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January 5, 2005

Division of Dockets Management  
 HFA-305  
 Food and Drug Administration  
 5630 Fishers Lane, Rm. 1061  
 Rockville, MD 20852

Re: Docket No. 2004N-0432, published in Fed. Reg. 69(192):59569-59572, 5  
 Oct.2004.

Dear Sir/Madam:

After much thought and experience with the above-referenced issue, I wish to submit comments on the subject of the Federal Register article. I was not at the meeting because of overriding personal circumstances, but am nevertheless deeply concerned about the topics in the article as well as related issues.

Before I start, I need to make certain that several terms are carefully defined. The term "drug" is defined in accordance with the Food, Drug, and Cosmetic Act (FDCA). According to the Act, "drug" means "(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C); but does not include devices or their components, parts or accessories." The **metabolic tracers** that are the subject of 21 CFR 361.1 are not drugs, as they do not fit the definition. This is also elegantly stated by FDA's Robert Temple, M.D., in his letter to FDA Chairpersons dated March 27, 1985, where he shows that RDRRC tracers are not "new drugs". As they cannot possibly be "old drugs"---virtually none were in use before 1938---they cannot be drugs, period. The term "metabolic tracers" will be used for the purposes of this letter only to mean the tracers originally intended for Radioactive Drug Research Committee (RDRRC) review under 21 CFR 361.1. The term "**molecular imaging**

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**probes**” will be defined for the purposes of this letter as the nearly massless entities labeled with positron emitters used for positron emission tomography (PET). While some molecular imaging probes are “drugs” by FDCA definition, others are “metabolic tracers” by virtue of intent. For example, when used to study the physiology of bone turnover, as was done in the late 1930’s, NaF-18 is a “metabolic tracer”. The same NaF-18 used for diagnosis of bone abnormalities is a “drug” under the FDCA. Similarly, F-18-FDG used to study glucose metabolism in diabetics is a “metabolic tracer”, but F-18-FDG used to diagnose cancer is a “drug”. **Diagnostic radiopharmaceuticals** include both PET entities and non-PET entities. For the purposes of this letter, “other diagnostic radiopharmaceuticals” refers to non-PET entities. The term “**therapeutic radiopharmaceuticals**” includes all radioactive therapeutic entities.

### History

As a member of FDA’s Radiopharmaceutical Advisory Committee beginning in 1971, I was one of a subcommittee of three charged with conceiving of a regulatory approach for FDA oversight of a category of human radioactive tracer research regulated by the Atomic Energy Commission (AEC). The AEC wished to terminate its activities regulating metabolic tracers and diagnostic/therapeutic radiopharmaceuticals, and had convinced the FDA to take these over. While regulation of radiopharmaceuticals fell within the usual FDA activities of drug regulation, the use of metabolic tracers to elucidate basic biochemistry was something with which FDA had no experience. In addition, it was an area in which FDA had virtually no interest, and FDA wished to conceive of a regulatory mechanism in which FDA had to perform little, if any, work. The current system of an institutional Radioactive Drug Advisory Committee (RDRC) to oversee human tracer research for purposes of biodistribution, kinetics, and metabolic pathway elucidation was conceived of by the subcommittee. Tying radiation absorbed dose limits to what a radiation worker could receive each year was also conceived of by the subcommittee. We were concerned at the time with tracers labeled with C-14, H-3, P-32, S-35, and the like.

The RDRC mechanism worked so smoothly for metabolic tracers that it quickly became the regulatory mechanism to use for doing the basic research to investigate molecules that might have some future use as radiopharmaceuticals. FDA recognized this, and supported this concept in a letter written to RDRC chairpersons by Robert Temple, M.D., on March 27, 1985. Several years later Carl Peck, M.D., as CDER Director trying to insert some intelligent life into the FDA morass surrounding PET molecular imaging probes, announced at a public meeting that that RDRC mechanism could be used for *all* PET work, whether basic science or clinical, and that INDs would no longer be required. I attended that meeting as an invited speaker. Details were never worked out by Dr. Peck, and the nation’s RDRCs simply interpreted that PET exemption as they saw fit.

There have been no other major changes to the RDRC mechanism since then.

