget about it. Business as usual until the NRC finally acted on the Petition. If this prescription requirement had been tested in court it would probably have been thrown out, but it was so simple in concept we felt that no one would bother and NRC would presumably have acted on the Petition in a relatively short time and it wouldn't matter. (You may recall that NRC was working on the "fast track" portion of the Petition at the time we were negotiating this. The fact that the "fast track" rule was a complete failure that had to be trashed in late December, 1989, and that it apparently died completely at that point, was not known to us during the November and early December discussions.)

When the Interim Rule appeared, only certain convoluted categories of deviations were to be "permitted", and it was almost impossible to figure out what they were by reading the Rule. In the original agreement, any physician decision was to be "allowed". The Interim Rule made the tacit assumption that no one was committing package insert departures. The truth is that package insert departures have nevertheless been a prominent part of the standard of medical practice,

especially with the nit-picking interpretive escalation that occurred at NRC in 1990. Virtually all NRC licensees had become "paper criminals" at some time or other, except some of the broad licensees who are exempt, and the situation has become ridiculous. Many procedures depend on departures which may well be disallowed with the Interim Rule.

One reason, therefore, that we cannot comply with the record-keeping requirements is the simple fact that by today's NRC interpretations as we understand them, most of our departures are in "disallowed" categories and we will have to continue to perform them without reporting the "unreportable". We have been surviving on Mr. Cunningham's memo to the Regions of Dec., 1988. As NRC never resolved the difficulties mentioned in the memo, NRC would be wise not to rescind its policy as derived from that memo. If the Interim Rule were interpreted along the lines suggested in this report, at least all our departures would be "allowed". On 3 May 90, I sent a letter to Harold Denton concerning departures from package inserts in the reconstitution and preparation of non-radioactive drugs, to compare similar situations. This letter was sent to Mr. Cunningham and Mr. McElroy as well. It is included here as Appendix VII. Departures from package insert instructions in preparing non-radioactive drugs at Los Angeles County-U.S.C. Medical Center in the Medical Intensive Care Unit occurred about 25% of the time. It is the standard of pharmacy practice and very important. It is also, of course, entirely "allowable". I sincerely believe that if this issue of "allowable" departures ever came to court, NRC would lose without question. Even FDA, which crowed for months about how they were going to take over a portion of pharmacy practice through an interesting court case in which a pharmacist caused several patient deaths, had to back down recently, presumably because the Justice Department would not take the case. I hardly think the courts would back NRC's non-existent drug "expertise" with no adverse reactions to point to when they rejected FDA's expertise with deaths to point to. As your consultant, I would recommend that you avoid court at all costs if at all possible.

Now let us get to the really serious problem with the record-keeping requirements, which is the tallying. With NRC's current interpretation of 35.200(b), we will have about ten million departures a year to tally, or about twelve million to tally over three years by NRC licensees, assuming no duplication of tallying by physicians and pharmacists. (This is unclear in the Interim Rule, which reads as though both physicians and centralized pharmacies have to tally duplicatively. If this is the case, add another six million.) There are

millions of instances in which either the physician or the pharmacist or both will not know that a tallyable departure has occurred (see Section III, Note (2) at end.) It is clear that NRC had no idea of the magnitude of this clerical nightmare, but neither physicians nor pharmacists can do it. The physicians are gambling at present that NRC will alter its interpretations so that millions of these "departures" will be excluded. The truth is that most physicians have no idea how often they have "departed" and are unaware of the magnitude of this potential mess. The nuclear pharmacists have good reason not to expect reasonableness from NRC, and are hedging their bets with an appeal of the Interim Rule.

If NRC subscribes to the interpretations recommended in this report, the tallying requirements would go down considerably but would still be repugnant to licensees. There will, of necessity, be gross underreporting and the value of the entire survey will be exceedingly questionable. We are not getting anywhere.

I highly recommend that NRC use Section III as a more accurate survey and tally for the projected three years than NRC would obtain through its Interim Rule, and abandon the tallying requirement entirely as a bare minimum and the prescription record-keeping as well as it would not serve any useful function. We would then expect NRC to present this document to its ACMUI at the Jan 14-15, 1991 meeting, amputate the Interim Rule at 5 months (late January, 1991) as long as the ACMUI approves and substitute the deletion of 35.200(b) and the last sentence of 35.300. Give it a reasonable public comment period and let the FDA make their comments public. Or, just withdraw the Interim Rule immediately and publish the substitution immediately after nuclear medicine and pharmacy leadership and industry representatives have seen it, so that there is no more opportunity for mischief. I would hope that NRC has learned its lesson by now.

As an aside, I cannot understand why NRC made a 3 year Interim Rule when the Petition should be decided in its entirety long before then.

SUMMARY OF SPECIFIC RECOMMENDATIONS

The NRC has attempted to inflict an inappropriate "gold standard" on nuclear medicine and pharmacy practice. The ensuing discontent caused Mr. Cunningham to request a Petition to correct the problems. The Petition was received in June, 1989. An Immediately Effective Interim Final Rule to address a minor portion of the Petition was published on Aug. 23, 1990.

The Interim Rule is seen to be illegal, insulting, naive, and unworkable. It is recommended that NRC adopt the interpretations described herein, accept Section III. of this report as a surrogate recordkeeping entity, then discontinue the Interim Rule and immediately substitute unchanged the portions of the Petition that relate to this issue (for physicians and nuclear pharmacies).

SECTION III.

THE SURROGATE SURVEY

(Departures +3 year frequency estimates)

RADIOPHARMACEUTICAL DEPARTURES

1. CIS NaI-131 stablized with sodium thiosulfate-EDTA. Sixty per cent of our 150,000 NaI-131 doses per year use this NaI-131 product. There is a very high volatility rate otherwise which jeopardizes workers and the public. Patients get less than the dose calibrator reading. One reputable laboratory reported sixteen (16) per cent volatility with unstabilized material which resulted in an action level worker thyroid burden and a therapeutic "misadministration" (underdosed by sixteen percent). Three year nationwide tally based on 1989 data = 270,000 departures.

2. Amersham medronate package insert directs that 2-8 ml $NaTcO_4$ generator eluant be added to the kit. Centralized nuclear pharmacies, which use 10 and 16 Ci Mo-99/Tc-99m generators, would fry the kit contents if they used so much activity (the package insert for the generator calls for a 5cc elution volume). In order to avoid a useless product destroyed by radiolysis it is necessary to dilute the generator eluant with normal saline. The amount of dilution depends on the activity, age, elution efficiency, and time since previous elution. The nuclear pharmacist must use his own judgement here. The physician cannot write a prescription for this. It would be malpractice for a nuclear pharmacist to reconstitute the kit according to the package insert. The three year nationwide tally estimate, assuming that this brand of kit represents about 60% of the market, is 1,800,000.

3. Addition of ascorbic acid (approximately 1 mg per dose) to DTPA and MDP kits. This addition of antioxidant retards the inevitable tendency of Tc-99m to undergo oxidation to TcO_4^- and assures optimal radiopharmaceutical performance for highest quality diagnostic accuracy. From 1974-1987, this was common practice (about 40-50% of doses). In 1987 NRC insisted that nuclear pharmacies stop, and they did. One nuclear pharmacy requested a license amendment at the time but information requested by the agency (NRC), in reality, required the filing of a paper IND. The nuclear pharmacy asked the agency who would review the amendment. NRC stated no one within the agency was qualified. The nuclear pharmacy then refused to submit the data and dropped the request for an amendment. NRC therefore degraded radiopharmaceutical drug quality. The practice continues to some extent by other nuclear pharmacies and some nuclear medicine departments, although it is not very widespread. Once this departure is "permitted", one nuclear pharmacy chain's three year tally would be about 3,3000,000, because it makes about 40% of the nation's patient doses. Other centralized nuclear pharmacies, which make about 14%, would probably use ascorbic acid as well. I cannot estimate how many individual departments,which make up 46% of doses.

would use ascorbic acid. Probably many of the better ones would do so.

4. Na_3PO_4-P-32 for treatment of idiopathic hemorrhagic thrombocytosis. This has been the drug of choice for this bone marrow disorder for about 50 years. Three year nationwide tally estimate = 25.

5. Preparation of NaI-131 (an oral drug) into a parenteral preparation by buffering and administration through a millipore filter. This is necessary in patients who cannot swallow dependably or effectively or who are vomiting. Three year nationwide tally estimate = 25.

6. Use of P-32 chromic phosphate for intrapericardial metastases. This route of administration does not appear on the package insert, which includes intrapleural and intraperitoneal administration. Three year nationwide tally estimate = 25.

7. Adding more Tc-99m activity than stated on package insert. The activity maximum listed on a package insert for reconstitution purposes must be applicable in the most extreme case, which is Tc-99m obtained from a two week old generator that was never eluted until just before expiration. The nannomolar concentration of Tc-99 is far greater than that of Tc-99m, ties up most of the kit ligand and limits Tc-99m activity that may be added. Centralized nuclear pharmacies elute generators daily and often two to six times a day; the relative quantity of Tc-99 accompanying the Tc-99m is much lower. There is plenty of ligand available for increased Tc-99m activity. In order to maintain medical costs ALARA, while still maintaining safe and effective drugs that meet USP standards, it is appropriate to add increased Tc-99m activity. The Tc-99/Tc-99m ratio in a generator eluted for the first time just before expiration is about 400. A generator eluted 1 hr. after the previous elution has a Tc-99/Tc-99m ratio of about 0.43. There are probably about four million deviations per year in this category in the U.S., or about 12 million over three years.

8. Deviations from the "six hour rule" for any applicable radiopharmaceutical due to emergent or urgent time constraints in patient care.

   The physician is obligated to do the best he can with what he has available within the time constraints appropriate to the patient. The same is true of a pharmacist providing a drug to a physician for patient use. In the

event that the drug can be expected to meet USP standards, there is absolutely no problem in using it after six hours. In the event that the drug is not expected to meet USP standards, the Food, Drug and Cosmetic Act is very clear. It is perfectly acceptable to provide and use the drug so long as "USP" is not used in the label. Professionalism requires that a physician be informed that the drug is possibly or probably not up to USP standards. In radiopharmaceuticals, this nearly always means more Tc-99m oxidation has occurred than one would usually expect. For example, let us assume that a recent renal transplant patient is suspected of having acute renal artery or renal vein thrombosis. The urologist wants a renal flow and function study now. The nuclear physician has enough Tc-99m-DTPA or Tc-99m-MAG-3 around to perform the study, but it was made fourteen(14) hours before and might have fifteen(15) or twenty(20) per cent free technetium (pertechnetate). Would the physician use it? Of course. I would use it with the possibility of one-hundred per cent free pertechnetate. I could still get an answer that would help the surgeon decide if he needed to perform emergency surgery.

It is instructive to review the basis for the "six hour rule", in order to understand why so few professionals consider it particularly critical. The "six hour rule" is not based on product stability. It was based on a fear of an FDA chemist many years ago that as the kits contained no bacteriostatic agent, bacterial contamination at the time of kit preparation could cause contamination problems that got worse with time and so a recommended six hour maximum from reconstitution to administration was arbitrarily devised as a practical limit. This occurred before the development of centralized nuclear pharmacies, for which it was impractical. For the centralized nuclear pharmacies, the essential question became radiopharmaceutical stability. This was ascertained for most products out to twelve(12) hours. Bacterial contamination has never been a problem with radiopharmaceuticals, as documented previously in review articles sent to Mr. Cunningham in May, 1990.

Of the ten million nuclear medicine procedures performed per year, about eight million involve Tc-99m. Four million of them are provided by centralized nuclear pharmacies. Of that four million, probably two and one half to three million ignore the "six hour rule". Of the four million made within the nuclear medicine department, probably about one million are used after six hours, especially if one counts the departments that use "instant

tech" that was milked at 1 to 2 AM and has a "twelve hour rule" for the eluant. So, about four million patient doses per year do not conform to this package insert recommendation, which tallies to 12 million over three years. (This includes Departures no. 8 and 9.)

9. Departures from the "six hour rule" in nonemergent or non-urgent cases. If the physician has reason to believe that the product stability is such that a perfectly acceptable diagnostic study will ensure, it is acceptable to use the drug in order to maintain medical costs ALARA. The patient may have arrived late; the nuclear pharmacy may not be able to deliver another fresh dose for several hours. The patient may not be able to stay and may opt to skip the study rather that wait. This is usually not to the patient's advantage and the referring physician may be appropriately annoyed that the study was not performed in the time frame he felt acceptable.

10. Lack of performance of quality control after kit reconstitution. Only a few recent package inserts include Q/C under kit reconstitution instructions, and it is generally not necessary. In most cases, Q/C is performed to ascertain % TcO_4^-. It is time consuming, adds cost to the procedure, and in many departments is performed only when there is a question of product stability (very seldom) or to validate a reconstitution procedure or stability measurement over time. Q/C procedures are often performed after the drug has been administered, as a random batch check, or to check a nuclear medicine technologist's or nuclear pharmacist's performance. In emergent or urgent situations it is generally ignored, and in routine situations it is often difficult to justify the time and cost commitment. A physician needs to use his limited resources in the most appropriate and productive manner possible. The centralized nuclear pharmacies routinely perform much more extensive Q/C than individual departments.

11. Tc-99m-albumin colloid for lymphoscintigraphy. No lymphoscintigraphy agent is approved by FDA. Albumin colloid, labeled with Tc-99m, is approved for liver-spleen imaging. High specific activity preparations, such as those used for phagocytic WBC labeling, are appropriate for lymposcintigraphy. If the final product is centrifuged before injection, the lighter particles on the top may be used and this agent provides even more rapid information than the standard preparation. At present use rates, this would give a three year tally of about 25. It could rise into the thousands.

12. Tc-99m-albumin colloid for bone marrow imaging. High specific activity albumin colloid is a better bone marrow imaging agent than Tc-99m-sulfur colloid. About 30-40% of high specific activity Tc-99m-albumin colloid goes to marrow; this % decreases as the number of particles increases and the marrow sites become saturated. At present use rates, this would give a three year tally of about 15. This could rise to hundreds.

13. Extemporaneous compounding of cold kits.FDA law and policy and all state Boards of Pharmacy permit the extemporaneous compounding of cold kits. Nuclear pharmacists whose NRC license precludes this may obtain IND's from FDA to make these kits. Such kits have no "manufacturer's instructions" from which to deviate.

14. Homologous Tc-99m-HMPAO, Tc-99m-albumin colloid, or In-111-labeled leukocyte scans. The patient may be too leukopenic for autologous labeling, so homologous WBC's are used instead. Three year tally would be about 150.

15. Reconstitution of cold kits with radionuclides other than Tc-99m. Some kits, such as DTPA, can chelate a variety of metals. Quantitative radioaerosol clearances may be performed with In-113m-DTPA, for example, after the patient has received a Tc-99m labeled radiopharmaceutical and a higher energy radionuclide is preferable. Unusual at present; three year tally about 15.

16. Reconstitution of a cold kit that was never intended to be a radiopharmaceutical. Many parenteral cold drugs are lyophilized and meant for reconstitution with normal saline. One can take desferroxamine, for example, and radiolabel it with Ga-67 or Tc-99m (after reduction) and use it for quantitative aerosol measurements when a larger molecular size than DTPA is required. Unusual at present; three year tally about 75.

17. High activity Tc-99m-MAA particles. These are useful in several situations:

    a) Pulmonary hypertension
    b) Intrapulmonary or intracardiac shunt
    c) Morbidly obese patient in whom one uses the standard particle number but twice the activity.
    d) A dose purposely set aside for emergency use at night, perhaps 12 hours or more after reconstitution.
    e) Everyone, in case any of the above applies. We perform about 1 million perfusion lung scans per year. Tally of three years of departure would be about 2 million.

18. In-111-oxine for platelet labeling (autologous or homologous). Package insert is for WBC labeling only. Labeled platelets are useful for platelet halflife, splenic sequestration, clot demonstration; some have found them useful for renal rejection. Homologous (donor) platelets labeled with In-111 may be used to assess transfusion efficacy in patients with antibodies (who are hard to cross-match). Estimated three year tally = 10,000.

19. In-111-RBC's for RBC labeling. Autologous or homologous labeled RBC's are useful for RBC mass, halflife, splenic sequestration, and intermittent GI bleeding. Homologous RBC's may be used for in vivo crossmatching as well. Estimated three year tally = 300.

20. Tc-99m-albumin colloid, high activity per particle for phagocytic PMN and monocytic labeling. Useful for locating and evaluating inflammations and infections. Labeling takes half the time of In-111; cheaper materials; faster study (within 4 hours instead of 24 hours); lower radiation absorbed dose. This study may be performed in children or pregnant women, and autologous as well as homologous WBC's may be used. Estimated three year tally= 600.

21. Use of intravenous SnPYP followed by in vitro RBC labeling with TcO_4. Useful for gated cardiac studies, GI bleeds, pulmonary bleeds, hemangioma detection, renal artery anastomosis bleeds, deep vein thrombosis and other types of venous blockade, and vascular graft patency. The package insert includes instructions for in vivo RBC labeling only. Estimated three year tally = 2 million (unless FDA approves the Cadema RBC kits).

22. Tc-99m-gelfoam. Gelfoam has an NDA and Tc-99m pertechnetate has an NDA and gelfoam may be labeled with reduced Tc-99m to trace vascular occlusions performed angiographically. Estimated three year tally = 75.

23. Tc-99m mother's milk for aspiration studies in newborns. Mother's milk is food, but it has never been approved by FDA. There is a large body of anecdotal evidence concerning its safety and efficacy, however. Unfortunately, the USP has not published standards. The containers have always aroused interest and careful study. Tc-99m (reduced) may be labeled to milk protein, fed to an infant, and imaged for evidence of aspiration. Estimated three year tally = 3.

24. Reconstitution of several identical kits with saline, transfer to a single vessel, and single addition of $NaTcO_4$ eluant. This is in keeping with ALARA for workers and is especially important for compliance with the decreased hand dose standards to be released in the new Part 20.

25. Extemporaneous compounding of radiopharmaceuticals beginning with radiochemicals. Examples include Xe-133 for inhalation or dissolved in saline for injection and NaI-131 for solution or capsules for diagnosis and therapy. This is part of the practice of nuclear pharmacy as covered by State Pharmacy Law in all 50 states.

The reason for this in the case of Xe-133 is mainly economic; the difference between "radiochemical" Xe-133 and NDA-approved "radiopharmaceutical" Xe-133 is a Ge(Li) spectrum for radionuclide purity. Many nuclear pharmacists and nuclear physicians have access to a Ge(Li) spectrometer. The difference in cost per mCi 2 years ago was a factor of about 700.

The reason in the case of NaI-131 is both economy and convenience. It may not be possible to obtain uptake capsules of a desired activity from a manufacturer with the speed required; the nuclear pharmacist may simply prepare the capsule from stock radiochemical NaI-131. At present, all of our NaI-131 comes from Nordion (Canada), also CIS has an NDA with the USFDA. So, radiochemical NaI-131 goes to France, where it is "blessed", and radiopharmaceutical NaI-131 comes back to the U.S. and makes up 60% of our patient doses. We don't need the "French connection". Three year tally avoiding France = 270,000.

I-123-hippuran and I-123-MIBG are also examples. I-123-hippuran has been largely replaced by the recent Tc-99m-MAG-3 but I-123-MIBG is otherwise unobtainable. Estimated three year tally = 9000. (Before I-123-hippuran was replaced, it could be obtained commercially but the NDA-approved product was significantly contaminated with I-124 and I-125. If you wanted to decrease patient dose, you bought radiochemical I-123 from Nordion and chemical hippuric acid and made your own radiopharmaceutical. At Harbor-UCLA, we did this routinely.)