By the time the RDRC regulation (21 CFR 361.1) was published on July 25, 1975, the AEC had been split into the Nuclear Regulatory Commission (NRC) and the Energy Research and Development Agency (ERDA), which soon after was renamed the Department of Energy (DOE). While the AEC (and for about six months, the NRC) had been regulating not only metabolic

tracers but diagnostic and therapeutic radiopharmaceuticals since the Atomic Energy Act of 1954, it had in fact given over virtually the whole job of regulating diagnostic and therapeutic radiopharmaceuticals to a consultant at the National Institutes of Health, Capt. William H. Briner (ret.). Capt. Briner was essentially the “father” of nuclear pharmacy, and was the Chairperson of FDA’s Radioactive Drug Advisory Committee. It is important to understand that the decision as to whether or not a manufacturer could sell a radiopharmaceutical in the United States was in the hands of this one man, who took care of it in his spare time as a consultant to the AEC. This went on until 1975, when FDA lifted its exemption for radiopharmaceuticals and began to regulate them itself. It is critical to appreciate that during that entire time, *no radiopharmaceutical was ever recalled for safety or efficacy reasons*. Even more astonishing was the cost to a manufacturer for getting a drug through the AEC. **According to Captain Briner, the cost per drug averaged about \$1500.** The cost of radiopharmaceuticals was, as a result, so low that these costs were hardly even taken into account in the cost of running a Nuclear Medicine Department. After FDA took over the job, bureaucracy and costs rapidly escalated. A recently-approved radiopharmaceutical cost **over \$300,000,000** to obtain FDA approval, and the cost of the radiopharmaceutical is consequently enormous. *The FDA oversight has brought no increased safety or efficacy to radiopharmaceuticals. Diagnostic radiopharmaceuticals have virtually no safety issues anyway, and the major safety issue surrounding therapeutic radiopharmaceuticals is radiation itself, an aspect well understood and to which FDA has added nothing of value. And in case no one has noticed, FDA behavior has shrunk the once thriving and innovative radiopharmaceutical industry into a mere shadow of its former self.*

The AEC and later, the NRC, never regulated PET. The AEC/NRC only regulates radioactive materials that come from reactors, or are used to make reactor fuel. Consequently there was no regulation of PET and other accelerator-produced radiopharmaceuticals at all from the 1930’s until 1975. However, PET molecular imaging probes have short radioactive halflives, and are made in house or nearby, by physicians and pharmacists. Such establishments were assumed to be exempted from FDA regulation in 1975, and were formally exempted in 1984 by FDA (they are regulated by State Medical and Pharmacy Boards). It was only in the mid 1990’s that FDA launched an attempted “hostile takeover” of these facilities compounding PET molecular imaging probes. A successful lawsuit against FDA plus the 1997 PET law stopped it. *It is important to note that from the 1930’s until the present time, there have been no problems with molecular imaging probes. One might reasonably ask upon what basis the FDA wants to regulate them, as neither safety nor efficacy are issues.*

### **What Have We Learned About RDRCs?**

The RDRC regulation has been in effect for nearly 30 years. What have we learned over that time? Well, the first thing of interest is that this regulation should never have been promulgated in the first place, because FDA has no statutory authority over the metabolic tracers that are the subject of 21 CFR 361.1. **These tracers do not fall within the definition of a drug, as defined in the Food, Drug and Cosmetic Act.** This lack of statutory authority was actually an important issue when the regulation was being developed, but it has been ignored for the past 30 years. It should no longer be ignored. **21 CFR 361.1 should be withdrawn in its entirety.**

The second thing we have learned is that these metabolic tracers are so safe that we need no regulation of them from any state or federal source. **After all, we regulate things to decrease risk. If the activity has no risk, we do not need to regulate it.** Without RDRC requirements, these tracers would continue to be reviewed by institutional Radiation Safety Committees (RSCs) and Institutional Review Boards (IRBs). That is quite enough!

The third thing that we have learned is that the RDRCs themselves have worked very well. Efficient, economical, and run by highly qualified practicing professionals with personal knowledge of the integrity of the investigators at their institutions, this mechanism of review and oversight is a success. **Although the RDRC mechanism should be abandoned for metabolic tracers, the mechanism itself, somewhat altered, could prove to be an enormous improvement over direct FDA oversight for clinical trials of radiopharmaceuticals (i.e. an alternative to the Investigational New Drug or IND process).**

### PET and the FDA

Although FDA is frequently embarrassed by perceived oversights resulting in fatal consequences from standard, nonradioactive drugs, the COX-2 inhibitors being only the latest example, this has never happened with any radiopharmaceuticals. On the other hand, **FDA actions have killed tens of thousands of patients by depriving them of PET scans.** While this hasn't made the front pages of the nation's newspapers, *it should*. The sordid and unforgivable details of a vicious and malevolent plot to destroy PET by the FDA was the subject of a federal lawsuit (which FDA lost) and the reason for a law passed as part of FDAMA in 1997. At present, about one million PET scans are performed in the United States each year. Despite FDA's efforts to undermine reimbursement for these procedures by Medicare, they are now reimbursed. If the experience at UCLA is typical, something over half of the studies show previously undetected cancer or cancer metastases. If the cancer is detected relatively early, effective treatment can follow in many cases. If PET scans are not done, the cancers are often not detected until later, when they are larger and have spread and can no longer be readily controlled. So, let's do a very rough calculation. Say that 50% of cases show new cancer or cancer metastases. Let's conservatively estimate that in only 5% of these 50% can we catch the cancer early enough to cure it or control it for a long period of time. Five % of 500,000 patients is 25,000 patients *per year* that are saved thanks to a PET scan. From the time F-18 FDG was invented at Brookhaven National Laboratory with taxpayer's money in 1976 until the 1997 PET law, FDA and HCFA (now CMS) colluded to suppress PET and refuse reimbursement. Many private insurance companies followed HCFA's example, although most began to reimburse when the advantages were overwhelming and the USP published standards for these molecular imaging probes. Until 1997, only small numbers of "research" patients, and small numbers of wealthy patients who paid for the scans out of pocket, reaped the benefit of this imaging modality. In the 29 years since F-18-FDG was invented, *not a single adverse reaction has been reported in the United States or anywhere else in the world.* Just what was the FDA protecting us from? How many people suffered horribly and died needlessly from cancer? Tens of thousands? Hundreds of thousands? **Instead of letting the FDA get away with uttering vague warnings about potential dangers from these molecular imaging probes, let us look at the *real* dangers of letting FDA regulate them. These dangers are too terrible, and the conclusion is obvious. Remove FDA's regulatory power over PET molecular imaging probes immediately.**

Recently I co-authored a paper (Barrio JR, Marcus CS, Hung JC, Keppler JS: A rational regulatory approach for positron emission tomography imaging probes: from “first in man” to NDA approval and reimbursement. *Molecular Imaging and Biology* 6(6):361-367, 2004) suggesting an alternate regulatory approach for PET molecular imaging probes from the present FDA scheme. **The RDRC concept was kept, but for review of clinical trials.** We then conceived of an **independent advisory committee**, whose members are chosen by the knowledgeable professional societies, not by FDA. This advisory committee would replace FDA review, and decide on drug approval based on rational nuclear medicine criteria, not using any constraints in the Food, Drug, and Cosmetic Act, or in Title 21. The only FDA role would be to inspect traditional manufacturing facilities (not physician or pharmacy-based compounding facilities, which are under state regulation), and keep track of adverse tracer reactions, if any, (which should occupy about 0.001 FTE).

One can even argue whether it serves any logical purpose to have FDA inspecting manufacturer’s facilities. When the AEC regulated manufacturers, it never inspected the factories except for radiation safety concerns, and nothing terrible happened. What many fail to realize is that in addition to being unique because of radioactivity, PET molecular imaging probes and other diagnostic radiopharmaceuticals share another unique characteristic, which I call “visual chemistry”. By inspecting the image, a qualified professional can tell immediately if the molecular imaging probe or other diagnostic radiopharmaceutical was appropriately manufactured or compounded. This cannot be done with conventional, non-radioactive drugs. Due to the advantages of visual chemistry, any problem with the molecular imaging probe or other diagnostic radiopharmaceutical can be immediately communicated to the manufacturer or compounder, and the problem gets corrected. Another unique characteristic of all radioactive entities is that it is the only group of metabolic tracers or of drugs that is restricted to only a small minority of physicians with extensive specialized education, training, and experience. These physicians have excellent communication amongst themselves, so any uncorrected problems can be communicated (exceedingly rare). Any advantage of FDA inspection is therefore questionable, especially given current Good Manufacturing Practices (cGMPs) unsuited to molecular imaging probes or other radiopharmaceuticals.

The only logical alternative to the construct outlined in the paper cited above would be to simply exclude the FDA completely, and devise another system for reimbursement other than FDA approval.