NOTE: (1) Every example and classification of activity enumerated here had been perfectly legal in this country until April, 1987. Fifty years of experience showed that there were no problems. The April, 1987 changes in NRC regulations were incompatible with laws regulating pharmacy and medicine in all states and are not compatible with FDA law, regulations, guidelines, and policies.

(2) The record keeping requirement of the Interim Rule will of necessity be incomplete for certain of these deviations, such as for deviations 1,2,3,7,8,9,10, 24, and 25. However, ample experience with these deviations exists to show no evidence of problems.

Syncor®

April 17, 1990

Robert Temple, M.D.
Director, Office of Drug Research
and Review
U.S. Food and Drug Administration
5600 Fishers Lane
Parklawn Bldg., B-45
Rockville, MD 20852

Dear Dr. Temple:

Syncor has been contacted by Carol S. Marcus, Ph.D., M.D. to provide information relating to departures from package inserts (labeling) which Nuclear Pharmacists employ, or would like to employ, to improve radiopharmaceutical products. Most departures would normally be considered the practice of pharmacy, or the filling of physicians' prescriptions as part of their normal practice of medicine.

Package inserts are understood to be reflections of known drug information only at the time of Food and Drug Administration (FDA) approval of an original New Drug Application (NDA) or later amendments. A departure from package inserts is, therefore, typically based on technical information gained following FDA approval of NDAs for pharmaceuticals or radiopharmaceuticals. By medical history, this has been acknowledged as the practice of pharmacy as long as the prescribing physician is either aware of the proposed departure or has prescribed the departure.

Were the Nuclear Regulatory Commission (NRC) to regulate with the understanding that there should be no departures from package insert information for radiopharmaceuticals, then technical advancements in Nuclear Medicine would be severely curtailed. The NRC has seen fit to permit changes in clinical indications of radiopharmaceuticals (unapproved uses of approved products), but has severely limited the practice of pharmacy or physician prescribing to make improvements in the compounding and dispensing of radiopharmaceuticals.

The practice of Nuclear Medicine has, therefore, advanced at a far greater rate than the practice of Nuclear Pharmacy. This may also be related in part to the wisdom of the NRC and FDA in not permitting practicing Nuclear Pharmacists to participate as members of their advisory committees. There are Board Certified Nuclear Pharmacists who would be more than willing to serve on such advisory committees.

Regulation of the practice of Nuclear Pharmacy in this manner permits radiopharmaceutical manufacturers to increase sales by using the package insert to severely limit the compounding and dispensing capabilities of Nuclear Pharmacists. For example, manufactures can

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control the quantity of radiopharmaceuticals sold by decreasing the mCi of Tc-99m which can be added during formulation, shortening the shelf life, not adding anti-oxidants to prolong the effective life of products for certain indications, and not including known steps in labeling procedures which decrease preparation time or improve quality control.

GENERAL NUCLEAR PHARMACY CONSIDERATIONS

Clinical efficacy of radiopharmaceuticals is most often determined by the specific concentration and stability of the final product, the availability of quality control procedures for radiochemical and radionuclidic purity, and a knowledge of interactions which alter anticipated biodistribution.

Some examples where the experience of Nuclear Pharmacists could have been used to improve the clinical efficacy of radiopharmaceuticals are the following:

1. Protocol for testing product stability should include introduction of air following labeling which would mimic removal of doses prior to storage up to time of expiration. There is common agreement that Osteoscan-HDP for bone imaging is not stable for eight hours when the nitrogen atmosphere is compromised while removing doses.

2. Allowing solutions of technetium-99m to stand with heparin forms a complex which behaves like a kidney imaging agent. This should be a precaution when accomplishing In Vivo/In Vitro red blood cell labeling for myocardial perfusion or gastrointestinal bleeding studies.

3. Manufacturers are not required to define the potential effects radionuclidic contaminants have on the half life of approved radiopharmaceuticals. This is a special concern in (p,2n) iodine-123 products used for thyroid uptake where the clinical protocol provides for the nuclear medicine technologist to assay a capsule, administer it to a patient, and calculate a 100% value for the capsule when the patient thyroid is assayed using 13.2 hours as the half-life of the iodine-123.

   The iodine-124 radionuclidic contaminant has a longer half life than iodine-123, can reach a 15% concentration at time of expiration, and its high energies are assayed in the thyroid of a patient. This causes the calculated 100% value to be too low, and this results in a significant elevation of the true patient thyroid uptake value (false hyperthyroidism). This error is increased if the assay instrument is not corrected for potential lost counts when patient capsules are assayed.

4. Quality control procedures reflect stability of a radiopharmaceutical only at the time the tests begin, and not at later time intervals when the product is administered to a

patient. The quicker quality control is completed and a patient is administered a radiopharmaceutical, the more confidence can be placed on the quality control results.

If a quality control procedure is included as part of the Preparation Procedures in a package insert, then the FDA must be responsive to developments which improve quality control whether or not the manufacturer wants to amend the approved NDA.

5. Both the NRC and the FDA were notified that the product labels for MPI-MDP and MPI-DTPA were contributing to misadministrations where DTPA was dispensed for MDP because of unclear labels, and the MPI prefix has two of the three initials of MDP (Attachment 1). No reply was received from FDA, and the NRC suggested contacting the manufacturer (Attachment 2). This error most likely comprises the greatest single cause of patient misadministrations in the past two years, and having written prescriptions will not correct the problem.

6. As manufacturers are not required to submit data for unapproved uses which become routine procedures, nuclear pharmacists become the focal point of information regarding special product preparation requirements, methods which improve product stability, and precautions which maintain clinical efficacy of a product. Yet manufacturers are allowed to distribute references encouraging their use without amending the Approved NDA.

There are specific radiopharmaceutical products where knowledge gained from the experience of nuclear pharmacists could be useful to the NRC and FDA in its continual review of IND and NDA applications for similar products. The experience of nuclear pharmacists could be used by FDA and NRC to ensure proper precautions are introduced into package inserts for unapproved uses of approved products which require departures from existing package inserts.

GENERATORS

The preparation of all Tc-99m labeled radiopharmaceuticals begins with eluates from a Mo-99m/Tc-99m Generator. In practice, there are several characteristics of generators which must be understood in order for nuclear pharmacists to compound and dispense consistently high quality radiopharmaceuticals.

Molybdenum-99 is placed on an alumina column, and it is not soluble in saline. It decays to Tc-99m which is soluble in saline, and has a half life of six hours. The Tc-99m decays to Tc-99 which has all of the same chemical properties but negligible radioactivity (carrier). When sterile saline is passed through the column, both radioactive and non-radioactive technetium are eluted from the generator.

The more often a generator is eluted, the less non-radioactive technetium is present on the column to be eluted, so the specific concentration of Tc-99m is maintained at higher levels. There is also less non-radioactive Tc-99 (carrier) to compete with radioactive Tc-99m when labeling radiopharmaceuticals. Typically, carrier Tc-99 reaches its highest concentrations during shipment from a manufacturer to the end user because of the long interval between manufacturing and the first elution by the user. This is also the time when Mo-99 has the highest specific concentration for producing Tc-99m and Tc-99.

A nuclear medicine department which has a very low patient volume will have more Tc-99 carrier in its elutions than a high volume department which will elute each generator at least once a day. Nuclear pharmacies have minimal concentrations of carrier Tc-99 because generators are typically eluted more than once a day. With less carrier Tc-99, nuclear pharmacies are able to label radiopharmaceuticals with more Tc-99m than typical hospitals and clinics which must follow package insert guidelines more closely.

The first elution of a generator received from a manufacturer is either discarded, or used to compound prescriptions or calibration sources for which competition of carrier Tc-99 will not be a factor. This precaution does not appear in product labeling.

Generators eluates contain Tc-99m in a 7+ valence state which must be reduced and maintained in a 4+ valence state while compounding most radiopharmaceuticals. The reducing agent commonly used in kits is either stannous chloride or stannous fluoride. This is why kits are manufactured with a nitrogen atmosphere, and stabilized by the presence of an anti-oxidant such a ascorbic acid (Vitamin C). Even though the FDA would permit nuclear pharmacists to stabilize products with ascorbic acid, all attempts to gain NRC approval have failed to date.

As the specific concentration of Tc-99 activity decreases with the age of a generator, the volume of Tc-99m eluate required to compound a kit and radiopharmaceutical doses both increase. This is a time when pharmacists must be very careful not to exceed recommended patient doses (especially pediatric doses) such as MAA particles for lung imaging.

Generator eluates do not have a preservative, and the recommended time of use has decreased from 24 to 12 hours. Most radiopharmaceuticals have a recommended six hour time of use regardless of the expiration time of the generator eluate used to compound the product. Why has an arbitrary six hour use time been selected for radiopharmaceuticals when generator eluates used to make them go 12 hours, and there has never been pyrogenic responses to kits when they have had longer expiration times? Manufacturers would support short times of use in an effort to sell more product, but this also prevents servicing distant customers throughout the entire work day.

TECHNETIUM-99m DTPA

Technetium-99m DTPA kits are one of the products which are sensitive to the presence of Tc-99 in generator eluates. No commercial product contains ascorbic acid to increase stability, nor are nuclear pharmacists permitted to stabilize kits by the addition of ascorbic acid (Vitamin C).

The preferred MPI-DTPA product is associated with a high percentage of patient misadministrations which could most likely be overcome with a simple change in the design of the vial label.

Unapproved use of Tc-99m DTPA to assess kidney glomerular filtration rate (GFR) values is a common enough use that FDA has required a caution statement for this product to be used within one hour of preparation. Potential errors in GFR values are due to both protein binding, and free Tc-99m which is excreted at a different rate. Stabilizing DTPA products with ascorbic acid could prolong the time period for use of DTPA to determine GFR values.

TECHNETIUM-99m MAA for LUNG IMAGING

Technetium-99m MAA is approved for lung imaging, and several products are available on the market. This product is also sensitive to increases in non-radioactive Tc-99 concentrations in generator eluates, but there are no precautions to this in the package labeling. The recommended Tc-99m activity for preparing this product does not permit the administration of sufficiently small enough numbers of particles to meet the recommended pediatric doses (Table 1). The choice is to overdose children, or not follow package insert recommendations which violates current NRC policies.

This may also be a case where manufacturers attempted to decrease Tc-99m activity which can be used in a kit in order to limit the number of doses and increase sales. The FDA has approved adding 100 mCi to a MAA kit with 4-8 million particles, but only 50 mCi to a kit with 3.6-6.5 million particles.

Not all MAA kits have been required to add a suspending agent such as human serum albumin, and these products have a tendency to leave a significant percent of a dose in the syringe even if it is rinsed with patient blood. This warning is not required in the package labeling even though it may lead to false positive patchy lung images due to the administration of too few particles. Administering Tc-99m MAA through a catheter can result in the same problem in addition to clumping which results in hot spots in lung images.

If one compares the data in package labeling for all Tc-99m MAA products, there are many discrepancies which appear as though there was an attempt to make representations consistent for all products without recognizing actual differences between products (Table 1).

TABLE 1.

Tc-99m MAA LUNG IMAGING PRODUCT COMPARISON

TOPIC	MAL	SQUIBB	MEDI-PHYSICS 1 dose	MEDI-PHYSICS X dose	NEN	CIS
ALBUMIN CONTENT						
MAA (mg)	2.0	1.5	0.11	2.5	1.0	2.0
Human Serum (mg)	0.5	10	-0-	5.0	10	-0-
TOTAL TIN (mg)	0.12	0.19	0.09	0.11	0.12	0.21
AGGREGATES						
Total x 10^6	4-12	2-7	0.5-1	4-8	3.6-6.5	12-15
Ave Size (u)	10-40	20-40	15-90	20-40	15-30	15-90
% Trapped	90	80+	80+	80+	80+	80+
EXCRETION 24 Hr %	75	No Data	40	20	20	20
LUNG HALF LIFE (Hr)	3.8	2-3	1.0	2-3	5.0	5.0
Indications						
Lung	Yes	Yes	Yes	Yes	Yes	Yes
Venography	No	Yes	No	No	No	No
LeVeen Shunt	No	No	No	Yes	No	Yes
KIT LABELING						
Volume Saline (ml)	5-10	1-3	1.3	2-8	2-8	3-5
Maximum mCi	60	50	3.9-7.8	100	20-50	20-100
Use Time (Hr)	8	6	3	6	6	6
DOSES (1 - 4 mCi)						
Particles x 10^6						
Adult	.2-1.2	.2-.7	.2-.7	.2-.7	.2-.7	.2-.7
Pediatric	Newborn = 0.5 mCi per 10-50,000 particles					
	15 year = 2.8 mCi per 200-700,000 particles					
DOSIMETRY (rad/4mCi)						
Lungs	0.88	0.88	0.88	0.88	0.88	0.80
Liver	.072	.072	.072	.072	.072	.13
Bladder						
2 Hr Void	0.12	0.12	0.12	0.12	0.12	No Data
4.8 Hr Void	0.22	0.22	0.22	0.22	0.22	0.48

Product Package Inserts Used as Source of Data

- Mallinckrodt = August 1983
- Squibb = March 1987
- Medi-Physics
  - Unit Dose = October 1984
  - Mult Dose = February 1989
- NEN DuPont = March 1987
- CIS = January 1988

1. Mallinckrodt MAA has 75% Tc-99m excretion in 24 hours which is about 2 to 4 times greater than other products, but radiation dosimetry to the bladder wall is the same for all products.

2. Lung half-lives for MAA products vary from 1 to 5 hours, but the liver radiation dosimetry is the same for all products.

3. CIS radiation dosimetry is different from other products because a method for calculating dosimetry other than using MIRD values was permitted.

4. A pediatric dose of 0.5 mCi per 10,000 particles requires 250 mCi at time of labeling a MAA kit with 5 million particles. This means that 500 mCi are needed for compliance throughout the entire recommended 6 hour time of use (excluding Mallinckrodt which has an 8 hour time of use and requires even more Tc-99m).

5. If Mallinckrodt has had a recommended 8 hour time of use on its MAA kit for approximately 20 years with no adverse reactions, why should other formulations not have the same time of use unless manufacturers sell more kits with a shorter time? Based on Mallinckrodt's experience, is it improper for nuclear pharmacists to assume identical kits should have identical times of use?

TECHNETIUM-99m MDP for BONE IMAGING

Technetium-99m MDP is a bone imaging radiopharmaceutical that is sensitive to carrier Tc-99. Performance of an MDP product is maximized when an anti-oxidant is present to maintain Tc-99m in the 4+ valence state during initial labeling and throughout the recommended time of use. If Tc-99m becomes disassociated from MDP, it must be maintained at a 4+ valence state to recombine with a MDP molecule.

Manufacturers also maintain a nitrogen atmosphere in MDP vials to help prevent oxidation of Tc-99m. Withdrawal of patient doses immediately after labeling a MDP product introduces air, and compromises the effect of nitrogen. Under these conditions, most MDP products will not be stable through their useful time without the presence of ascorbic acid as an anti-oxidant. Adding ascorbic acid (Vitamin C) after a MDP product is labeled with Tc-99m is optimal to prevent any labeling of the ascorbic acid during the labeling procedures.

The addition of ascorbic acid (2mg/0.1 ml) has not been permitted by the NRC although it is already used in MDP products, and the FDA recognizes stabilization of a radiopharmaceutical as the practice of pharmacy. Product stability is recognized in the quality of bone images with higher target to background ratios.

Manufacturers have apparently attempted to increase sales by limiting Tc-99m activity to label MDP, and to maintain recommended time of use to 6 hours. The Mallinckrodt Osteoscan-HDP product has been marketed for over 20 years with an 8 hour time of use with no evidence that the

TABLE 2.

Tc-99m BONE IMAGING PRODUCT COMPARISON

TOPIC	MALLINCKRODT HDP	MALLINCKRODT MDP	SQUIBB MDP	MEDI MDP	NEN MDP	CIS MDP
Quantity Drug (mg)	2.0	10	20	10	10	10
Anti-Oxidant (mg)						
Ascorbic Acid	-0-	-0-	1.0	2.0	-0-	-0-
Gentisic Acid	0.56	-0-	-0-	-0-	-0-	-0-
Stannous/Tin (mg)	0.16	1.21	0.33	0.17	0.5	1.1
Blood Conc. (% dose)						
2 Hours	6.0	5.0	<5.0	No Data	No Data	4-10
3 Hours	4.0	No Data	No Data	No Data	3-5	3-5
4 Hours	3.0	No Data	<2.0	No Data	No Data	No Da
Urinary Excretion (% Dose 24 Hr.)	50	50	50	50	50	50
Preparation						
Volume Tc 99m (ml)	3-6	2-10	0.5-5	2-8	2-8	1-8
Total Tc-99m (mCi)	200	200	150	Any*	Any*	300
Sp. Conc. (mCi/mg)	100	20	7.5	- -	- -	30
Time of Use (Hr)	8	6	6	6	6	6

Any* = Activity to be determined by labeling experience with generator eluates and quality of clinical studies.

Product Package Inserts Used as Source of Data

- Mallinckrodt
  - HDP = November 1987
  - MDP = May 1984
- Squibb = November 1982
- Medi-Physics = August 1988
- NEN Dupont = March 1987
- CIS = October 1985

time should be shortened. There appears to be little reason why all MDP kits could not have their time of use extended to 8 hours, or to 12 hours which is the same as Tc-99m generator eluate used in the labeling procedure.

Tc-99m CERETEC

The package labeling for Tc-99m CERETEC is the first time FDA included a quality control procedure as part of the labeling instructions. The procedure requires at least 15 minutes of a 30 minute use time. Because the quality control results indicate the state of the product only at the time the chromatography strips are spotted, the end results do not account for product degradation during the 15 minutes of the procedure.

At least two better quality control procedures have been published, but there is no apparent way for the instructions to be changed by FDA unless the manufacturer wants to amend the NDA on its own accord. The practice of pharmacy should dictate using the best technical data and procedures to accomplish quality control on radiopharmaceuticals that have a procedure described in the package labeling.

Technetium-99m Ceretec is also a radiopharmaceutical that has an unapproved use for an approved drug. The drug can be used to reliably provide Tc-99m white blood cells which enable earlier diagnosis and reduced radiation dosimetry to spleen, liver, and bone marrow than In-111 WBCs. With this increase in safety and efficacy, one would expect that the NRC would have little problem approving its use by nuclear medicine physicians.

SODIUM IODIDE I-131 THERAPY SOLUTIONS

The FDA has not required all Sodium Iodide I-131 Therapy Solutions to have stabilizers, reducing agents, and proper pH although several reports on I-131 volatility were published. Volatility of I-131 from these products endangers pharmacists compounding doses, increases I-131 concentrations released into the atmosphere, and increases exposure to hospital staff who administer therapy doses to patients.

The simple addition of 2 mg EDTA to CIS I-131 therapy solution has decreased volatility of this product by making it the same as the Mallinckrodt product. Air monitoring results in nuclear pharmacies indicate decreases in I-131 release into the atmosphere, and the decreased volatility provides increased safety for nuclear pharmacists and hospital staff. The addition of EDTA to the CIS product makes in nearly identical to that of Mallinckrodt Sodium Iodide I-131 for Therapy.

SODIUM IODIDE I-131 THERAPY SOLUTIONS

The FDA has not required all Sodium Iodide I-131 Therapy Solutions to have stabilizers, reducing agents, and proper pH although several reports on I-131 volatility were published. Volatility of I-131 from these products endangers pharmacists compounding doses, increases I-131 concentrations released into the atmosphere, and increases exposure to hospital staff who administer therapy doses to patients.

The simple addition of 2 mg EDTA to CIS I-131 therapy solution has decreased volatility of this product by making it the same as the Mallinckrodt product. Air monitoring results in nuclear pharmacies indicate decreases in I-131 release into the atmosphere, and the decreased volatility provides increased safety for nuclear pharmacists and hospital staff. The addition of EDTA to the CIS product makes it nearly identical to that of Mallinckrodt Sodium Iodide I-131 for Therapy.

The package labeling for I-131 therapy solutions contains no warnings about potential exposure to nuclear medicine staff from patients exhaling I-131 following administration of these solutions. This is a case where nuclear pharmacists and or NRC staff could offer advice to the FDA which will increase safety to the health professionals who have to handle I-131 therapy solutions.

The package labeling for Sodium Iodide I-131 solutions does not contain instructions for determining and using K factors necessary to ensure patient doses are within 10% of prescribed quantities. This is area where FDA could benefit from outside expertise.

WHITE BLOOD CELL LABELING PROCEDURES

The two major problems with white blood cell labeling procedures is the slow gravity settling rate of red blood cells, and the ability to separate red blood cells (RBCs) from white blood cells (WBCs) because they preferentially label with In-111 Oxine, or convert Tc-99m Ceretec to the hydrophilic form which decreases labeling efficiency.

The use of hetastarch (Hespan) to increase the settling rate of RBCs by at least 30 minutes was used in the WBC labeling procedures since its origin in 1978. This step was not included as an option when In-111 Oxine was approved by the FDA even though its use helps maintain viability of WBCs by increasing the time for reinjection of In-11 WBCs, and permits labeling of WBCs for customers 15 to 30 minutes away from a centralized hospital or pharmacy site.

Syncor has developed proprietary procedures for separating RBCs from WBCs, and increasing the Tc-99m labeling of WBCs by at least twice the current published capabilities. Patient care will be the primary benefactor of these improvements in WBC labeling procedures through Syncor efforts.

SYNCOR GUIDELINE FOR COMPOUNDING Tc-99m RADIOPHARMACEUTICALS

Based on over 15 years of experience compounding and dispensing Tc-99m radiopharmaceuticals, Syncor has established corporate guidelines for compounding, dispensing, and specific expiration times (Attachment 3). These guidelines are designed to emphasize the positive aspects of compounding and dispensing Tc-99m radiopharmaceuticals, and guarding against any negative experiences which have occurred over the years. These guidelines are specific to Syncor nuclear pharmacies because they are based primarily on Syncor experience and not that of the nuclear pharmacy industry.

SUMMARY

The practice of Nuclear Pharmacy is a recognized specialty, and the expertise gained by compounding and dispensing radiopharmaceuticals has not been tapped by either the FDA or NRC. Although nuclear pharmacists have been accused of making changes in package labeling only to increase profits, this is far from the real Nuclear Pharmacy practice.

Some radiopharmaceutical changes a nuclear pharmacist makes is measured almost immediately in patient images. Communications between nuclear physicians and nuclear pharmacists are immediate when it comes to patient care. Changes which increase radiation safety, product viability, product stability, quality control, and more efficient utilization of products are not always measured immediately.

Just as nuclear physicians consult with nuclear pharmacists, the FDA and NRC could also benefit from better utilization of the knowledge base which practicing nuclear pharmacists can provide. The FDA and NRC may have to first recognize that nuclear pharmacists, nuclear technologists, and nuclear physicians operate as a professional team on a daily basis to provide the best patient care possible. As long as each member of the team is successful in practicing their specialty, medical care is maximized.

Whenever the FDA or NRC decides to take advantage of the expertise available from any specialty of the nuclear medicine team, they would find a ready source of information and experience to help them. It is not obvious why the FDA or NRC in their wisdom have not used a broader base of advisors in matters relating to radiopharmaceuticals and Nuclear Medicine.

Sincerely,

Dennis R. Hoogland, Ph.D., BCNP
Manager Technical Development and Training

cc: Richard E. Cunningham, USNRC
Carol S. Marcus, Ph.D., M.D., UCLA

ATTACHMENT 3.

SYNCOR GUIDELINES FOR COMPOUNDING Tc-99m RADIOPHARMACEUTICALS

S Y N C O R

Guidelines for Compounding Tc-99m Radiopharmaceuticals

September 1, 1989

TABLE 1. TECHNETIUM-99M MACROAGGREGATED ALBUMIN (MAA)

Manufacturer	Activity(mCi)(1)	Tc-99m Volume(ml)	Expiration(2)
DuPont (3.6-6.5M particles)	125 mCi	2-8 ml	12 hours
CIS 12-15M particles	340 mCi	3-5 ml	12 hours
Squibb 2-7M particles	115 mCi	1-3 ml	12 hours
Medi+Physics 1.5-2.5M particles	50 mCi	up to 3 ml	12 hours
Mallinckrodt 4-12M particles	200 mCi	5-10 ml	12 hours

1 Amounts used for MAA based on 200,000 particles and 5 mCi per dose, average number of particles per vial at time of preparation. These values may be increased to account for decay up to the time of calibration of the dispensed doses. For example, Dupont MAA which is to be used 4 hours after preparation could be compounded with 200 mCi of Tc-99m.

2. Not to exceed the 12 hour expiration of the Tc-99m elution.

TABLE 2. TECHNETIUM-99M BONE IMAGING AGENTS

Product	Manufacturer	Maximum[1] Activity(mCi)	Tc-99m Volume(ml)	Expiration
MDP	Squibb	400 mCi	0.5 - 5 ml	12 hours
MDP	Medi+Physics	400 mCi	2 - 8 ml	12 hours
MDP	DuPont	200 mCi	2 - 8 ml	6 hours
MDP	CIS	200 mCi	1 - 8 ml	6 hours
MDP	Amersham	100 mCi	1 - 8 ml	6 hours
HDP	Mallinckrodt	150 mCi		6 hours
PYP	DuPont	200 mCi	3 - 7 ml	6 hours
PYP	Squibb	75 mCi	2 - 4 ml	6 hours
PYP	Mallinckrodt	100 mCi	1 - 10 ml	6 hours

1. These activities are maximums and lesser amounts should be used where experience dictates.

SYNCOR GUIDELINES FOR RADIOPHARMACEUTICAL KIT PREPARATION

TABLE 3. TECHNETIUM-99M DTPA

Procedure	Manufacturer	Activity(mCi)	Tc-99m Volume(ml)	Expiration
Brain Scan	Squibb	300 mCi	up to 5 ml	6 hours
Renal Scan	Squibb	300 mCi	up to 5 ml	4 hours
Aerosol	Squibb	300 mCi	up to 5 ml	6 hours
Assess GFR	Squibb	(See Note 1)		
Brain Scan	Medi+Physics	300 mCi	2 - 8 ml	6 hours
Renal Scan	Medi+Physics	300 mCi	2 - 8 ml	4 hours
Aerosol	Medi+Physics	300 mCi	2 - 8 ml	6 hours
Assess GFR	Medi+Physics	50 mCi	2 - 8 ml	1 hour
	CIS	DO NOT USE THIS PRODUCT!!		

1. Squibb DTPA (Ca-DTPA) is not recommended to assess GFR even though it is listed in the package insert. Syncor experience shows Medi+Physics DTPA (Na-DTPA) is the drug of choice for GFR.

TABLE 4. TECHNETIUM-99M GLUCOHEPTONATE

Procedure	Manufacturer	Activity(mCi)	Tc-99m Volume(ml)	Expiration
Brain Scan	DuPont	150 mCi	3 - 7 ml	6 hours
Renal Scan	Dupont	150 mCi	3 - 7 ml	4 hours

TABLE 5. TECHNETIUM-99M HEPATOBILIARY IMAGING AGENTS

Product	Manufacturer	Activity(mCi)	Tc-99m Volume(ml)	Expiration
Choletec	Squibb	200 mCi	2 - 5 ml	18 hours (Note 1)
Hepatolite	Dupont	150 mCi	2 - 5 ml	8 hours

1. Preservative in formulation allows 18 hour expiration. Tc-99m must have Mo-99 concentration within limits at time of expiration.

TABLE 6. TECHNETIUM-99M LIVER IMAGING AGENTS

Product	Manufacturer	Activity(mCi)	Tc-99m Volume(ml)	Expiration
Sulfur Colloid	CIS	500 mCi	1 - 3 ml	12 hours
Sulfur Colloid	Mallinckrodt	400 mCi	0.1 - 5 ml	12 hours
Sulfur Colloid	Squibb	500 mCi	0.1 - 5 ml	12 hours
Sulfur Colloid	Medi+Physics	400 mCi	0.5 - 5 ml	12 hours
Microlite	DuPont	75 mCi	2 - 8 ml	6 hours

TABLE 7. TECHNETIUM-99M HUMAN SERUM ALBUMIN (HSA)

Product	Manufacturer	Activity(mCi)	Tc-99m Volume(ml)	Expiration
Multidose	Medi+Physics	200 mCi	3 ml	6 hours
Unitdose	Medi+Physics	70 mCi	1.3 ml	6 hours

TABLE 8. TECHNETIUM-99M DMSA

Product	Manufacturer	Activity(mCi)	Tc-99m Volume(ml)	Expiration
DMSA	Medi+Physics	44 - 88 mCi	2.2 ml reagent 2.2 -4.4 ml Tc-99m	30 minutes

TABLE 9. TECHNETIUM-99M HMPAO (Ceretec)

Product	Manufacturer	Activity(mCi)	Tc-99m Volume(ml)	Expiration
HMPAO	Amersham	30 mCi	up to 5 ml.	30 minutes

LIST OF APPENDICES

I. Section 104, Atomic Energy Act

II. 42USC 10001 - 10008

III. FR Article lifting AEC exemption, 1975

IV. Chapter explaining transfer of responsibility

V. FDA Nuclear Pharmacy Guideline

VI. 21 CFR 361.1; Metabolic research regulations

VII. Package insert departures for non-radioactive drugs

APPENDIX I.

Section 104, Atomic Energy Act

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 the public.

b. As provided for in subsection 102 b. or 102 c., or where specifically authorized by law, the Commission is authorized to issue licenses 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 obligations 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 104 b. 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.

APPENDIX II.

42 USC 10001-10008

as the Omnibus Budget Reconciliation Act of 1981. For complete classification of this Act to the Code, see Tables.

SECTION REFERRED TO IN OTHER SECTIONS

This section is referred to in section 9911 of this title.

CHAPTER 107—CONSUMER-PATIENT RADIATION HEALTH AND SAFETY

Sec.
10001. Statement of findings.
10002. Statement of purpose.
10003. Definitions.
10004. Promulgation of standards.
10005. Model statute.
10006. Compliance.
(a) Implementation by Secretary.
(b) Accreditation or certification program.
(c) Noncompliance; proposed legislative changes.
(d) Monitoring; report to Congress.
(e) Existing standards and guidelines.
10007. Federal radiation guidelines.
10008. Applicability to Federal agencies.

§ 10001. Statement of findings

The Congress finds that—

(1) it is in the interest of public health and safety to minimize unnecessary exposure to potentially hazardous radiation due to medical and dental radiologic procedures;

(2) it is in the interest of public health and safety to have a continuing supply of adequately educated persons and appropriate accreditation and certification programs administered by State governments;

(3) the protection of the public health and safety from unnecessary exposure to potentially hazardous radiation due to medical and dental radiologic procedures and the assurance of efficacious procedures are the responsibility of State and Federal governments;

(4) persons who administer radiologic procedures, including procedures at Federal facilities, should be required to demonstrate competence by reason of education, training, and experience; and

(5) the administration of radiologic procedures and the effect on individuals of such procedures have a substantial and direct effect upon United States interstate commerce.

(Pub. L. 97-35, title IX, § 977, Aug. 13, 1981, 95 Stat. 598.)

SHORT TITLE

Section 975 of subtitle I (§§ 975 to 983) of title IX of Pub. L. 97-35, provided that: "This subtitle [enacting this chapter] may be cited as the 'Consumer-Patient Radiation Health and Safety Act of 1981'."

§ 10002. Statement of purpose

It is the purpose of this chapter to—

(1) provide for the establishment of minimum standards by the Federal Government for the accreditation of education programs for persons who administer radiologic procedures and for the certification of such persons; and

(2) insure that medical and dental radiologic procedures are consistent with rigorous safety precautions and standards.

(Pub. L. 97-35, title IX, § 977, Aug. 13, 1981, 95 Stat. 599.)

§ 10003. Definitions

Unless otherwise expressly provided, for purposes of this chapter, the term—

(1) "radiation" means ionizing and nonionizing radiation in amounts beyond normal background levels from sources such as medical and dental radiologic procedures;

(2) "radiologic procedure" means any procedure or article intended for use in—

(A) the diagnosis of disease or other medical or dental conditions in humans (including diagnostic X-rays or nuclear medicine procedures); or

(B) the cure, mitigation, treatment, or prevention of disease in humans;

that achieves its intended purpose through the emission of radiation;

(3) "radiologic equipment" means any radiation electronic product which emits or detects radiation and which is used or intended for use to—

(A) diagnose disease or other medical or dental conditions (including diagnostic X-ray equipment); or

(B) cure, mitigate, treat, or prevent disease in humans;

that achieves its intended purpose through the emission or detection of radiation;

(4) "practitioner" means any licensed doctor of medicine, osteopathy, dentistry, podiatry, or chiropractic, who prescribes radiologic procedures for other persons;

(5) "persons who administer radiologic procedures" means any person, other than a practitioner, who intentionally administers radiation to other persons for medical purposes, and includes medical radiologic technologists (including dental hygienists and assistants), radiation therapy technologists, and nuclear medicine technologists;

(6) "Secretary" means the Secretary of Health and Human Services; and

(7) "State" means the several States, the District of Columbia, the Commonwealth of Puerto Rico, the Commonwealth of the Northern Mariana Islands, the Virgin Islands, Guam, American Samoa, and the Trust Territory of the Pacific Islands.

(Pub. L. 97-35, title IX, § 978, Aug. 13, 1981, 95 Stat. 599.)

§ 10004. Promulgation of standards

(a) Within twelve months after August 13, 1981, the Secretary, in consultation with the Radiation Policy Council, the Administrator of Veterans' Affairs, the Administrator of the Environmental Protection Agency, appropriate agencies of the States, and appropriate professional organizations, shall by regulation promulgate minimum standards for the accreditation of educational programs to train individuals to perform radiologic procedures. Such standards shall distinguish between programs for the education of (1) medical radiologic technologists (including radiographers), (2) dental

auxiliaries (including dental hygienists and assistants), (3) radiation therapy technologists, (4) nuclear medicine technologists, and (5) such other kinds of health auxiliaries who administer radiologic procedures as the Secretary determines appropriate. Such standards shall not be applicable to educational programs for practitioners.

(b) Within twelve months after August 13, 1981, the Secretary, in consultation with the Radiation Policy Council, the Administrator of Veterans' Affairs, the Administrator of the Environmental Protection Agency, interested agencies of the States, and appropriate professional organizations, shall by regulation promulgate minimum standards for the certification of persons who administer radiologic procedures. Such standards shall distinguish between certification of (1) medical radiologic technologists (including radiographers), (2) dental auxiliaries (including dental hygienists and assistants), (3) radiation therapy technologists, (4) nuclear medicine technologists, and (5) such other kinds of health auxiliaries who administer radiologic procedures as the Secretary determines appropriate. Such standards shall include minimum certification criteria for individuals with regard to accredited education, practical experience, successful passage of required examinations, and such other criteria as the Secretary shall deem necessary for the adequate qualification of individuals to administer radiologic procedures. Such standards shall not apply to practitioners.

(Pub. L. 97-35, title IX, § 979, Aug. 13, 1981, 95 Stat. 599.)

§ 10005. Model statute

In order to encourage the administration of accreditation and certification programs by the States, the Secretary shall prepare and transmit to the States a model statute for radiologic procedure safety. Such model statute shall provide that—

(1) it shall be unlawful in a State for individuals to perform radiologic procedures unless such individuals are certified by the State to perform such procedures; and

(2) any educational requirements for certification of individuals to perform radiologic procedures shall be limited to educational programs accredited by the State.

(Pub. L. 97-35, title IX, § 980, Aug. 13, 1981, 95 Stat. 600.)

§ 10006. Compliance

(a) Implementation by Secretary

The Secretary shall take all actions consistent with law to effectuate the purposes of this chapter.

(b) Accreditation or certification program

A State may utilize an accreditation or certification program administered by a private entity if—

(1) such State delegates the administration of the State accreditation or certification program to such private entity;

(2) such program is approved by the State; and

(3) such program is consistent with the minimum Federal standards promulgated under this chapter for such program.

(c) Noncompliance; proposed legislative changes

Absent compliance by the States with the provisions of this chapter within three years after August 13, 1981, the Secretary shall report to the Congress recommendations for legislative changes considered necessary to assure the States' compliance with this chapter.

(d) Monitoring; report to Congress

The Secretary shall be responsible for continued monitoring of compliance by the States with the applicable provisions of this chapter and shall report to the Senate and the House of Representatives by January 1, 1982, and January 1 of each succeeding year the status of the States' compliance with the purposes of this chapter.

(e) Existing standards and guidelines

Notwithstanding any other provision of this section, in the case of a State which has, prior to the effective date of standards and guidelines promulgated pursuant to this chapter, established standards for the accreditation of educational programs and certification of radiologic technologists, such State shall be deemed to be in compliance with the conditions of this section unless the Secretary determines, after notice and hearing, that such State standards do not meet the minimum standards prescribed by the Secretary or are inconsistent with the purposes of this chapter.

(Pub. L. 97-35, title IX, § 981, Aug. 13, 1981, 95 Stat. 600.)

§ 10007. Federal radiation guidelines

The Secretary shall, in conjunction with the Radiation Policy Council, the Administrator of Veterans' Affairs, the Administrator of the Environmental Protection Agency, appropriate agencies of the States, and appropriate professional organizations, promulgate Federal radiation guidelines with respect to radiologic procedures. Such guidelines shall—

(1) determine the level of radiation exposure due to radiologic procedures which is unnecessary and specify the techniques, procedures, and methods to minimize such unnecessary exposure;

(2) provide for the elimination of the need for retakes of diagnostic radiologic procedures;

(3) provide for the elimination of unproductive screening programs;

(4) provide for the optimum diagnostic information with minimum radiologic exposure; and

(5) include the therapeutic application of radiation to individuals in the treatment of disease, including nuclear medicine applications.

(Pub. L. 97-35, title IX, § 982, Aug. 13, 1981, 95 Stat. 601.)

§ 10008. Applicability to Federal agencies

(a) Except as provided in subsection (b) of this section, each department, agency, and instrumentality of the executive branch of the Federal Government shall comply with standards promulgated pursuant to this chapter.

(b)(1) The Administrator of Veterans' Affairs, through the Chief Medical Director of the Veterans' Administration, shall, to the maximum extent feasible consistent with the responsibilities of such Administrator and Chief Medical Director under title 38, prescribe regulations making the standards promulgated pursuant to this chapter applicable to the provision of radiologic procedures in facilities over which the Administrator has jurisdiction. In prescribing and implementing regulations pursuant to this subsection, the Administrator shall consult with the Secretary in order to achieve the maximum possible coordination of the regulations, standards, and guidelines, and the implementation thereof, which the Secretary and the Administrator prescribe under this chapter.

(2) Not later than 180 days after standards are promulgated by the Secretary pursuant to this chapter, the Administrator of Veterans' Affairs shall submit to the appropriate committees of Congress a full report with respect to the regulations (including guidelines, policies, and procedures thereunder) prescribed pursuant to paragraph (1) of this subsection. Such report shall include—

(A) an explanation of any inconsistency between standards made applicable by such regulations and the standards promulgated by the Secretary pursuant to this chapter;

(B) an account of the extent, substance, and results of consultations with the Secretary respecting the prescription and implementation of regulations by the Administrator; and

(C) such recommendations for legislation and administrative action as the Administrator determines are necessary and desirable.

(3) The Administrator of Veterans' Affairs shall publish the report required by paragraph (2) in the Federal Register.