### **Other Diagnostic and Therapeutic Radiopharmaceuticals**

Would the mechanism outlined above for PET molecular imaging probes suit other diagnostic radiopharmaceuticals? Absolutely. Large drug companies might not like simplifying the rules for approval, because they could now suffer from competition from nimble, innovative small companies. However, that would be excellent for patients and those who pay for medical costs.

Would the mechanism outlined above for PET molecular imaging probes suit therapeutic radiopharmaceuticals? Certainly. While therapeutic radiopharmaceuticals do have adverse reactions, those reactions are mainly limited to effects of radiation. This is no surprise, and those

physicians educated to use these radiopharmaceuticals expect these effects and take care of them. FDA does not contribute any value here.

Another side effect of certain classes of therapeutic radiopharmaceuticals, and certain classes of diagnostic radiopharmaceuticals as well, is the production of antibodies and an occasional allergic reaction. Such reactions may occur on occasion with almost every nonradioactive drug, and physicians are prepared to deal with such reactions. Some drugs are more immunogenic than others, but physicians need to be prepared to treat any reaction in any patient. FDA makes no contribution here. Because allergic reactions are often the *only* adverse reactions of a particular radiopharmaceutical, FDA makes a “big deal” about them. I do not think that it makes sense to do so, I do not think that allergic reactions justify FDA regulation, and I do not agree with FDA that allergic reactions are “pharmacologic effects”. Pharmacologic effects are different. They are chemically specific actions characteristic of certain molecular structures. They are predictable and dose-dependent. Immunologic reactions are not like this at all.

### **Issues Raised in FDA’s Fed. Reg. Article**

The FDA has raised six specific issue categories. The issues raised tend to limit discussion to those issues, instead of looking at the big picture and the larger issues. Commenters should not be fooled into letting FDA use this trick to constrain discussion of the broader topic of FDA dysregulation of radiopharmaceuticals, and what to do about it.

#### *1. Pharmacology Issues*

There are no pharmacology issues with metabolic tracers or PET molecular imaging probes. The tracers and probes provide information without perturbing the system. Why has FDA not provided even *a single example* of a pharmacologic effect of metabolic tracers or PET imaging probes? Probably because FDA doesn’t have such a database in the first place.

With no documentation of any examples of metabolic tracers or PET molecular imaging probes that have exhibited pharmacologic effects, FDA seeks to enormously constrain the expert scientific and medical members of the RDRC in their learned judgment by making “limits” that make no sense but can be used by FDA staff to discredit RDRC decisions or inhibit research altogether. Furthermore, FDA seeks to destroy any category of research tracer that *could* cause an allergic reaction “...unless they have been shown to have no immunologic response.” This is preposterous. If there is an allergic reaction, doctors can treat it. The questions FDA asks either cannot be answered, or can only be answered for a few compounds, and are probably different for most tracers. “One size fits all” nonsense needs to be completely avoided. We are doing just fine with professional judgment. RDRCs don’t need FDA’s “help”, “guidance”, or regulatory requirements on how to think. If FDA cannot think as well as RDRC members can, that’s not news, but we must not allow FDA to “dumb down” decision-making to its own level.

While it is always conceivable that researchers might desire to use a radioactive tracer of a highly toxic poison that could conceivably cause adverse effects even at tracer quantities, this is easily handled by having the RDRC request appropriate animal studies first. RDRC’s have requested animal data on biodistribution and kinetics in order to approximate human radiation

absorbed dose, they have requested animal studies of tracers and molecular imaging probes that exhibit very slight molecular alterations from the parent compound known to be safe, and can certainly ask for such studies if deadly poisons are the subject of a study. Naturally occurring radioactive tracers have been used in humans since the 1920's, and artificially created radioactive tracers have been used since the 1930's from accelerators and the 1940's from reactors. Approximately 400,000,000 clinical procedures have been performed in the United States. If toxic problems have not yet occurred, *it seems highly unlikely that they will, and it is folly that we need the FDA to protect us from this theoretical possibility.*

The history of the FDA shows us that FDA does not brilliantly discern adverse effects before they occur. Rather, physicians using drugs discover effects themselves, and report them to FDA. Reporting them to RDRCs would be even easier, and appropriate action would likely be much swifter. Having personally been the first person to report serious adverse reactions to FDA from two FDA-approved drugs and watched the reports settle into a bureaucratic "black hole", I find it difficult to believe that we need FDA here. Professional communication through lectures and publications, and now the internet, works very well to protect America's patients.