(Pub. L. 97-35, title IX, § 983, Aug. 13, 1981, 95 Stat. 601.)

CODIFICATION

Title 38, referred to in subsec. (b)(1), in the original read "subtitle 38", which for purposes of codification was translated as "title 38" as the probable intent of Congress.

CHAPTER 108—NUCLEAR WASTE POLICY

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SUBCHAPTER I—DISPOSAL AND STORAGE OF HIGH-LEVEL RADIOACTIVE WASTE, SPENT NUCLEAR FUEL, AND LOW-LEVEL RADIOACTIVE WASTE

Sec.
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APPENDIX III.

FR Article lifting AEC exemption, 1975

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Docket No. 73N-0067]

RADIOACTIVE NEW DRUGS AND RADIOACTIVE BIOLOGICS

Termination of Exemptions

In a notice of proposed rule making published in the FEDERAL REGISTER of July 29, 1974 (39 FR 27598), the Commissioner of Food and Drugs proposed to terminate the present exemption for radioactive new drugs (including radioactive biological products) for investigational use from new drug requirements and classify, by use, radioactive drugs either as "new drugs" or as generally recognized as safe and effective for their intended use and therefore not "new drugs" when used under the conditions specified. Interested persons were invited to submit comments on the proposal by September 27, 1974.

The Commissioner of Food and Drugs is terminating the present exemption for radioactive drugs, including radioactive biological products, from the investigational new drug requirements of the Federal Food, Drug, and Cosmetic Act. The Food and Drug Administration (FDA) is establishing regulations to assure that after August 25, 1975 all radioactive drugs, except those for certain research uses, introduced into interstate commerce are subject to a "Notice of Claimed Investigational Exemption for a New Drug" (IND), an approved new drug application (NDA), or a biological product license. In addition, the FDA is establishing regulations setting forth specific conditions under which radioactive drugs for certain research uses, other than clinical trials to determine safety and effectiveness, are not subject to the new drug requirements of the act.

The Commissioner, for the purpose of an orderly development of regulations relating to the establishment of procedures for codifying old drug monographs for prescription drugs which are generally recognized as safe and effective and not misbranded, has redesignated proposed new 21 CFR Part 370 as 21 CFR Part 361 and limited it to drugs used in research. All future old drug monographs for such drugs will be incorporated into Part 361.

The U.S. Nuclear Regulatory Commission (NRC), a new agency created by Pub. L. 93-438 and Executive Order 11834 assumed the licensing and related regulatory responsibilities of the former Atomic Energy Commission (AEC) on January 19, 1975. To conform to this organizational change, all references to the AEC in this regulation and in the preamble have been changed to the NRC. In the quotation from and discussion of comments received from members of the public on this proposed regulation, references to the AEC have been changed to the NRC even though the comments from the public were made prior to the organizational change.

Elsewhere in this issue of the FEDERAL REGISTER the Commissioner is issuing an order effecting a transfer of responsibility for radioactive biological products from the Bureau of Biologics to the Bureau of Drugs.

Comments on the proposal were received from 21 different sources; namely, hospitals, universities, professional organizations, trade associations, manufacturers, Agreement States (i.e., States which, under formal agreement with the NRC, are authorized to license, under Federal law, persons engaged in the possession, use, or transfer of reactor-produced radionuclides in their respective states), and State health departments.

The major areas of concern as expressed by the comments were the composition of the Radioactive Drug Research Committee (proposed as the Radiation Safety Committee), the use of State advisory committees, radiation dosimetry, procedures for providing the summary of information on radioactive drugs for investigational use and the "Report on Research Use of Radioactive Drug" to the NRC and appropriate Agreement States, limitation on pharmacological dose for research not under an IND, and the applicability of the proposed regulation to radiopharmacies. Eight comments supported the proposal in principle but offered suggestions for modification, clarification, and addition to some areas. The principal comments received and the Commission's conclusions are as follows:

DEFINITION OF A RADIOACTIVE DRUG

1. One comment pointed out that in § 312.1 the additional information to be supplied in new items 6.d, 10.a, and 16 of Form FD-1571 is required only if the investigational drug is a "radioactive drug" but the term "radioactive drug" is not defined in the proposed regulation.

The Commissioner has determined that a "radioactive drug" is any substance defined as a drug in section 201 (g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance. The term "radioactive drug" includes a "radioactive biological product" as defined in 21 CFR 600.3(ee). This definition does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. Section 310.3 has been amended to include this definition in paragraph (n).

IND REQUIREMENTS FOR RADIOACTIVE NEW DRUGS

2. Several comments suggested that the Summary of Information as required by § 312.1 be forwarded directly by the manufacturer to the NRC or Agreement States rather than by the Food and Drug Administration. Such a procedure would enhance the manufacturer's efforts to protect the confidentiality of any proprietary information contained in the summary, would free the FDA from further administrative workload, and would eliminate the possibility of administrative delays in forwarding the necessary information to the NRC or Agreement States. Comments also pointed out that the proposed regulation does not provide a procedure for notifying the NRC and Agreement State authorities that the FDA has approved an NDA or issued a biological product license.

This proposed regulation was not intended to preclude the sponsor from forwarding the Summary of Information directly to the NRC or Agreement States. The proposal was merely a service which FDA would provide to IND sponsors and to the Federal and State licensing agencies to expedite the processing of licensing applications. The Summary of Information serves no regulatory purpose for the FDA. Failure of the IND sponsor to submit the Summary of Information, or to authorize its release to licensing agencies, would not alter the status of the IND.

The Commissioner had intended that the release of the Summary of Information to Federal and State licensing bodies would not waive any confidentiality to which the sponsor of the IND would be entitled under the FDA Public Information regulations (21 CFR Part 4; 21 CFR 312.4; and 21 CFR 314.14). Under these regulations, FDA records which are normally exempt from disclosure (e.g., existence and contents of an IND) may be disclosed, without requiring disclosure to the public at large, to a department or agency that has concurrent jurisdiction over the matter and separate legal authority to obtain the specific information involved. 21 CFR 4.84. The NRC (and through it, the Agreement States) would satisfy these criteria. The regulations require, however, that such disclosure "be pursuant to an agreement that the record shall not be further disclosed by the other department or agency except with the written permission of the Food and Drug Administration." The NRC has informed the FDA that it would not agree to this restriction and would not assure any confidential treatment for the Summary of Information.

The Commissioner believes that, under these circumstances, retaining the Summary of Information would not be justified because the administrative problems which would arise are too numerous. First, separate agreements would be required for each of the 35 Agreement States; besides the practical difficulties involved, the legality of these agreements would be in doubt, since the Agreement States derive authority from the NRC. Secondly, each IND submission with a Summary of Information would have to be examined to determine in which states the IND drug might be used; those with agreements for confidentiality would be notified, but those without, and those under NRC jurisdiction, would not be notified. In short, providing this service would become very complicated. One alternative, to provide that an explicit waiver of confidentiality be signed by the IND sponsor if he chose to submit the Summary of Information, seemed unlikely to generate a significant num-

ber of cases in which FDA could disclose the Summary of Information. It might also confuse sponsors and lead to erroneous or unindicated waivers.

Therefore the Commissioner has deleted item 16 from the proposed amendments to IND Form FD-1571 and item 6 and item 9 from the proposed amendments to Forms FD-1572 and FD-1573, respectively. The Commissioner advises that he remains quite willing to adopt a procedure for providing information regarding INDs directly to Federal and State agencies if and when all such agencies agree not to disclose any confidential information so provided without the written permission of the FDA.

The Commissioner advises that the FDA has notified Agreement States and the NRC of all existing approved NDA's and biological product licenses for radioactive drugs and radioactive biological products. Procedures have been established to continue to notify the NRC and all Agreement States of all new approvals of NDA's for radioactive drugs and radioactive biological products. These procedures do not, however, preclude an applicant from notifying the NRC or an Agreement State of an NDA approval.

3. One comment suggested that § 312.1 should include concise and complete details for an acceptable protocol and pointed out that such areas as dosimetry, expected or documented clearance rates, and rationale of diagnosis or therapy were not contained in the new proposed rules.

The Commissioner is of the opinion that the present IND regulations (§ 312.1) and Form FD-1571 with the additions set forth in the proposal, are adequate as requirements for the development of a protocol for producing well-controlled clinical data on radioactive drugs. Each protocol for an IND study for a radioactive drug will be evaluated individually. In § 312.1, item 10.a of Form FD-1571 requires that the protocol include studies which will obtain sufficient data for dosimetry calculations and that these studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material. The FDA is currently preparing guidelines for research protocols on radioactive drugs; the Radioactive Pharmaceuticals Advisory Committee is assisting in this and, as drafts are developed, they will be discussed in open sessions of that advisory committee. When adopted, these guidelines will be available from the Agency.

4. One comment questioned whether it was necessary to amend or otherwise alter an existing IND for a nonradioactive investigational new drug if the drug is "tagged" with a radioactive element in accordance with the limitations set forth in proposed § 370.100. The comment also expressed the opinion that, if an investigational drug is "tagged" and administered at or near a pharmacologic dose, the new information required in items 6.d and 10.a of Form FD-1571 should be submitted as an amendment to the existing IND and a new IND should not be required.

The Commissioner concludes that it is not necessary to amend an existing IND for a nonradioactive investigational new drug if the drug is "tagged" with a radionuclide in accordance with the limitations set forth in § 361.1 (proposed § 370.100), and the specific research study is within the purposes set forth by that section. The results of the research study using the "tagged" compound must, however, be submitted to the existing IND. If pharmacological data are not sufficient to permit compliance with the requirements of § 361.1, it would of course be necessary to submit a new IND or, preferably, to amend the existing IND for the nonradioactive investigational new drug to conduct a study on the drug "tagged" with a radionuclide, even though the radioactivity limits set forth in § 361.1 are met. To amend an IND in this way, the information required in items 6.d and 10.a of Form FD-1571 must be submitted.

5. One comment suggested that, to assist the Federal and State regulatory agencies in fulfilling their responsibility for licensing the use of radioactive materials, the Summary of Information required in Form FD-1571 should be expanded to include: information describing the plan of investigation in sufficient detail to permit a critical evaluation of the methods and controls to be used; an indication as to whether any complementary drug or radionuclide administration is planned or contemplated in conjunction with the study; an indication of the expected fate of the radiopharmaceutical administered; if for therapeutic purposes, an indication of the expected effects; and calculations of the radiation doses delivered to the whole body and to the critical organ(s).

As stated in paragraph 2 above, the Commissioner has deleted item 16 (Summary of Information) from the amendments to IND Form FD-1571. Information needed by the NRC and Agreement States for licensing purposes must be obtained from the IND sponsors.

6. One comment suggested that, although radiopharmaceuticals are relatively simple organic compounds with little or no toxicological/pharmaceutical activity and may not require chronic toxicity studies, the regulations should require semichronic toxicity studies in anticipation that radiopharmaceuticals may, in the near future, be considerably more complex.

The Commissioner recognizes that an IND for radioactive drugs may in some cases require chronic or subacute toxicity studies. The preamble to the proposed regulations only noted that chronic toxicity studies may not be required for some radioactive drugs. The requirements for any IND will depend on the specific nature of the drug and its proposed uses.

7. One comment argued that the proposed regulations failed to distinguish between "hot" (radioactive) and "cold" (nonradioactive) pharmaceuticals and between diagnostic and therapeutic agents by applying to radioactive pharmaceuticals the same clearance procedures applicable to nonradioactive pharmaceuticals. The comment further suggested that a definitive statement was needed recognizing the difference between these two types of pharmaceuticals, as well as clear guidelines setting forth a workable format from which manufacturers can fashion their studies to comply with investigational new drug as well as new drug application requirements. These guidelines should be specifically tailored to reflect realistically the unique problems in the field of radiopharmaceuticals.

The Commissioner realizes that IND requirements for radioactive drugs will differ in various ways from those involving nonradioactive drugs, and this is clearly stated in the preamble to the proposed regulations. This situation is not unique, however, since requirements for one nonradioactive drug may differ sharply from those for a different nonradioactive drug. The requirements of § 312.1 are general requirements and are regularly adapted as appropriate for specific drugs. The FDA is currently in the process of drafting guidelines for conducting clinical trials involving radioactive drugs.

NDA Requirements for Radioactive New Drugs Generally

8. One comment questioned whether or not a mechanism had been established for filing abbreviated new drug applications for diagnostic radiopharmaceuticals.

The Commissioner advises that no mechanism has been established yet for submitting an abbreviated new drug application for a radioactive drug. The Commissioner recognizes, however, that the amount of clinical data necessary to approve an NDA varies among radioactive drugs, depending on several factors. Applicants are invited to meet with representatives of the FDA, Bureau of Drugs, Division of Oncology and Radiopharmaceutical Drug Products, to discuss the amount of data needed prior to submission of an NDA.

9. One comment suggested that there be a mechanism whereby previous work performed under an IND or an NDA could be referenced for a radiopharmaceutical for which a new use is being developed, provided the previous work is applicable to the new use.

The Commissioner advises that previous unpublished studies relating to a radioactive drug for which a new use is being developed may be incorporated by reference from one IND or NDA file into another only if the sponsor of the previous IND or applicant of the previous NDA authorizes the new sponsor or applicant to use these data.

NDA Requirements for Certain Radioactive New Drugs

10. One comment indicated that, at the outset of the preamble to the proposal, a statement is made that "any radiopharmaceutical which is not a 'new drug' i.e. when used under the conditions specified will require neither an IND nor an NDA but will require certain documentation to establish that the drug is in fact being

the conditions set forth in the regulation." The proposed rules then go on to set dates for the filing of an NDA for all radioactive pharmaceuticals with well-established medical uses. The comment requested clarification as to how those pharmaceuticals listed in § 310.503 (f)(1) relate to those referred to above.

The Commissioner advises that § 310.503(f)(1) lists a group of new reactor-produced radionuclides and their chemical forms which the FDA and the NRC have determined have well-established medical uses. In view of the extent of experience with drugs containing these radionuclides, the FDA and NRC have concluded that they should be distributed under investigational labeling when they are actually intended for use in medical practice. Such products have not been used to a material extent or for a material time and are not yet regarded as generally recognized as safe and effective for their indications. However, it may reasonably be expected that adequate evidence of safety and effectiveness can be developed by manufacturers and distributors for use of these drugs as recommended in appropriate labeling. In order to continue shipping in interstate commerce drugs containing these radionuclides, manufacturers and distributors must submit an NDA, IND, or application for a biological product license, on or before August 25, 1975. An IND will, however, permit continued commercial marketing of these drugs.

On the other hand, § 361.1 (proposed as 21 CFR 361.1) specifies conditions under which prescription drugs are generally recognized as safe and effective and are not new drugs. Such drugs may be marketed without an NDA, biological product license, or IND. The statement quoted in paragraph 29(1) referred to the fact that, in such cases, reports will be required to be submitted of annual or special reports of investigational new drug (IND) (see paragraph 29(1) to assure that the drug remains within the conditions under which the drug is considered as safe and effective.

One comment questioned whether the August 25, 1974 deadline for submission of NDA's applies only to those radionuclides listed in "§ 130(c) of the November 3, 1971 FEDERAL REGISTER" or also included in § 310.503(f) of the February 1974 proposal.

The Commissioner assumes that the comment intended to refer to "§ 130.4(c) of the regulations of November 3, 1971, as amended by § 130(c) in the FEDERAL REGISTER of December 13, 1971." The Deadline set forth in the regulations for submission of applications for a biological product applies only to drug products containing radionuclides listed in the "Chemical and Physical Forms" column of § 310.503(f)(1) of the proposal. The deadline has now been extended to August 25, 1975. The purpose of this deadline is to assure that manufacturers and distributors currently marketing any of the radionuclides listed in § 310.503(f)(1) of the proposal have sufficient time to submit to the FDA information necessary for continued marketing of these products. This deadline is not applicable to drug products, including biological products, containing any of the radionuclides listed in § 310.503(c) (formerly § 130.4(c)). Manufacturers and distributors were given until March 3, 1972 to submit an NDA, IND, or application for a biological product license to continue distribution of those products for any of the indications listed.

12. One comment pointed out that the November 1971 regulations allowed the submission of a new drug application for an existing product without requiring the prior submission of either clinical data or an investigational new drug application and questioned whether such a policy was still in effect.

The Commissioner advises that this policy is applicable to those radioactive drugs listed in § 310.503(f)(1). These are products which the FDA and the NRC consider to have well-established medical uses. The Commissioner has concluded that manufacturers and distributors of these drugs may reasonably be expected to be able to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling without conducting additional clinical studies to obtain such data. The policy is the same as that announced in the November 3, 1971 order for similar radioactive drugs.

13. One comment stated that this proposal "would create a new structure, on a temporary basis, to regulate a relatively small number of drugs." The comment further stated that "it may be more effective to require immediate submission of an IND and to permit the drug's continued use in interstate commerce for a shorter period under the same circumstances as it had been heretofore used."

The Commissioner assumes that the comment is in reference to § 310.503 which lists a group of new drugs, reactor-produced radionuclides and their chemical forms, which the FDA and the NRC determined have well-established medical uses. No new structure is proposed to deal with these drugs. In view of the extent of experience with the radionuclides listed in § 310.503(f)(1), the FDA and NRC concluded that they should not be distributed under investigational use labeling when they are actually intended for use in medical practice, and that manufacturers and distributors may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling. To continue shipping drugs containing these radionuclides in interstate commerce an NDA, IND, or application for a biological product license, must be submitted. An IND will not, however, permit continued commercial marketing of these drugs.

14. One comment requested clarification as to what effect, if any, the revision of § 310.503 would have on lists of "well-established uses" which many Agreement States have developed but which do not totally agree with those of the NRC. Another comment proposed the addition of Indium-113m to the list in § 310.503(f)(1).

The Commissioner has determined that only those radioactive drugs listed under § 310.503 shall be considered by the FDA to have well-established uses in medical practice. In the preamble to the proposal the Commissioner invited any person who believed that other radioactive drugs are widely used in medical practice and should be added to this list to submit comments and data proposing and justifying the addition of such drugs. The request for addition of the isotope Indium-113m to the well-established list was submitted in support of the request (which is on display in the Hearing Clerk's office) have been reviewed, the Radioactive Pharmaceuticals Advisory Committee consulted, and the request approved. Section 310.503(f)(1) has been modified accordingly.

15. A comment requested that the regulations for radioactive new drugs include provisions to clarify the requirements regarding reactor-produced by-product materials when such products are processed and shipped in bulk to other manufacturers for reprocessing into finished drug forms.

The Commissioner advises that bulk by-product materials intended for processing, repacking or use in the manufacture of another drug shall be processed, shipped, and labeled in compliance with 21 CFR 201.122 (formerly 21 CFR 1.106 (i)).

NUCLEAR PHARMACY ISSUE

16. One comment questioned whether the FDA had jurisdiction over radioactive drugs in the investigational stage or for well-established medical uses, that are prepared by the using physician and qualified associate staff rather than procured from a commercial pharmaceutical concern. The comment further stated that the provision of nuclear medicine services and the continued development of techniques, methods and products would be severely inhibited by requiring an IND or NDA under such circumstances, particularly in the larger clinical and research centers where much of the innovative and developmental advances evolve. Another comment questioned whether the proposed regulation was applicable to those so-called "regional radiopharmacies" which manufacture their own radioactive drugs including the non-radioactive components.

Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing a notice regarding the Food and Drug Administration's policy on the "nuclear pharmacy" issue.

REQUIREMENTS FOR RESEARCH USES OF RADIOACTIVE DRUGS GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

A. SCOPE OF DETERMINATION

17. One comment stated that in medical institutions operating under an NRC Broad Medical License new radiopharmaceuticals are sometimes developed in-

ternally and subjected to clinical trials to establish diagnostic or therapeutic efficacy. The comment questioned whether it is necessary for these institutions to submit an IND even though in the developmental and testing phase the drug is not shipped in interstate commerce. The comment further questioned whether such clinical trials relating to diagnostic efficacy were covered by proposed § 370.100 and whether it would be necessary to file reports on investigators of this type approved by a radioisotopes committee under a broad license either annually or immediately. If such clinical trials are not covered by proposed § 370.100, would the dose restrictions specified under that section apply?

The Commissioner advises that the FDA has jurisdiction over all drugs, including radioactive drugs, shipped in or introduced into interstate commerce whether prepared by a medical institution, physician, or a commercial drug manufacturer. "Shipment in interstate commerce" is determined not only by the interstate shipment of the final dosage form of the drug product, but also by the interstate shipment of the components of the drug product, as well as other factors. Therefore, where a determination is made that interstate commerce is involved (also see paragraph 16 of this preamble), an IND must be submitted before the drug product may be used in clinical trials.

As stated in the preamble to the proposal, the Commissioner has concluded that the provisions of § 361.1 (proposed § 370.100) are not applicable to clinical trials intended to determine the safety and/or effectiveness of a radioactive drug. Section 361.1 only applies to research "intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry but not intended for immediate therapeutic, diagnostic, or similar purposes." Clinical trials using new radioactive drugs are subject to the requirements of an IND as set forth in § 312.1. Section 361.1 of this regulation has been clarified to reflect this. The dose restrictions set forth in § 361.1 do not apply to clinical trials conducted under § 312.1.

18. One comment expressed confusion in interpreting the scope of the exemption provided by proposed § 370.100 as it relates to the development of new radioactive diagnostic agents. The comment further stated that it was not clear why the particular agent being studied cannot be used specifically for diagnostic purposes if the criteria for exemption under proposed § 370.100 are met (i.e., radiation safety, pharmacological inactivity, and Radioactive Drug Research Committee approval).

Section 361.1 (proposed § 370.100) provides for the use of tracer amounts of radionuclides, attached to various compounds, in research studies to obtain basic information on drug metabolism, specific physiologic or pathophysiologic processes in humans, and the kinetics, distribution, and localization of the various "tagged" compounds. Certain studies included in this category may be essential parts of the development of a new diagnostic agent (for example, studies conducted to determine where the radioactive drug is localized or the extent to which it is concentrated in certain organs or tissues). Such studies fall within the scope of § 361.1 if other requirements of that section are met. These studies must be distinguished from studies intended to evaluate the safety and effectiveness of a radioactive drug as a diagnostic agent. In this case the drug is used, not as a research tool, but as a new diagnostic agent for which safety and effectiveness must be proven; therefore, there is no basis for concluding that it is generally recognized as safe and effective as a diagnostic agent. The radioactive diagnostic agent, therefore, must be studied under an IND.

B. LIMITS ON PHARMACOLOGICAL DOSE

19. Several comments were received regarding the requirements under the proposed § 370.100 that the pharmacological dose shall be known not to cause any clinically detectable pharmacological effect in human beings. One comment expressed the thought that such a limit on the pharmacological dose was unrealistic and unnecessary and would place severe and unnecessary restrictions upon research in such vital areas as human drug metabolism. The comment further noted that since doses known not to cause any clinically detectable pharmacological effect are often substantially below the therapeutic dose, radioactive studies conducted with such minute doses would not be representative of the pharmacokinetics of the drug studied at the therapeutic dose. Further, it was stated that such studies would not furnish enough labeled metabolites to conduct metabolite studies. Another comment suggested that the exemption from IND requirements should include the tagging of a drug at a dose level having a pharmacologic effect if that dose level is safe and effective, as evidenced by an approved NDA.

In the preamble to the proposed regulation, the Commissioner made it clear that for radioactive drugs to be considered not new drugs for certain uses it was necessary to conclude that they were generally recognized as safe for such uses. The Commissioner suggested that such a conclusion could certainly be reached, with regard to the pharmacological safety of the drug, if the drug was known not to produce clinically detectable pharmacological effects on the basis of data from studies in human beings. If such data are not available, even the smallest amount of that drug must be assumed to produce pharmacological activity. Once pharmacological activity is known or assumed to occur, pharmacological safety cannot be presumed and other evidence of general recognition of safety is necessary. Without this evidence, the drug is considered to be a new drug, and any research with it must meet the requirements of § 312.1, including the submission of an IND.

The fact that a drug is approved for certain specific uses means that it is considered safe and effective for these uses. It is not considered safe and effective for other uses or for non-therapeutic uses. The Commissioner recognized that the proposed standard for demonstrating general recognition of safety (i.e., the absence of pharmacological activity) was a strict standard and interested persons were invited to submit comments on the appropriateness of the proposed standard. While proposing this standard, the Commissioner also invited comments on an alternative test; namely, that the amount of radioactive drug administered not exceed a dose of 10 percent of the lowest single dose recommended by the drug's labeling, or in the absence of approved labeling, 10 percent of the lowest single dose recommended by recognized medical texts, with the exact dosage being reviewed by a peer committee for safety. Although comments objected to the proposed standard and, in some cases, suggested alternatives, no comments were received which provided reasons for considering any standard, other than the absence of clinically detectable pharmacological activity, as demonstrating general recognition of safety. While the Commissioner may at some future time reconsider this issue, he has concluded that, at present, for the purpose of this regulation, general recognition of pharmacological safety can be considered to exist only when the drug has no clinically detectable pharmacological effect in human beings.

It should be stressed that it is not anticipated that there will necessarily have been a formal dose-response study that defined the lower threshold dose for a clinically detectable pharmacological effect. For example, if the circulating blood levels or excretion rate of an endogenously produced substance is well known, it may be possible for the Radioactive Drug Research Committee (see paragraph 39) to conclude that some small fraction of these levels or rates (e.g., administration over a given interval of a low percentage of the amount of a substance that is produced endogenously during the same interval) represents an amount without detectable pharmacological effect. Or, if large amounts of a substance such as an amino acid or sugar are regularly consumed as foodstuffs, it may be possible for the Radioactive Drug Research Committee to conclude that a small amount of it (e.g., a small percentage of the amount usually consumed during a meal), at least by the oral route, would be without detectable pharmacological activity.

The Commissioner is aware that pharmacokinetic studies or studies requiring isolation of metabolites may require larger amounts of a drug. Such studies may either be conducted under an IND or in persons already receiving the nonradioactive drug for a therapeutic purpose.

20. One comment suggested modification of proposed § 370.100(b)(2) to allow, under well-defined conditions, the administration of the radio-labeled ver-

sion of a pharmacological agent when this pharmacological agent is administered to the patient in pharmacological doses as part of a therapeutic treatment and to assess the effectiveness of that particular therapy. The comment suggested adding the statement "If a drug is used under protocol for therapeutic purposes, then a minimal dose of the radio-labeled isomer of this drug can be added to help evaluate the radiopharmacokinetics of this drug."

The Commissioner advises that this regulation in no way restricts the use of a nonradioactive drug, i.e., under an IND, NDA, or old drug status, whether or not the radioactively labeled version of this drug is administered at the same time to evaluate the pharmacokinetics of the drug. For such a study to be permitted under § 361.1, the conditions of that section must be met, except that in this case the limitation on pharmacological dose will be such that the aggregate amount of the drug administered (nonradioactive drug and tagged compound) shall be known to remain an appropriate dose for the use for which the nonradioactive drug is being given. The regulation has been clarified to reflect this. The Commissioner also advises that if the nonradioactive drug has an IND, the results of any research studies using the radioactively labeled version of the drug and performed under § 361.1 must be included as part of the required IND reports.

21. One comment stated that the fundamental information to determine what "traditional pharmacology based judgment" means needed amplification and the term "no response" was not clear.

In paragraph D.1 of the preamble to the proposal, the Commissioner stated that "when radioactive drugs are administered in amounts which have been demonstrated not to produce clinically detectable pharmacologic activity in human beings such drugs are and must be generally recognized as safe from the viewpoint of traditional pharmacology." In this context "traditional pharmacology" was intended only to distinguish hazards related to the toxic effects of the drugs (traditional pharmacology/toxicology) from those related to hazards of radiation. The term "clinically detectable pharmacologic activity" in human beings has been discussed above. Neither the term "no response" nor "traditional pharmacology" are used in the regulation; therefore no change is needed.

C. LIMITS ON RADIATION DOSE

22. One comment indicated that the intent of proposed § 370.100(b)(3) was not clearly stated in the preamble but presumed that the radiation limits are stated so that it will not be necessary to file an IND for research projects which do not lead to diagnostic tests.

The Commissioner advises that the intent of § 361.1 (proposed § 370.100) is to identify a class of drugs that are not new drugs because they are generally recognized as safe and effective under specific circumstances. One of those circumstances is that the radiation dose to subjects does not exceed certain limits. The identification of this drug class as not new drugs has the effect of making it unnecessary to submit an IND before using them.

23. One comment questioned whether it was necessary that there be a radiation dose limit included among the conditions under which the use of radioactive drugs for research is considered safe and effective. The comment stated that "If a local committee is deemed to have the judgment to assess and approve varied lesser dose procedures, need they be limited in regard to the far less frequent situations of a particularly important research study that might necessitate a larger organ dose?" The comment suggested that it might be preferable to offer the option to the local committee of referring to an FDA-sponsored "super-committee" research proposals which, because of larger dosage or other unusual considerations, the local committee would prefer to have acted upon by a higher authority.

The Commissioner disagrees with the suggestion of the comment. When a pharmacologically inactive amount of a radioactive drug is used, the issue of safety for use in human subjects is entirely related to the amount of radiation administered. Because any exposure to radiation is presumed to have an attendant risk (due to a lack of evidence showing any absolutely safe level of exposure), it is obvious that no radiation exposure can be justified or considered generally recognized as safe as a research tool if the study in which it is used is of poor quality or is not likely to provide useful information. The Commissioner has concluded that the Radioactive Drug Research Committee (see paragraph 29) can assure the quality of studies and the minimization of the radiation dose. Nevertheless, despite this conclusion, the Commissioner has no basis for concluding that all doses of a radioactive drug, even if used for research purposes and monitored by a properly functioning committee, are generally recognized as safe for the intended use. He has therefore concluded that a limit on radiation dose is necessary to make a determination of general recognition of safety for research uses. As discussed below (in paragraph 24), the Commissioner has concluded that the basic occupational radiation protection criteria established by the NRC under 10 CFR 20.101 and 20.102, even though they were not intended to be criteria related in any way to subjects in clinical research, provide a reasonable basis for the determination that a radioactive drug, when administered in amounts such that the pharmacological and radiation dose from such drug is within the limits of § 361.1(b), and under the cognizance of an FDA-approved committee, is generally recognized as safe. It should be emphasized that this limit for purposes of establishing general recognition of safety in no way represents a conclusion that such radiation doses do not represent some element of risk to the individual nor that larger doses are necessarily unsafe. It is further emphasized that setting a limit on radiation dose for purposes of § 361.1 does not alter the requirement that the radiation dose, even though it is within the limit, should be the smallest amount needed to carry out the study. It is only concluded that within the context of the benefit to be obtained from the research study, that such radiation doses are generally recognized as safe. Radioactive drugs which deliver larger doses are considered to represent new drugs and would require an IND or approved NDA.

24. One comment questioned whether it was appropriate to use the occupational permissible exposure criteria as a limit upon the approval authority of the proposed Radiation Safety Committee (under proposed § 370.100(b)(3)) since such limits were developed for a specific purpose and should not be extended to research use of radiation in human volunteer subjects.

As stated in the preamble to the proposal the Commissioner fully agrees with the National Council on Radiation Protection and Measurements who, in discussing radiation dose to research subjects, noted that "each proposed human research application must be judged on its merit after review by competent peers, and that dose-limiting recommendations for radiation workers or the public do not apply to the individual to be irradiated." The Commissioner concludes that § 361.1 of this regulation embodies this recommendation and requires that each study be approved by competent peers (the Radioactive Drug Research Committee) and that the radiation dose be kept as low as practicable. The radiation dose criteria in § 361.1(b)(3) are for the purpose of stating that such research studies are generally recognized as safe and not to set a specific dose limit for research subjects.

The Commissioner referred, in the preamble to the proposal, to various studies and published literature which reflect a consensus which permitted the establishment of exposure levels acceptable from the standpoint of radiation safety. The NRC criteria, set forth in 10 CFR 20.101 and 20.102, accord with this consensus.

The NRC requirements take into account both the risk to the public health of larger doses of radiation for a particular group of persons and the risk to the individuals involved. Investigational subjects, like radiation workers, represent a limited segment of the total population; the public health implications of doses of radiation to research subjects appear no different from those resulting from exposure of radiation workers and the risks are equally acceptable to society. Considerations of risk to the individual also appear reasonably similar for both groups. An informed potential research subject is able to make a decision regarding participation in a study because he will, in effect, be deciding whether or not he is willing to participate in the study and assume a risk in the same sense as does a radiation worker. Although the benefits to the individual are quite different, in one case the opportunity to earn a livelihood, in the other the opportunity to participate in a scientific study, each situation in-

volves a decision to take a specified risk for a specified purpose. The Commissioner concludes that these doses represent a minimal risk to the individual and are appropriate criteria for a general recognition of safety where there are potential benefits from research studies.

25. One comment expressed the opinion that use of the occupational radiation exposure limitation (as an upper limit for exposure of research subjects in studies covered by proposed § 370.100) is too high in comparison with the intended scope of the studies.

The Commissioner notes that it is probable that many studies under § 361.1 (proposed as § 370.100) can be carried out using smaller doses of radiation than would be permitted under the limits on radiation dose. As noted earlier, it is the responsibility of the Radioactive Drug Research Committee (see paragraph 29) to assure that the smallest dose that can be used without jeopardizing the study is used. The Commissioner believes that doses up to the limits set forth in § 361.1 and used under conditions specified in that section can be considered generally recognized as safe and effective and constitute a reasonable limit for research studies conducted under this section. The Food and Drug Administration will continually evaluate the use of radioactive drugs under § 361.1 through the review of the required annual reports submitted by the Radioactive Drug Research Committee. The present criteria for establishing a radiation dose limit will be reconsidered if justified by this evaluation.

26. Several comments questioned the particular radiation dose limits selected. One comment suggested that it would be preferable to state any limitation as a maximum organ dose in any one year with the further qualification that in the event of a very long effective half-life situation, the total dose over the life expectancy of the concerned subject would not exceed some considered value. Another comment stated that it was not clear how the yearly cumulative total for whole body exposure for adults and the yearly total for critical organs were derived.

The Commissioner has reconsidered the proposed maximum radiation doses in light of the comments above and further intra-agency discussion. As originally proposed, maximum yearly doses were given. To provide adequate protection for subjects in special circumstances where long half-life radionuclides are used, the wording has been changed so that there will be both an annual limit on dose received and a limit on the total dose commitment resulting from studies conducted in a single year. Thus, the regulation has been modified to include both the "annual dose" and "total dose commitment" from a study or studies conducted within a single year. In addition, maximum whole body dose and the dose to critical organs (active blood-forming organs, lens of the eye, and gonads) have been made identical. The proposed notice specified limitations for "critical" organs that should have been applied to other organs. This has been corrected in the final order. As modified, the total dose commitment to any research subject from a single study or cumulatively from a number of studies within a single year may not exceed the total commitment value of 5 rems for exposure to the whole body and critical organs (active blood-forming organs, lens of the eye, and gonads) or 15 rems for exposure to other organs. The designation of whole body, critical organs, and other organs within the various dose categories has been modified in the regulation to conform to terminology used by the NRC.

It is further recognized that significant radioactive contaminants or impurities in a radioactive drug may affect the results of a study or alter the validity of the dose calculations. Therefore, any contribution to dose due to significant radioactive contaminants or impurities shall be included in calculating the total radiation dose and dose commitment. In addition, in determining maximum permissible dose limitations, the possibility of followup studies shall be considered for inclusion in the dose calculations. Section 361.1(b)(3) (proposed as § 370.100(b)(3)) has been revised accordingly.

27. One comment raised a question regarding the relationship between exposure history and the radiation limitations. The comment stated that the repeated reference to occupational exposure limitations in proposed § 370.100 (b)(3) and (d)(1) appear to sanction a quarterly occupational exposure of 3 rems. The comment further stated that this level of exposure is allowed in Agreement State and NRC regulations only with a properly completed exposure history and that there is no provision for an exposure history in the proposed regulation. The comment did not object to the 3 rems limit but to the use of such phrases in the proposed § 370.100 as "occupational exposure limitations" and "absorbed dose * * * permissible for occupationally exposed personnel."

The Commissioner believes that the limitations on radiation dose have been clarified in the final order. With the addition of an annual dose, an indication of a quarterly radiation dose is unnecessary. It is thus clear that, with a total annual dose of 6 rems for whole body and critical organs, 3 rems cannot be administered in each quarter.

"Exposure history," as required under NRC and Agreement State regulations, refers to previous occupational exposure. The Commissioner is of the opinion that very few research subjects will have been radiation workers and therefore they will not have an "exposure history." The Commissioner advises that, in revising paragraph (b)(3) and (d)(1) of § 361.1 of the regulation, the phrases "occupational exposure limitations" and "absorbed dose * * * permissible for occupationally exposed personnel" have been deleted.

28. One comment expressed concern that some research programs may also involve radiation doses from radiographic or fluoroscopic procedures such that the total subject dose may exceed the occupational permissible dose limits. The comment further stated that the x-ray dose may or may not be totally or partly of direct diagnostic benefit to the concerned subject or may or may not be part of medical care that the subject would receive if not volunteering for the study. The comment requested clarification as to whether any limitations on radiation dose to the subject that may be set under proposed § 370.100(b)(3) are applicable only to the dose attributable to the radionuclide procedure or only to the dose attributable to the research aspect of the subject's radiation experience during the period of concern, or to some other dose calculation. The comment expressed the opinion that it is not practicable to attempt to set regulatory limits based on the total radiation experience associated with a research use of radioactivity, because of the many considerations involved in assessing the value-risk ratio of an individual research proposal.

The Commissioner advises that the radiation dose limitations under § 361.1 (b)(3) (proposed § 370.100(b)(3)) are the total doses attributable to the research study including the radioactive drug and any doses from x-ray procedures which are considered and integral part of the research study, i.e., would not have occurred but for the study. An x-ray procedure which would have occurred whether or not the patient was part of the research study should not be included in determining the doses attributable to the research study. The Commissioner considers the determination of whether or not a given x-ray procedure is a part of the patient's medical care, as opposed to part of the research procedure, to be one which the Radioactive Drug Research Committee (see paragraph 29) can readily make.

D. RADIOACTIVE DRUG RESEARCH COMMITTEE

29. Comment was received from the Nuclear Regulatory Commission (NRC) requesting that the term Radiation Safety Committee as used in § 361.1 be changed to Radioisotope Research Committee or any other appropriate name. The NRC stated that the term Radiation Safety Committee is used by many hospitals and academic institutions for the committee that reviews the institution's overall program for use of radioactive materials and radiation producing machines, especially from the standpoint of radiation protection which is frequently called health physics.

The Commissioner has therefore concluded that, to distinguish between this committee and the committee required for approval of research uses of radioactive drugs under § 361.1 of this regulation, the term "Radiation Safety Committee" as used in § 361.1 shall be changed to "Radioactive Drug Research Committee." The regulation has been modified accordingly. In stating the following comments and their discussion, the revised committee name is used.

30. One comment recommended that the field of pharmacology be included as a discipline to be considered for repre-

sentation on a Radioactive Drug Research Committee under the proposed § 370.100(c)(1). Other comments expressed the feeling that a pharmacologist should be a required member of such committee. Comments also differed as to whether a radiopharmacist should be included in the membership of the Radioactive Drug Research Committee. Some comments indicated that there may be some misunderstanding as to who the required members of a Radioactive Drug Research Committee are.