## *2. Radiation Dose Limits for Adult Subjects*

While reconsideration of radiation dose limits seems to imply that it could go either up or down, the references chosen by FDA are all from organizations intractably committed to the "Linear, Non-Threshold Hypothesis", or LNT. FDA did not seek to use references from the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) or any of several thousand papers on radiation hormesis at low dose, that is, the *beneficial* effects of low dose radiation.

Reference no.1 is from the Radiation Effects Research Foundation, RERF. The Life Span Study has followed 85,572 survivors of Hiroshima and Nagasaki since the atomic bombs were dropped in August of 1945.

The analysis of the Life Span Study of the atomic bomb survivors is exceedingly complex and questionable at all doses, and especially so at low doses. As these are the data upon which RERF studies depend, it is important to evaluate it. First, there is considerable difficulty assigning radiation doses to survivors, and doses originally assigned were all redone in 1986. Difficulties surfaced, however, and new dosimetry is planned shortly. The effect of neutrons has apparently been significantly underestimated, and consequently the effect of gamma rays has been overestimated. As we are not interested in neutrons at all in tracer research, but mainly in gamma rays, reanalysis after the new dosimetry may show changes downgrading the presumed hazards of gamma rays. Another category of problem with the Life Span Study is the determination of the normal baseline cancer rate. Originally, a "control" group was chosen which was more than 3 kilometers (km) from where the bombs fell. Another "control" group was considered which was within the 3 km radius, whose inhabitants incurred a radiation dose less than 0.5 rem. As time went on, the baseline cancer fatality rate of the control group outside the 3 km radius grew to be 10% *higher* than the control group within the 3 km radius. Although some scientists would call this "hormesis", a *beneficial* effect of low dose radiation to the group within the 3 km radius, the authors of the Life Span Study chose to ignore the higher baseline

cancer rate group and use only the lower baseline cancer rate group within the 3 km radius. This then creates more "excess" cancers which are then attributed to radiation. There is another problem which is a statistical issue. The Life Span Study authors use a "one tailed test", which nullifies evidence that low doses may be beneficial, and only considers hazard. One of the problems that is emphasized by the authors of the Life Span Study is the difficulty in interpreting age-at-exposure effects, and also that the possibility that the radiation risk estimates are biased due to selection by survival. They are also concerned with the validity of extrapolation of results from one race and culture to another that is very different. One of the most important arguments against the purported finding of low dose effects in the Life Span Study is that numerous other studies on patients with better dosimetry information, and workers with excellent dosimetry data, do not show increased carcinogenesis at such low doses, and occasionally show beneficial effects ("hormesis").

The Life Span Study data has so far been analyzed up to 1997, *52 years after the bombs*. The total number of cancers *claimed* by these authors to be caused by radiation *over 52 years* is now up to *340 cases*. **If there is one clear message here, it is that radiation is a really poor carcinogen.** Unfortunately, there are too many vested interests to declare this and stop flogging the data.

Most radiation and radiation protection professionals today accept an operational threshold for adverse radiation effects starting *at least* at 5 rem/year or 10 rem once. This is the official policy of the Health Physics Society, the Society of Nuclear Medicine, and the American College of Nuclear Physicians. For decades the radiation dose permitted for radiation workers by the Nuclear Regulatory Commission has been 5 rem/year, every year, without evidence of deleterious effects and often *with* evidence of beneficial effects. Recommended radiation limits for emergency workers in the event of a radiation accident or terrorist event is 50-75 rem. While these are not thought to be harmless, they are not thought to be very harmful, either.

The existing yearly NRC dose limits are 5 rem effective dose equivalent (ede), 15 rem to the lens of the eye, and 50 rem to all other organs including skin. The old RDRC limits were not changed to the new NRC limits which were published about 15 years ago. RDRCs should use the ede and the organ limits now set by NRC as a general guideline of a limit for a normal adult, but under certain circumstances (e.g. the human subjects population being studied has a fatal disease) these limits could be increased. **I therefore believe that while there should be guidance based upon what a radiation worker may receive each year, that there be no absolute radiation dose limit.** As the RDRC, the RSC, and the IRB will have to concur, I believe that there are enough controls to protect human subjects. Recall that I am assuming that a somewhat altered RDRC system is overseeing clinical trials for PET and possibly other diagnostic and/or therapeutic radiopharmaceuticals.