The Commissioner concludes that the composition of the Radioactive Drug Research Committee as set forth in § 361.1 (c)(1) is adequate. As stated in the proposed regulation, approval of a Radioactive Drug Research Committee shall be based upon an assessment of the qualifications of the members of the committee and the assurance that all of the necessary fields of expertise are covered. Certification in a particular discipline is not necessary. For example, one of the required members of the Committee shall be a person qualified to formulate radioactive drugs. This person need not necessarily be a radiopharmacist; he may be a physician or other qualified individual. The Commissioner also sees no reason to specify additional disciplines as required members because § 361.1 (c)(1) states that the addition of consultants in other pertinent medical disciplines is encouraged. Expertise in any needed area can thus be obtained. The Commissioner advises that the only three required fields of specialization of a Radioactive Drug Research Committee are (1) a physician recognized as a specialist in nuclear medicine, (2) a person qualified by training and experience to formulate radioactive drugs, and (3) a person with special competence in radiation safety and radiation dosimetry. The remaining members shall be selected from individuals qualified in varied disciplines pertinent to the field of nuclear medicine (e.g., radiology, internal medicine, clinical pathology, hematology, endocrinology, radiation therapy, radiation physics, radiation biophysics, health physics, and radiopharmacy). Section 361.1(c)(1) has been rewritten to indicate more explicitly the required members.

31. One comment pointed out that the proposed § 370.100(c) gave no guidance regarding notification of changes in the membership of the Radioactive Drug Research Committee (e.g., because of relocation, retirement, or death of members) and the effect of such changes upon FDA approval of the Committee. The comment suggested that such changes be reported and documented in the annual report and that approval or disapproval of the revised Committee be determined by the FDA following receipt of the annual report.

The Commissioner has studied the comment and concludes that all changes in the membership of the Radioactive Drug Research Committee and selection of new members shall be communicated to the FDA as early as possible so that the FDA may review the qualifications of the new member(s) and the composition of the Committee and be assured that the Committee continues to include all of the necessary fields of expertise. Section 361.1(c)(4) (proposed § 370.100(c)(4)) has been revised to provide for this procedure. The Commissioner advises that once a Radioactive Drug Research Committee is approved, it continues in such status until the approval is withdrawn by the FDA. Individual changes in membership may therefore be implemented without FDA approval; FDA disapproval of a new member would take the form of withdrawal of approval of the Committee.

32. One comment expressed concern over the proliferation of duplicative committees deriving their authority from various Federal and State regulatory agencies. It recommended that FDA limit, at least initially, those committees which it approves pursuant to proposed § 370.100(c)(4) to those already established medical advisory committees of radioactive material licensing agencies and the radiation safety committees of broad medical licensees of the NRC. Another comment expressed concern that the FDA might not approve a Radioactive Drug Research Committee which has been approved as a Broad License Committee by an Agreement State or the NRC, or vice versa, and suggested that there be some criteria for mutual acceptance of a Radioactive Drug Research Committee. The comment further questioned whether the regulation would allow the Medical Committee of a State Radiation Advisory Board to review and approve research programs for small user licensees.

The Commissioner has determined that, to conclude that a radioactive drug is generally recognized as safe and effective when used for certain research studies, it is necessary to establish criteria for use of the drug which include a monitoring of that use by a Radioactive Drug Research Committee. The standards for the composition and functioning of the Radioactive Drug Research Committee are a fundamental element in the Commissioner's determination. The Commissioner cannot assume that the requirements for advisory or review committees of other Federal or State regulatory agencies will assure a committee that meets FDA criteria for a Radioactive Drug Research Committee. Therefore the FDA cannot, without an independent determination, approve a Committee that has been approved by another Agency. However, any established committee, such as the Medical Committee of a State Radiation Advisory Board, may, if constituted in accordance with § 361.1 (c)(1), apply to the FDA for approval as a Radioactive Drug Research Committee.

33. One comment questioned the need for each Radioactive Drug Research Committee to meet at least quarterly, as provided in proposed § 370.100(c)(2), because the quantity of business to be considered by the Committee may not justify such frequent meetings.

The Commissioner concurs in part and has concluded that the Radioactive Drug Research Committee shall meet at least once each quarter in which a research activity has been authorized or conducted. No more than 90 days should pass between the start of the research and the monitoring of the study's progress by the Committee. More frequent meetings may be held at the discretion of the Committee.

The Commissioner has also determined that to provide reasonable assurance that the expertise available within the committee will be utilized in committee deliberations, it is necessary to indicate the number of members needed to constitute a quorum. He has concluded that more than 50 percent of the membership of the Committee must be present to constitute a quorum and that there must be appropriate representation of the required fields of specialization. Section 361.1(c)(2) (proposed as § 370.100(c)(2)) has been revised accordingly.

34. One comment expressed the opinion that more efficient use of the concept of a Radioactive Drug Research Committee as a "watchdog body" in cases of experimental use of radioactive drugs should be to expand its function to cover both new and not new radioactive drugs.

The Commissioner advises that review of investigations of new radioactive drugs submitted pursuant to § 312.1 is clearly a regulatory function of the Food and Drug Administration and cannot be delegated to a Radioactive Drug Research Committee. Institutional review is also required for investigational new drugs under an IND where the clinical studies are conducted on institutionalized subjects or are conducted by an individual affiliated with an institution which agrees to assume responsibility for the study. The Radioactive Drug Research Committee would not fulfill this requirement because its composition lacks lay membership. The FDA would, however, look favorably upon a Radioactive Drug Research Committee serving as a subcommittee of an Institutional Review Committee when the Investigational new drug is a radioactive drug. The Commissioner advises that this regulation does not in any way prohibit an institution from involving its Radioactive Drug Research Committee in other policy matters, including use of radioactive new drugs, if it so chooses.

35. One comment suggested that because of the inherent time delays involved in obtaining protocol review and approval from a Radioactive Drug Research Committee as envisioned by the regulations, and because of the relatively short shelf life of many of the tagged drugs utilized, the regulations include a maximum time limit within which the Committee would have to approve or reject a proposed protocol.

The Commissioner concludes that regulation of the time required for approval or rejection by a Radioactive Drug Research Committee of a proposed protocol must be left to the institution or State or Federal agency with which the Committee is associated. The Commissioner cannot predict the workload of each Radioactive Drug Research Com-

studies; therefore, it is not feasible for the FDA to establish a time frame for review and approval or rejection of a proposed protocol. The FDA believes, however, that since the Radioactive Drug Research Committee is composed of persons familiar with the unique problems of research with radioactive drugs, committee review will be responsive to the needs of individual researchers. The Commissioner further assumes that ordinarily approval of a protocol will be sought before the tagged drug is obtained; therefore, the shelf life of the tagged drug will not be germane.

30. Several comments suggested that the "Report on Research Use of Radioactive Drug" which each Radioactive Drug Research Committee is required to submit annually under proposed § 370.100(c)(3) for each study conducted during the preceding year be made available to Agreement States or other licensing agencies for future licensing actions without forfeiting the nondisclosure provisions which apply to proprietary information. Another comment suggested that FDA consider establishing some mechanism of advising its approved Radioactive Drug Research Committees of any studies which have been approved under proposed § 370.100 by any other approved Radioactive Drug Research Committee.

The Commissioner advises that contents of the "Report on Research Use of Radioactive Drug" are available for public disclosure unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in 21 CFR 4.61. A trade secret, as defined in 21 CFR 4.61, may consist of any formula, pattern, device, or compilation of information which is used in one's business and which gives him an opportunity to obtain an advantage over competitors who do not know or use it. Commercial information that is privileged or confidential means valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs. Data and information submitted or divulged to the Food and Drug Administration which fall within the definitions of a trade secret or confidential commercial information are not available for public disclosure.

The note under "Report on Research Use of Radioactive Drug" set forth in proposed § 370.100(c)(3), stated that the name of the investigator would not be disclosed publicly. Under the new regulation promulgated under the Freedom of Information Act, such information may be publicly disclosed. Section 361.1(c)(3) (proposed § 370.100(c)(3)) has been revised accordingly.

Therefore, information from this report which is available for public disclosure is also available to Agreement States or other licensing agencies and all Radioactive Drug Research Committees and will be disclosed in accordance with procedures set forth in 21 CFR Part 4. The Commissioner has concluded that it is impractical, because of resource limitations, to provide these reports to Agreement States and other licensing agencies and to other FDA Radioactive Drug Research Committees on a continuing basis. A specific request will be required under the public information regulations (21 CFR Part 4).

31. One comment recommended that the age of all research subjects, not just minors, be included in the "Report on Research Use of Radioactive Drug" set forth in proposed § 370.100(c)(3). Another comment suggested that the number of adults and children be specified separately on each report.

While such data are not necessary to monitor compliance, the Commissioner concludes that data such as the age and sex of all research subjects would be useful in evaluating the total risk to the public health and to individuals. Further, the Commissioner notes that this data would be useful to the FDA in studies of the radiation dose to the public from all radioactive drugs. Accordingly, § 361.1(c)(3) of the regulation has been modified to require the "Report on Research Use of Radioactive Drug" to include the dose to each research subject by age and sex.

38. One comment objected to the requirement of reporting immediately when more than 30 research subjects were involved in a research project under proposed § 370.100 since the individual risks to a human subject receiving radioactive materials are independent of the number of subjects. Another comment felt that annual reporting by the Radioactive Drug Research Committee and their function as a peer review group were sufficient and therefore objected to immediate reporting as stated above or when the research subject is under 18 years of age.

The Commissioner wishes to be certain that the requirements of § 361.1 (proposed § 370.100) are being interpreted and followed in a satisfactory manner. Relatively large research studies, such as those resulting in the exposure of more than 30 research subjects, represent a category of study in which it may be particularly appropriate to examine whether the need for the number of subjects chosen is documented, the radiation dose is well justified, and the distinction between research protocols and clinical trials is observed. Similarly, any study involving radiation exposure to research subjects less than 18 years of age may need special attention to examine the basis for carrying out the study in that age group and assure that the protocol is adequate for the safety of such subjects. The Commissioner emphasizes that the early notification of FDA under these circumstances in no way implies that such studies are unacceptable or inappropriate or that these studies require preclearance by the FDA. Notification is entirely for FDA's internal monitoring of this new regulation.

34. One comment suggested that item 8 of the "Report of Research Use of Radioactive Drug" be revised to read as follows:

8. Radiation Absorbed Dose:
a. Radionuclide identification.
b. Administered activity dose—child, adult (max).
c. Maximum number of activity doses per patient.
d. Estimated absorbed dose per single procedure—whole body, gonad and critical organ.

The Commissioner has reviewed the terminology in item 8 and is of the opinion that the requirements should be stated in more specific terms. He has therefore revised these parts of the "Report of Research Use of Radioactive Drug" to read as follows:

8. Name of the radionuclide(s) used, including any present as significant contaminants or impurities.
9. Radiation absorbed dose. Give the methods by which radiation dose commitment was estimated, such as by calculation, by in vivo measurements, by uptake excretion, or by other methods. For each subject, provide:
a. Age, sex.
b. Amount of each radionuclide administered.
c. Estimated absorbed dose per single administration of radioactive drug, expressed as whole body, active blood-forming organs, lens of the eye, gonads, and other organ dose.
d. If more than one administration of a radioactive drug per subject, cumulative radiation dose and dose commitment, expressed as whole body, active blood-forming organs, lens of the eye, gonads, and other organ doses from the administered radionuclides.

E. OTHER COMMENTS

40. Three comments expressed the opinion that proposed § 370.100(d)(1) should require the radioassay of the pharmaceutical prior to administration and one comment suggested that the use of a dose calibrator be required. One comment assumed that a dose calibrator would be required.

Although proposed § 370.100 implies that the radioactive drug will be assayed prior to use, this is not stated explicitly. The Commissioner therefore concurs with this part of the comment, concluding that radioassay of some kind is necessary prior to use of the radioactive drug. Specific designation of a dose calibrator is inappropriate, however, since other assay methods would be acceptable. Section 361.1(d)(1) (proposed § 370.100 (d)(3)) is therefore amended to require radioassay of the radioactive drug prior to its use.

The Commissioner advises that § 361.1 (d)(3) has also been amended to state more specifically the requirements which the Radioactive Drug Research Committee must consider to assure that the radiation dose to research subjects is as low as practicable to perform the study and to meet the criteria set forth in § 361.1(b)(3). To help achieve this assurance, two additional requirements have been added to this paragraph; namely, that the radioactive drug chosen for the study has that combination of half-life, types of radiation, radiation

energy, metabolism, chemical properties, etc., which results in the lowest dose to the whole body or specific organs with which it is possible to obtain the necessary information and that the investigator utilize adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide.

41. One comment stated that proposed § 370.100(d)(5) appeared to prohibit research studies involving metabolism during pregnancy and felt that the acceptability of performing a specific study on pregnant females should be the decision of the FDA-approved Radioactive Drug Research Committee.

Both the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP) have expressed concern over the possible adverse effects on the human embryo and fetus from radiation exposure to pregnant women. The Commissioner has determined that, because of the potential risk to an embryo or fetus, the use of a radioactive drug during pregnancy cannot be generally recognized as safe; therefore, such studies cannot be conducted under § 361.1. This limitation in no way reflects, however, any prejudgment as to whether such a study may be conducted under an IND. The Commissioner emphasizes that the radiation dose limits, pharmacological dose limits, Radioactive Drug Research Committee requirements, and all other requirements of § 361.1 relate only to a specific group of radioactive drugs for certain research uses. There is no intent that any of these limits represent actual or de facto limits for studies conducted under an IND. Therefore, research studies in pregnant women may be permitted where the sponsor submits an IND and complies with the requirements of § 312.1.

42. One comment requested clarification of proposed § 370.100(d)(7) as to whether the statement in "No study involving * * *, no matter how small the amount of radioactivity, shall be permitted * * *." would require Radioactive Drug Research Committee approval for the use of any compound containing naturally occurring radioisotopes such as potassium which contains 0.012 percent K-40.

The Commissioner advises that § 361.1 (proposed § 370.100) pertains only to compounds to which tracer quantities of certain radionuclides have been deliberately attached and not to an element, such as potassium, which contains trace amounts of radioisotopes in its natural state. Section 361.1(d)(7) has been modified to reflect this.

43. One comment questioned the meaning of the word "active" as used in the term "active ingredient," relative to information required on the label by section 502(e) of the act and proposed § 370.100(f), and expressed the feeling that all ingredients in an injectable preparation should be specified and listed under proposed § 370.100(f) and a determination made later on whether they are "active" or not.

The Commissioner advises that the definition of "active ingredient" in 21 CFR 210.3(d)(5) (formerly 21 CFR 133.1(d)(5) prior to recodification published in the FEDERAL REGISTER of March 27, 1975 (40 FR 13996)) is applicable to § 361.1(f)(4) of these regulations. Active ingredient is defined as "any component which is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term shall include those components which may undergo chemical change in the manufacture of the drug and be present in the finished drug product in a modified form intended to furnish the specified activity or effect." The Commissioner agrees that radioactive drug products intended for parenteral administration under § 361.1 should be labeled to identify all inactive ingredients in the same way as other drug products for parenteral administration under § 201.100(b)(5)(iii) (formerly § 1.106(b)(2)(v)(c)) and has modified § 361.1(f) correspondingly. All other label requirements imposed by section 502 (b) and (e) of the act which were stated in the preamble to the proposal have also been listed under § 361.1(f).

The Commissioner also advises that the proposal (in the preamble and proposed § 370.100(f)) indicated label and labeling requirements for radioactive materials. Such requirements are specific label requirements as imposed by section 502 (b) and (e) of the act and certain other requirements and are to appear on the label of the immediate container and shielded container unless otherwise specified. The wording in the final order has been revised to reflect this.

44. One comment suggested revising paragraph (f) of proposed § 370.100 to read: "A radioactive drug prepared, packaged, distributed and primarily intended for use in accordance with the requirements of this section shall be exempt from section 502(f)(1) of the act and section 1.106 of this chapter if the packaging, label and labeling are in compliance with Federal, State, and local law regarding radioactive materials and if the packaging, label and labeling required for radioactive materials by the Nuclear Regulatory Commission and by State and local radiological health authorities bear the following: * * *." The comment further proposed the addition of a new paragraph (f)(6) to read "whether the drug is for investigational use only," and a new paragraph (f)(7) to read "The expiration date, special storage conditions, pyrogenicity, specific concentration and addition of bacteriostatic agents" and addition of a new sentence reading "In the event that the immediate container of any radioactive drug is too small to contain the information set forth in paragraph seven (7) above, the information shall be furnished in the product's accompanying label."

The Commissioner concludes that the initial wording of § 361.1(f) (proposed § 370.100(f)) is preferable to the suggested alternative. The requirements by the FDA for labeling may be in addition to the requirements of the NRC, other Federal authorities, or State and local radiological health authorities. Paragraph (f) of proposed 370.100 was therefore written to allow the NRC or the State and local health authorities to decide whether they wanted a distinct radioactive warning on the label apart from other labeling. The suggested alternative does not provide for this.

The suggested paragraph (f)(6) is not applicable since these are not investigational drugs, as that term is normally used (i.e., a drug under an IND), although these drugs are used for research. The statement described in § 361.1(f)(2) is proper for radioactive drugs for research use under this section.

With regard to the suggested paragraph (f)(7), the name and quantity of all bacteriostatic agents and other inactive ingredient(s) are required by 21 CFR 201.100(b)(5)(iii) (formerly 21 CFR 1.106(b)(2)(v)(c)). If a drug product is for parenteral use Section 361.1(f) (proposed 370.100(f)) has been modified to include this requirement. Section 502(h) of the act requires that drugs liable to deterioration shall bear a statement of such precaution as necessary for the protection of the public health. The Commissioner concludes that, because of the special nature of radioactive drugs, i.e., radioactive decay, the label for such drugs shall contain an expiration date. If special storage conditions are necessary to maintain the drug product's stability for its anticipated shelf life, manufacturers are responsible for providing such information in the labeling. If a radioactive drug is recognized in an official compendium, it shall be labeled as prescribed by such compendium.

Current good manufacturing practices require that the manufacturer assure that the drug finished dosage form has the identity, strength, quality, and purity stated in the labeling. For radioactive drugs for parenteral use, manufacturers must therefore have evidence that the methods of manufacture and sterilization employed are adequate to ensure that each final product is sterile and pyrogen free. It is the responsibility of the Radioactive Drug Research Committee to determine that radioactive materials for parenteral use under § 361.1 are prepared in sterile and pyrogen-free form.

The Commissioner has also concluded that the specific concentration for each radioactive drug should be expressed on the label. Section 361.1(f) (proposed § 370.100(f)) has been revised to require that the label include the total quantity of radioactivity in the drug product's immediate container and the amount of radioactivity per unit volume or unit mass at a designated referenced time. Section 361.1(f) has also been revised to require that the label bear the route of administration if the drug is for other than oral use, as is required for all prescription drugs under 21 CFR 201.100. Information which may be placed on the label of the shielded container only if

the immediate container label is too small to accommodate all of the necessary information is also specified.

Miscellaneous

40. One comment suggested changing paragraph (b) of proposed § 370.100 to read: "The conditions under which use of any radioactive drug for research, which has been, are now or will be regulated by the Food and Drug Administration or which is introduced into interstate commerce, as safe and effective are:". The comment also suggested adding a new paragraph (d) to proposed § 370.100 to state "These regulations will not act to exempt any drug covered by this part from any other provision of law or regulation applicable thereto."

The Commissioner has concluded that the suggested changes to proposed § 370.100 are unnecessary. This regulation in no way implies that other provisions of law or regulation are not applicable. In fact, the regulation clearly alludes to the licensing requirements of the NRC. This regulation will apply to all radioactive drugs that are generally recognized as safe and effective until future developments, experience, or knowledge necessitates revision.

46. One comment stated that there were no recommendations in the proposed regulations pertaining to the proper disposal of isotopes.

The Commissioner advises that the NRC and Agreement States control radiation safety during the manufacture, use and disposal of radioactive drugs.

47. One comment asked if a separate office within the FDA had been assigned responsibility solely for radiopharmaceuticals.

The Commissioner advises that for all radioactive drug products, including radioactive biological products, review of a "Notice of Claimed Investigational Exemption for a New Drug," amendments to such notice, a new drug application, amendments and supplements to such application, and approving and monitoring the activities of the Radioactive Drug Research Committee shall be the responsibility of the Radiopharmaceutical Group, Division of Oncology and Radiopharmaceutical Drug Products, (HFD-150), Bureau of Drugs, 5600 Fishers Lane, Rockville, MD 20852. Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing an order transferring responsibility for radioactive biological products from the Bureau of Biologics to the Bureau of Drugs to consolidate processing of all radioactive drug matters in one office.

48. One comment indicated that proposed § 370.100(f) permits the label and labeling of "tagged" compounds to contain information required by the NRC or State authorities, but this is not mentioned regarding those radioactive drugs covered under topics A, B, and C of the preamble to the proposal.

The Commissioner has determined that all radioactive drugs, including those which require the submission of an NDA, IND, or an application for a biological product license, as discussed under topics A, B, and C of the preamble to the July 29, 1974 proposal, are permitted to have on their label and labeling information required by the NRC and State and local radiation control authorities, if all of the FDA labeling requirements of section 502 of the act and 21 CFR 201.100 (formerly 21 CFR 1.106(b)) are met.

49. One comment expressed concern as to the effect these regulations will exert on existing competition within the radiopharmaceutical industry during the transition from regulation by the NRC to regulation by the FDA. Further, the comment expressed concern regarding the cost of the transition and any competitive disadvantage or restrictions imposed during this transition period. The comment emphasized that it is essential that nothing in these regulations create a competitive advantage for one manufacturer over another.

The Commissioner sees no basis for the concern expressed by the comment.

50. Two comments pointed out a typographical error in the paragraph heading for proposed § 1.106(p). The word "radiocative" should read "radioactive."

The typographical error as noted in the comment has been corrected. In addition, proposed § 1.106(p) has been recodified as § 201.129 in the final regulation in accordance with the recodification of § 1.106 into Part 201, published in the FEDERAL REGISTER of March 27, 1975 (40 FR 13996).

Effective Dates

51. One comment requested that the December 31, 1974 and July 1, 1975 deadlines as set forth in the proposal be extended by the FDA on a drug-by-drug and manufacturer-by-manufacturer basis to provide adequate time to comply with the final regulations, following any any modification resulting from comments submitted.

The proposal identified effective dates for specific changes to implement FDA regulations regarding radioactive new drugs. Due to the length of time needed to review the comments and prepare the final regulation, the Commissioner has found it necessary to extend these proposed effective dates as follows: (1) the December 31, 1974 date for submission of an NDA, IND, or an application for a biological product license for each drug containing those radionuclides listed under § 310.503(f)(1) and for submission of the information for an investigational new drug as required by § 310.503(g) is extended to August 25, 1975; (2) the October 1, 1974 date referred to in § 310.503(g) is extended to July 25, 1975; (3) the January 1, 1975 date referred to in § 310.503 (f) (4) and (5) and (h) is extended to after August 25, 1975; (4) the effective date for deleting the "Note" that appears at the end of § 312.1 is extended to after August 25, 1975; and (5) the July 1, 1975 date referred to in § 310.503 (d)(3), (f)(5), and (g) is extended to February 20, 1976. The regulations have been revised accordingly. The Commissioner concludes that there has been adequate discussion and notice of these requirements, and that the time periods established should not result in a hardship to any manufacturer.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 505, 701 (a), 52 Stat. 1052-1053, as amended, 1055 (21 U.S.C. 355, 371(a))), the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)), authority delegated to the Commissioner (21 CFR 5.120), and in cooperation with the Nuclear Regulatory Commission, Title 21 of the Code of Federal Regulations is amended as follows:

PART 201—LABELING

1. In Subpart D a new § 201.129 is added to read as follows:

§ 201.129 Drugs and devices; exemption for radioactive drugs for research use.

A radioactive drug intended for administration to human research subjects during the course of a research project intended to obtain basic research information regarding metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry (but not intended for immediate therapeutic, diagnostic, or similar purposes), under the conditions set forth in § 361.1 of this chapter, shall be exempt from section 502(f)(1) of the act if the packaging, label and labeling are in compliance with § 361.1(f) of this chapter.

PART 310—NEW DRUGS

2. In § 310.3 add a new paragraph (n) to read as follows:

§ 310.3 Definitions and interpretations.

* * * * *

(n) The term "radioactive drug" means any substance defined as a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes a "radioactive biological product" as defined in § 600.3(ee) of this chapter.

3. In § 310.503 revise paragraph (d) and add new paragraphs (f), (g), and (h), to read as follows:

§ 310.503 Requirements regarding certain radioactive drugs.

* * * * *

(d) (1) In view of the extent of experience with the isotopes listed in paragraph (c) of this section, the Nuclear Regulatory Commission and the Food and Drug Administration conclude that such isotopes should not be distributed under investigational-use labeling when

they are actually intended for use in medical practice.

(2) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the "chemical form" and intended for the uses stated, is terminated on March 3, 1972, except as provided in paragraph (d)(3) of this section.

(3) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (c) of this section, in the "chemical form" and intended for the uses stated, for which drug a new drug application or a "Notice of Claimed Investigational Exemption for a New Drug" was submitted prior to March 3, 1972, or for which biologic an application for product license or "Notice of Claimed Investigational Exemption for a New Drug" was submitted prior to March 3, 1972, is terminated either upon issuance of a nonapprovable notice for the new drug application or application for product license or termination of the "Notice of Claimed Investigational Exemption for a New Drug," or on February 20, 1976, whichever occurs first.

* * * * *

(f) (1) Based on its experience in regulating investigational radioactive pharmaceuticals, the Nuclear Regulatory Commission has compiled a list of reactor-produced isotopes for which it considers that applicants may reasonably be expected to submit adequate evidence of safety and effectiveness for use as recommended in appropriate labeling; such use may include, among others, the uses in this tabulation:

Isotope	Chemical form	Use
Fluorine 18	Fluoride	Bone imaging.
Iodine 131	Diethylenetriamine pentaacetic acid (DTPA).	Brain imaging; kidney imaging.
Do	Chromic	Placenta imaging; blood pool imaging.
Technetium 99m	Human serum albumin macro-spheres.	Lung imaging.
Do	Diethylenetriamine pentaacetic acid (dtpa).	Kidney imaging; kidney function studies.
Do	do	Brain imaging.
Do	Polyphosphate	Bone imaging.
Do	Technetated serum albumin (human).	Lung imaging.
Do	Thiosulfate	Bone imaging.

(2) In view of the extent of experience with the isotopes listed in paragraph (f)(1) of this section, the Nuclear Regulatory Commission and the Food and Drug Administration conclude that they should not be distributed under investigational-use labeling when they are actually intended for use in medical practice.

(3) Any manufacturer or distributor interested in continuing to ship in interstate commerce drugs containing the isotopes listed in paragraph (f)(1) of this section for any of the indications listed, shall submit, on or before August 25, 1975 to the Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852, a new drug application or a "Notice of Claimed Investigational Exemption for a New Drug" for each such drug for which the manufacturer or distributor does not have an approved new drug application pursuant to section 505(b) of the act. If the drug is a biologic, a "Notice of Claimed Investigation Exemption for a New Drug" or an application for a license under section 351 of the Public Health Service Act shall be submitted to the Bureau of Biologics, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20014, in lieu of any submission to the Bureau of Drugs.

(4) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (f)(1) of this section, in the "chemical form" and intended for the uses stated, is terminated August 25, 1975 except as provided in paragraph (f)(5) of this section.

(5) The exemption referred to in paragraph (a) of this section, as applied to any drug or biologic containing any of the isotopes listed in paragraph (f)(1) of this section in the "chemical form" and intended for the uses stated, for which drug a new drug application or a "Notice of Claimed Investigational Exemption for a New Drug" was submitted to the Bureau of Drugs on or before August 25, 1975 or for which biologic an application for product license or "Notice of Claimed Investigational Exemption for a New Drug" was submitted to the Bureau of Biologics on or before August 25, 1975 is terminated either upon issuance of a nonapprovable notice for the new drug application or application for product license or termination of the "Notice of Claimed Investigational Exemption for a New Drug," or on February 20, 1976 whichever occurs first.

(g) The exemption referred to in paragraph (a) of this section, as applied to any drug intended solely for investigational use as part of a research project which use had been approved on or before July 25, 1975 in accordance with 10 CFR 35.11 (or equivalent regulation of an Agreement State) is terminated on February 20, 1976 if the manufacturer of such drug or the sponsor of the investigation of such drug submits on or before August 25, 1975 to the Food and Drug Administration, Bureau of Drugs, HFD-150, 5600 Fishers Lane, Rockville, MD 20852, the following information:

(1) The research project title;

(2) A brief description of the purpose of the project;

(3) The name of the investigator responsible;

(4) The name and license number of the institution holding the specific license under 10 CFR 35.11 (or equivalent regulation of an Agreement State);

(5) The name and maximum amount per subject of the radionuclide used;

(6) The number of subjects involved; and

(7) The date on which the administration of the radioactive drugs is expected to be completed.

(h) The exemption referred to in paragraph (a), as applied to any drug not referred to in paragraphs (d), (f), and (g) of this section, is terminated after August 25, 1975.

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

4. In § 312.1, amend paragraph (a)(2) in Form FD-1571 by adding a new item 6.d and two new sentences to item 10.a and delete in its entirety, effective August 25, 1975, the "Note" regarding an order of the Commissioner of Food and Drugs published in the FEDERAL REGISTER on January 8, 1963 (28 FR 183), as it appears at the end of § 312.1 to read as follows:

§ 312.1 Conditions for exemption of new drugs for investigational use.

(a) * * *

(2) * * *

Form FD-1571

* * * * *

6. * * *

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

* * * * *

10. * * *

a. * * *

If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

* * * * *

PART 361—PRESCRIPTION DRUGS FOR HUMAN USE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED: DRUGS USED IN RESEARCH

5. Add a new Part 361, consisting this time of one section, to read as follows:

AUTHORITY: Federal Food, Drug, and Cosmetic Act, Sec. 505, 701(a), 52 Stat. 1052–1053, as amended, 1055 (21 U.S.C. 355, 371(a)); Public Health Service Act, Sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262).

§ 361.1 Radioactive drugs for certain research uses.

(a) Radioactive drugs (as defined in § 310.3(n) of this chapter) are generally recognized as safe and effective when administered, under the conditions set forth in paragraph (b) of this section, to human research subjects during the course of a research project intended to obtain basic information regarding the metabolism (including kinetics of distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial). Certain basic research studies

At any time a protocol is approved which involves exposure either of more than 30 research subjects or of any research subject under 18 years of age, the committee shall immediately submit to the Food and Drug Administration a special summary of information in the format shown in this paragraph. Contents of these reports are available for public disclosure, unless confidentiality is requested by the investigator and it is adequately shown by the investigator that the report constitutes a trade secret or confidential commercial information as defined in § 4.61 of this chapter.

(4) *Approval.* Each Radioactive Drug Research Committee shall be specifically approved by the Bureau of Drugs of the Food and Drug Administration. Applications shall be submitted to the Food and Drug Administration, Bureau of Drugs, HFD-150, 5600 Fishers Lane, Rockville, MD 20852 and shall contain the names and qualifications of the members of the committee, and a statement that the committee agrees to comply with the requirements set forth in this section. Approval shall be based upon an assessment of the qualifications of the members of the committee, and the assurance that all necessary fields of expertise are covered. Approval of a committee may be withdrawn at any time for failure of the committee to comply with any of the requirements of this section. Approval of a committee shall remain effective unless and until the FDA withdraws such approval. Changes in membership and applications for new members shall be submitted to the Food and Drug Administration as soon as, or before, vacancies occur on the committee.

(5) *Monitoring.* The Food and Drug Administration shall conduct periodic reviews of approved committees. Monitoring of the activities of the committee shall be conducted through review of its annual report, through review of minutes and full protocols for certain studies, and through on-site inspections.

(d) In making the determinations required in paragraph (b)(1) of this section, a Radiation Safety Committee shall consider the following requirements and assure that each is met:

(1) *Radiation dose to subjects.* To assure that the radiation dose to research subjects is as low as practicable to perform the study and meet the criteria of § 361.1(b)(3), the Radioactive Drug Research Committee shall require that:

(i) The investigator provide absorbed dose calculations based on biologic distribution data available from published literature or from other valid studies.

(ii) The investigator provide for an acceptable method of radioassay of the radioactive drug prior to its use to assure that the dose calculations actually reflect the administered dose.

(iii) The radioactive drug chosen for the study has that combination of half-life, types of radiations, radiation energy, metabolism, chemical properties, etc., which results in the lowest dose to the whole body or specific organs with which it is possible to obtain the necessary information.

(iv) The investigator utilize adequate and appropriate instrumentation for the detection and measurement of the specific radionuclide.

(2) *Pharmacological dosage.* To determine that the amount of active ingredients to be administered does not exceed the limitations set forth in paragraph (b)(2) of this section, the committee shall require that the investigator provide pharmacological dose calculations based on data available from published literature or from other valid human studies.

(3) *Qualifications of investigators.* Each investigator shall be qualified by training and experience to conduct the proposed research studies.

(4) *License to handle radioactive materials.* The responsible investigator or institutions shall, in the case of reactor-produced isotopes, be licensed by the Nuclear Regulatory Commission or Agreement State to possess and use the specific radionuclides for research use or be a listed investigator under a broad license, or in the case of non-reactor-produced isotopes, be licensed by other appropriate State or local authorities, when required by State or local law, to possess and use the specific radionuclides for research use.

(5) *Human research subjects.* Each investigator shall select appropriate human subjects and shall obtain the consent of such human beings or their representatives in accordance with § 310.102 of this chapter. The research subjects shall be at least 18 years of age and legally competent. Exceptions are permitted only in those special situations when it can be demonstrated to the committee that the study presents a unique opportunity to gain information not presently available and requires the use of research subjects less than 18 years of age and is without significant risk to the subject. Studies involving minors shall be supported with review by qualified pediatric consultants to the Radioactive Drug Research Committee. Each female research subject of child-bearing potential shall state in writing that she is not pregnant, or, on the basis of a pregnancy test, be confirmed as not pregnant before she may participate in any study.

(6) *Quality of radioactive drug.* The radioactive drug used in the research study shall meet appropriate chemical, pharmaceutical, radiochemical, and radionuclidic standards of identity, strength, quality, and purity as needed for safety and be of such uniform and reproducible quality as to give significance to the research study conducted. The Radioactive Drug Research Committee shall determine that radioactive materials for parenteral use are prepared in sterile and pyrogen-free form.

(7) *Research protocol.* No matter how small the amount of radioactivity, no study involving administration of a radioactive drug, as defined in § 310.3(n) of this chapter, to research subjects under this section, shall be permitted unless the Radioactive Drug Research Committee concludes, in its judgment, that scientific knowledge and benefit is likely to result from that study. Therefore, the protocol shall be based upon a sound rationale derived from appropriate animal studies or published literature and shall be of sound design such that information of scientific value may result. The radiation dose shall be only sufficient and no greater than necessary to obtain valid measurement. The proposed number of subjects shall be sufficient but no greater than necessary for the purpose of the study. The number of subjects shall also reflect the fact that the study is intended to obtain basic research information referred to in paragraph (a) of this section and not intended for immediate therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial).

(8) *Adverse reactions.* The investigator shall immediately report to the Radioactive Drug Research Committee all adverse effects associated with the use of the radioactive drug in the research study. All adverse reactions probably attributable to the use of the radioactive drug in the research study shall be immediately reported by the Radioactive Drug Research Committee to the Food and Drug Administration, Bureau of Drugs, HFD-150, 5600 Fishers Lane, Rockville, MD 20852.

(9) *Approval by Institutional Review Committee.* The investigator shall obtain the review and approval of an Institutional Review Committee which conforms to the requirements of 45 CFR Part 46.

(e) The results of any research conducted pursuant to this section as part of the evaluation of a drug pursuant to § 312.1 of this chapter shall be included in the submissions required under § 312.1 of this chapter.

(f) A radioactive drug prepared, packaged, distributed, and primarily intended for use in accordance with the requirements of this section shall be exempt from section 502(f)(1) of the act and §§ 201.5 and 201.100 of this chapter if the packaging, label, and labeling are in compliance with Federal, State, and local law regarding radioactive materials and if the label of the immediate container and shielded container, if any, either separate from or as part of any label and labeling required for radioactive materials by the Nuclear Regulatory Commission or by State or local radiological health authorities bear the following:

(1) The statement "Caution: Federal law prohibits dispensing without prescription";

(2) The statement "To be administered in compliance with the requirements of Federal regulations regarding radioactive drugs for research use (21 CFR 361.1)";

(3) The established name of the drug, if any;

(4) The established name and quantity of each active ingredient;

(5) The name and half-life of the radionuclide, total quantity of radioactivity in the drug product's immediate con-

tainer, and amount of radioactivity per unit volume or unit mass at a designated referenced time.

(6) The route of administration, if it is for other than oral use;

(7) The net quantity of contents;

(8) An identifying lot or control number from which it is possible to determine the complete manufacturing history of the package of the drug;

(9) The name and address of the manufacturer, packer, or distributor;

(10) The expiration date, if any;

(11) If the drug is intended for parenteral use, a statement as to whether the contents are sterile;

(12) If the drug is for other than oral use, the names of all inactive ingredients, except that:

(i) Trace amounts of harmless substances added solely for individual product identification need not be named.

(ii) If the drug is intended for parenteral use, the quantity or proportion of all inactive ingredients, except that ingredients added to adjust pH or to make the drug isotonic may be declared by name and a statement of their effect; if the vehicle is water for injection, it need not be named: *Provided*, *however*, That in the case of containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, the information required by paragraph (f) (1) and (12) of this section may be placed on the shielded container only.

Effective date. This regulation shall become effective on July 25, 1975. This date is necessary because of the various effective dates set forth for specific changes relating to the transitional regulation of radioactive new drugs from the Nuclear Regulatory Commission to the Food and Drug Administration, and the need for this regulation to be in force as soon as possible so that there will be regulatory control over the safety and effectiveness of all radioactive drugs.

(Secs. 505, 701(a), 52 Stat. 1052-1053, as amended, 1055 (21 U.S.C. 355, 371(a)); the Public Health Service Act (sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262))

Dated: July 18, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.75-19516 Filed 7-24-75;8:45 am]

[Docket No. 75N-0068]

RADIOACTIVE BIOLOGICAL PRODUCTS

Reassignment of Responsibility

By this regulation, the Commissioner of Food and Drugs is reassigning responsibility within the Food and Drug Administration for regulating radioactive biological products from the Bureau of Biologics to the Bureau of Drugs. As a result of this reassignment, manufacturers of radioactive biological products will be required to comply with the requirements for drugs (including submitting new drug applications and periodic reports) for such products in lieu of the requirements for biological products (including submitting establishment and product license applications). All future correspondence and submissions regarding radioactive biological products shall be directed to the Bureau of Drugs. This order becomes effective August 25, 1975.

The Division of Biologics Standards (DBS) was transferred from the National Institutes of Health to the Food and Drug Administration (FDA) and renamed the Bureau of Biologics (notice of which was published in the FEDERAL REGISTER of June 29, 1972 (37 FR 12865)). As the first step in effecting an orderly transfer, the DBS was expanded to the FDA as a Bureau without any realignment of overlapping or related functions that had developed between DBS and FDA based on historical, statutory, and organizational distinctions.

Since the transfer of DBS to FDA, the Commissioner has reviewed those activities that historically have been conducted by DBS and the Bureau of Biologics under section 351 of the Public Health Service Act as well as those conducted by the FDA, principally the Bureau of Drugs, under the Federal Food, Drug, and Cosmetic Act. He concludes that there is a need for some reassignment of activities regarding radioactive drugs between the Bureau of Biologics and the Bureau of Drugs to provide uniformity in processing and a focal point for action within FDA for this category of products.

The Bureau of Biologics currently exercises primary control over those radioactive drugs which contain a biological product in addition to a radionuclide; such products have been subject to licensure under section 351 of the Public Health Service Act. The Bureau of Drugs regulates all other radioactive drugs.

Radioactive biological products, however, in addition to being subject to section 351 of the Public Health Service Act, are also "drugs" and "new drugs" as those terms are defined in section 201 (g) and (p), respectively, of the Federal Food, Drug, and Cosmetic Act and are therefore subject to the drug provisions of the Federal Food, Drug, and Cosmetic Act, including the new drug provisions. Recognizing this dual jurisdiction over biological products, the Department of Health, Education, and Welfare decided many years ago (prior to the transfer of DBS to FDA) that to market a biological product a manufacturer should not be required to submit both a license application under section 351 of the Public Health Service Act and a new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act. To require such dual submissions would have resulted in unnecessary duplication of effort, both by the manufacturer and by the Department. Instead, to avoid such duplication, only license applications under section 351 of the Public Health Service Act would be required. The new drug regulations (21 CFR 310.4) were amended to state that a new drug would not be deemed subject to the new drug provisions of the Federal Food, Drug, and Cosmetic Act if it is a drug licensed as a biological product under the Public Health Service Act.

The Commissioner now concludes that, since radioactive drugs including radioactive biological products, are drugs in which the radioactive component is of primary interest, all radioactive drugs should be regulated through only one Bureau to achieve uniformity of treatment through a single contact point. The Commissioner further concludes that the Bureau of Drugs should be responsible for all radioactive drugs because of its existing organizational structure and staffing. The Bureau of Biologics will provide the Bureau of Drugs needed expertise with respect to the biological component of radioactive biological products and will test all samples of such products that are submitted in support of new drug applications.

As a result of this decision to transfer responsibility for radioactive biological products from the Bureau of Biologics to the Bureau of Drugs, all future applications and submissions for radioactive drugs, including radioactive biological products, shall be in the format and follow the procedures prescribed in 21 CFR Part 314. For radioactive biological products, the new drug application prescribed in 21 CFR 314.1 will be deemed to constitute the establishment and product license applications required for biological products; approval of the new drug application shall be in lieu of issuing a product and an establishment license. The requirement to submit new drug applications is not expected to impose any hardship on manufacturers of radioactive biologicals. The evidence required to establish safety and effectiveness are essentially the same for both biological products and new drugs. There are firms now holding biological product licenses for radioactive biological products, and all of them also manufacture other products requiring new drug applications. The impact on the regulated industry should, therefore, not be significant. The Commissioner advises that, if any person is preparing a biological product license application, he should submit it within 30 days in order to have it processed in that form.

In addition, compliance with the provisions of 21 CFR Part 311 shall be deemed to constitute compliance with the provisions of Subchapter F, the biological product regulations unless the Commissioner makes a determination that a particular regulation in Subchapter F shall be applicable to radioactive drugs containing a biological product. Application of a Subchapter F regulation will only be made when the Commissioner concludes that it is necessary to assure the safety or effectiveness of the product, is not duplicative of the requirements in Part 314, and is to assure the same degree of regulatory control currently exercised over such products. The Commissioner has reviewed the provisions of Subchapter F and concludes at this time that the provisions of § 610.2 Requests for samples and protocols; official release shall remain applicable to radioactive drugs containing

a biological product. Appropriate changes have been made to this section to reflect that the Director of the Bureau of Drugs may use this section for radioactive drugs containing a biological product when it is deemed necessary for the safety, purity, or potency of the product.

To effect the transfer of responsibility, amendments must be made in 21 CFR Parts 310, 312, 314, 600, 601, and 610. In Part 310, § 310.4 provides the exemption, previously discussed, that a licensed biological product need not also be subject to an approved new drug application; that section is amended to exclude radioactive biological products from this exemption. In Part 312, § 312.1(g) currently provides that a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for a biological product be submitted to the Bureau of Biologics; this section is amended to provide that an IND for a radioactive biological product be submitted to the Bureau of Drugs. In Part 314, § 314.110(a)(7) provides that a new drug application will be refused for filing if the drug is subject to licensing under the Public Health Service Act; this section is amended to permit filing of a new drug application for a radioactive biological product. Part 600 is amended in § 600.3 to include a definition of a radioactive biological product, which is defined as a biological product labeled with a radionuclide or a biological product intended solely to be labeled with a radionuclide. (Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing a final regulation on radioactive drugs which includes a definition of "radioactive drug" in Part 310; this definition cross-references the new definition in Part 600.) In Part 601, § 601.2 currently outlines the procedures for filing applications for establishment and product licenses or biologics; this section is amended to provide that radioactive biological products shall be covered by new drug applications and not by biological product licenses. Part 610 is amended as discussed above.

These changes are prospective in nature. Every biological product licensed prior to July 1, 1972, is currently under review for safety, effectiveness, and appropriate labeling, as described in 21 CFR 601.25. The product license for such a radioactive biological product, together with portions of the establishment license relevant to the requirements for a new drug application, now constitutes an approved new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act. Any such products, even though now subject to new drug applications, will remain subject to the biological product review, because they were licensed as biological products before July 1, 1972. Those products which are found to be unsafe, or ineffective, or misbranded will be subject to regulatory action. Those which are determined to be safe, effective and not misbranded may continue to be marketed; in addition, the conditions under which an identical, similar or related product may be introduced to the market (i.e., full new drug application, abbreviated new drug applications, or other conditions) will be determined at that time.

A new drug application does not have to be submitted for any radioactive biological product licensed after July 1, 1972 and before the effective date of this order. The product license for such a radioactive biological product, together with portions of the establishment license relevant to the requirements for a new drug application, now constitutes an approved new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act.

Any radioactive biological product for which a license application is pending on the effective date of this order will be processed and approved or disapproved as submitted. Again, no new drug application need be submitted for these products. If the product is found acceptable for licensure, it will be approved as a new drug application in lieu of issuance of a product license.

Future changes in all approved radioactive biological products will be subject to supplemental new drug applications (21 CFR 314.8) rather than amendments to the license. Likewise, all radioactive biological products are subject to the records and reports requirements of 21 CFR 310.300 after the effective date of this section.

Every current "Notice of Claimed Investigational Exemption for a New Drug" for a radioactive biological product will be transferred to the Bureau of Drugs. Any amendments of or supplements to any such notice, and all progress reports regarding such notice, shall be filed in the future with the Bureau of Drugs. Any new "Notice of Claimed Investigational Exemption for a New Drug" for a radioactive biological product shall be submitted directly to the Bureau of Drugs.

For all radioactive biological products, including any subject to pending application for licensure on the effective date of this order, all correspondence, "Notices of Claimed Investigational Exemption for a New Drugs," and original and supplemental new drug applications shall be submitted to the Division of Oncology and Radiopharmaceutical Drug Products (HFD-150), Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852. All samples of radioactive biological products submitted in support of a new drug application shall, when notified by the Bureau of Drugs, be sent directly to the Bureau of Biologics, Food and Drug Administration, Bldg. 29A, 8800 Rockville Pike, Bethesda, MD 20014.

The Commissioner notes that the labeling standards under Part 610, Subpart O, of Subchapter F will no longer apply to radioactive biological products; instead, the requirements of 21 CFR Part 201 of Subchapter C will be applicable. In particular, this means that the manufacturer's license number appearing on the container and package labels (21 CFR 610.60(a)(2) and 610.61(b)) is no longer required. To permit an [illegible] and economical transition [illegible] garding labels and labeling of marketed products, the Commissioner will select the effective date on which marketed radioactive biological products must comply with the requirements of Part 201 until the date on which new labels and of labeling is printed by the manufacturer of such product, or July 26, 1977, whichever occurs first.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 505, 701 (e), 52 Stat. 1052-1053 as amended (21 U.S.C. 355, 371(a)), the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)), and under authority delegated to the Commissioner (21 CFR 2.120), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

PART 310—NEW DRUGS

1. In Subpart A by revising § 310.4 to read as follows:

§ 310.4 Biological products subject to license control.

(a) Except for radioactive biological products intended for human use, a new drug shall not be deemed to be subject to section 505 of the act if it is a drug licensed under the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)) or under the animal virus, serum, and toxin law of March 4, 1913 (37 Stat. 832 (21 U.S.C. 151 et seq.)).

(b) A radioactive biological product (as defined in § 600.3(ee) of this chapter) intended for human use is subject to section 505 of the act. Any license for such a radioactive biological product which is issued under the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)) and which has not been revoked or suspended as of August 25, 1975 shall constitute an approved new drug application in effect under the same terms and conditions as set forth in such license and such portions of the establishment license relating to such product, which include data and information required under Part 312 of this chapter for a new drug application. Any such radioactive biological product for which licensure under the Public Health Service Act is pending on August 25, 1975 shall, upon determination that it is acceptable for licensure, be approved as a new drug application in lieu of issuance of a biological product license.

PART 312—NEW DRUGS FOR INVESTIGATIONAL USE

2. In § 312.1 by revising paragraph (g) to read as follows:

§ 312.1 Conditions for exemption of new drugs for investigational use.

* * * * *

(g) A "Notice of Claimed Investigational Exemption for a New Drug" which pertains to a product subject to the licensing provisions of the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)) shall

be submitted initially to the Director, Bureau of Biologics, 8800 Rockville Pike, Bethesda MD 20014. Radioactive biological products for human use are not deemed to be subject to the licensing provisions of the Public Health Service Act (see § 310.4 of this chapter) and a "Notice of Claimed Investigational Exemption for a New Drug" which pertains to radioactive biological products shall be transmitted to the Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, 8800 Rockville Pike, Bethesda, MD 20014. Amendments of or supplements to such notice, and progress reports, communications, or other communications with regard to the investigation shall be directed to the same office to which the original notice was sent. A submission for a "Notice of Claimed Investigational Exemption for a New Drug" submitted to the Bureau of Biologics shall substitute in reading this section "Bureau of Biologics" for "Bureau of Drugs" wherever it appears.

* * * * *

PART 314—NEW DRUG APPLICATIONS

3. In § 314.110 by revising paragraph (a) (7) to read as follows:

§ 314.110 Reasons for refusing to file applications.

(a) * * *

(7) The new drug is a drug, other than a radioactive biological product (as defined in § 600.3(ee) of this chapter) intended for human use, subject to licensing under the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended (42 U.S.C. 201 et seq.)).

* * * * *

PART 600—GENERAL PROVISIONS

4. In § 600.3 by adding a new paragraph (ee) to read as follows:

§ 600.3 Definitions.

* * * * *

(ee) "Radioactive biological product" means a biological product which is labeled with a radionuclide or intended solely to be labeled with a radionuclide.

PART 601—LICENSING

5. In § 601.2 by redesignating the present text as paragraph (a) *General* and adding at the end a new sentence and by adding a new paragraph (b). As revised, § 601.2 reads as follows:

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Bureau of Biologics, on forms prescribed for such purpose, and in the case of an application for a product license, shall submit data derived from laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; a full description of manufacturing methods; data establishing stability of the product through the dating period; samples; representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels thereunder and containers proposed to be used for the product. An application for license shall not be considered as filed until all pertinent information and data shall have been received from the manufacturer by the Bureau of Biologics. In lieu of the procedures described in this paragraph, applications for radioactive biological products shall be handled as set forth in paragraph (b) of this section.

(b) *Radioactive biological products.* In lieu of submitting an establishment and product license for the manufacture of a radioactive biological product, as defined in § 600.3(ee) of this chapter, the manufacturer of such a product shall submit a new drug application to the Director, Division of Oncology and Radiopharmaceutical Drug Products, Bureau of Drugs, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20014, on form FD-356(H) as set forth in § 314.1(c)(2) of this chapter. For such products, the approval of the new drug application will be in lieu of issuing a product and an establishment license. Compliance with the provisions of Part 314 of this chapter shall be deemed to constitute compliance with the provisions of Subchapter A of this chapter unless the Commissioner makes a determination that a particular regulation from Subchapter F shall be applicable to radioactive drugs containing a biological product, e.g., § 610.2 of this chapter.

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

6. In § 610.2 by redesignating the present text as paragraph (a) *General* and revising it, and by adding a new paragraph (b). As revised, § 610.2 reads as follows:

§ 610.2 Request for samples and protocols; official release.

(a) *General.* Samples of any lot of any licensed product, except for radioactive biological products, together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Bureau of Biologics. Upon notification by the Director, Bureau of Biologics, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Bureau of Biologics: *Provided*, That the Director, Bureau of Biologics, shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

(b) *Radioactive biological products.* Samples of any lot of a radioactive biological product, as defined in § 600.3(ee) of this chapter, together with the protocols showing results of applicable tests, may at any time be required to be sent to the Food and Drug Administration for official release. Upon notification by the Director, Bureau of Drugs, a manufacturer shall not distribute a lot of a radioactive biological product until the lot is released by the Director, Bureau of Drugs: *Provided*, That the Director, Bureau of Drugs shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

Since these changes concern internal reassignment of activities and will provide uniform handling of all radioactive drug products, the Commissioner finds that the changes covered by this order are such that, under 5 U.S.C. 553, the notice and comment procedure for rule making are unnecessary and are not prerequisites to this promulgation. In reaching this decision, the Commissioner has considered the facts that less than ten firms currently hold biological product licenses for radioactive biological products, and that all of these firms also hold approved new drug applications. The Commissioner also advises that any person currently preparing a biological product license for a radioactive biological product may submit it within 30 days and thereafter will not be required to resubmit a new drug application for the product.

Interested persons may, however, on or before September 23, 1975, file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 8800 Rockville Pike, Rockville, MD 20852, written comments in quintuplicate on any portion of the order. Comments received will be available for public inspection at the office noted above during working hours, Monday through Friday. Any changes in this order justified by such comments will be the subject of a further order amending the specific regulations involved.

Effective date. This regulation shall be effective August 25, 1975, except for the requirements for labels and labeling of radioactive biological products. The labels and labeling of any marketed radioactive biological product must comply with the requirements of 21 CFR Part 201 on the date on which such labels and labeling are next printed or July 26, 1976, whichever occurs first.

(Secs. 505, 701(a), 52 Stat. 1052-1053 as amended, 1055 (21 U.S.C. 355, 371(a))); sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262))

Dated: July 18, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 75N-0069]

RADIOACTIVE DRUGS, INCLUDING BIOLOGICAL PRODUCTS

Notice to Nuclear Pharmacies Regarding the Development of Proposed Regulations and Interim Enforcement Policy

This notice states the interim enforcement policy of the Commissioner of Food and Drugs regarding nuclear pharmacies until definitive regulations on this matter are issued by the Food and Drug Administration. Under the conditions set forth in this notice, the agency will not take regulatory action for the failure of a nuclear pharmacy to comply with the requirements of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, except where such regulatory action is necessary to safeguard the public health.

Elsewhere in this issue of the FEDERAL REGISTER, the Commissioner is issuing a final regulation terminating the exemption from new drug requirements for radioactive drugs, including radioactive biological products. As a result, manufacturers and distributors of these products must comply with the requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and the regulations thereunder, including registration, drug listing, compliance with current good manufacturing practices, marketing under an approved new drug application or biological product license, research under the requirements for investigational drugs, and labeling and advertising requirements. In commenting on the proposal published in the FEDERAL REGISTER of July 29, 1974 (39 FR 27538), which preceded this final regulation, several persons inquired about the legal obligations of "nuclear pharmacies" under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act upon the effective date of the final regulation, especially insofar as these "nuclear pharmacies" may be deemed to be manufacturing or distributing these products other than as part of the compounding and dispensing of drugs in the ordinary practice of pharmacy.

Many radioactive drugs, including biological products, because of their short half-lives must be prepared in the final dosage form shortly before they are to be used for diagnosis or treatment of disease in man. In addition, the preparation of radioactive drugs requires a special knowledge of radioactive materials, involves the use of special equipment and facilities, and where reactor-produced radionuclides are involved, requires licensing by the Nuclear Regulatory Commission or an Agreement State. Certain pharmacies, referred to as "nuclear pharmacies," conduct operations which vary from repackaging or preparing radioactive drugs for administration to more extensive and complex manufacturing and compounding procedures. In most cases these nuclear pharmacies are affiliated with, or operated by, hospitals, medical groups, clinics, universities, medical schools, and public health agencies. Some of these pharmacies are not so affiliated, are privately owned, or are operated by several institutions on a cooperative basis. The radioactive drugs prepared by a nuclear pharmacy may be intended solely for use within the institution in which the pharmacy is located, or they may be prepared for distribution to other institutions. For example, a nuclear pharmacy in a university hospital may prepare radioactive drugs for distribution to other hospitals and clinics.

At present, pharmacies are subject to the misbranding and adulteration sections of the Federal Food, Drug, and Cosmetic Act and to the provisions of the Public Health Service Act regarding the licensing of biological products. If they engage in the manufacture of new drugs, they may also be subject to the new drug provisions of the Federal Food, Drug, and Cosmetic Act. Pharmacies are generally exempted under sections 510(g) and 704 (a) of the Federal Food, Drug, and Cosmetic Act from regulations regarding registration, drug listing, inspection, and compliance with current good manufacturing practices where their operations are in compliance with applicable local pharmacy laws and do not involve manufacturing procedures other than in the regular course of their business of dispensing or selling drugs at retail. Application of these rules and exemptions to nuclear pharmacies, which would be an immediate result of the final regulation referred to below, raises numerous complex issues or problems because of the unique nature of operations in nuclear pharmacies.

To clarify the obligations of nuclear pharmacies under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, the Food and Drug Administration is drafting regulations which will define those operations connected with the preparation of radioactive drugs and biological products which will be regarded as manufacturing procedures and not part of the practice of pharmacy. Nuclear pharmacies engaged in such operations will then be subject to regulations regarding registration, drug listing, inspection, new drug applications or biological product licenses, compliance with current good manufacturing practices, and related requirements. Operations not deemed to be manufacturing procedures will also be identified and will thereafter be treated as part of the practice of pharmacy. It is anticipated that these regulations will be proposed in the FEDERAL REGISTER in the near future. Interested persons will be given 60 days to comment on the proposed regulations and all such comments will be considered in the preparation and promulgation of the final regulation.

The Commissioner advises that, until the regulations outlined above are proposed and made final, the Food and Drug Administration will not take regulatory action for the failure of a nuclear pharmacy to comply with the requirements of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act, so long as the pharmacy (1) complies with applicable local laws regulating the practice of pharmacy and (2) is licensed, where applicable, by the Nuclear Regulatory Commission or an Agreement State to possess, use, or transfer radioactive drugs, except where the Commissioner determines that such regulatory action is necessary to safeguard the public health. The Food and Drug Administration is adopting this policy as an interim measure to avoid any disruption in the practice of nuclear pharmacy and nuclear medicine throughout the United States.

Dated: July 18, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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APPENDIX IV.

Chapter explaining transfer of responsibility.

* Note:- Copyrighted article removed (KS)

RADIOPHARMACY

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