NRC has not taken into account factors based upon whether the dose is delivered acutely or chronically. The more chronic the dose, the less the hazard per rem. The dose reduction factor for chronicity goes up to about 10. All doses from tracers are considered chronic, and so a dose reduction factor of at least two is scientifically reasonable and most likely conservative.

### *3. Assurance of Safety for Pediatric Subjects*

The current RDRC regulations essentially prohibit pediatric research because of the miniscule radiation dose limits permitted (one tenth of that of an adult). This runs counter to the need to obtain pediatric-specific information. While normal children are more radiosensitive than adults, a factor of 10 is without scientific basis and is much too conservative. A working limit of about one third of what a normal adult receives should be sufficient, but again, I would not put any absolute limits on this because the study group may be children with serious diseases who may reasonably be expected to have a shortened life span anyway. Let dose be decided by the RDRC, with RSC and IRB review as well, on a case-by-case basis.

The FDA asks about toxicity data, but as our tracers have no toxicity (except radiation toxicity for therapy tracers), we should skip toxicity requirements. Again, FDA does not give a single example of toxicity issues with metabolic tracers, PETmolecular imaging probes, other diagnostic radiopharmaceuticals, or therapy radiopharmaceuticals. The entire toxicity requirement should be dropped.

The FDA asks about INDs. To review my recommendations, as I imagine the new RDRC, it doesn't bother to review metabolic tracers, and I would hope that the entire IND process for PETmolecular imaging probes, and hopefully all other radiopharmaceuticals, would be terminated and replaced by a type of RDRC review and an independent advisory committee safety and efficacy decision.

#### *4. Quality and Purity*

The FDA infers that the safety of research subjects is at stake, but fails to report any data at all suggesting that this is in fact the case. I expect that little if any such data are available. RDRC members decide what is needed on a case-by-case basis, depending upon the molecule being produced and the opportunities for significant impurities. This works fine, and does not need to be changed, even as the RDRC mechanism takes over PET and other radiopharmaceutical research and development.

#### *5. Exclusion of Pregnant Women*

For metabolic tracers, PET molecular imaging probes, and all other diagnostic radiopharmaceuticals, verbal assurance of the female is enough. Even if she is wrong, there will not be adverse consequences. I would expect that an institution would require a pregnancy test before including a female in a therapy radiopharmaceutical trial. However, I think that we do not need any regulations about this. I know of no fetal abnormalities documented from females who entered research or clinical trials with radiopharmaceuticals and found out later that they were pregnant. Does FDA have such a database? There have been a number of patients who have been treated with therapy radiopharmaceuticals without ill effect on the fetus, except for definite fetal thyroid damage if the fetus had developed a thyroid and the mother was given NaI-131. I have given diagnostic radiopharmaceuticals to pregnant females knowing that they were pregnant, as have many other nuclear medicine physicians, with no problems (diagnostic NaI-131 is an exception).

## 6. RDRC Membership

An RDRC would not benefit from having either a pharmacologist or a toxicologist because metabolic tracers, PET molecular imaging probes, and diagnostic radiopharmaceuticals have neither pharmacology nor toxicology. Therapeutic radiopharmaceuticals have only rare pharmacologic effects, and these are easily handled by the physician(s) on the RDRC. Therapeutic radiopharmaceuticals have no toxicity other than radiation toxicity, and this field is already amply covered by existing RDRC membership. Bear in mind that any RDRC can get the temporary services of any professional it thinks it needs for a particular protocol, so it is foolish to make any new requirements for membership.

In the case of an institution putting unqualified members on the RDRC, I would assume that it is rare. I expect that a call or a letter to the Administrator of that institution should fix it. It is not necessary to punish the whole nation and create more bureaucracy because perhaps a couple of institutions did this. An institution that continues to use unqualified people should not have an RDRC for a specified time, say five years, but I'd like to see the data about this. Perhaps the people did not have the usual credentials but had the knowledge. In any case, I don't think that any change is required. What harms have occurred?

### **Why the Sudden FDA Interest in RDRCs?**

You will recall that FDA rather grudgingly accepted the responsibility to regulate metabolic tracers because the AEC was very insistent that this occur. You will also recall that FDA sought a mechanism to accomplish this in which it would have hardly any work to do. After treating the whole RDRC mechanism with an ample dose of benign neglect over the past 30 years, why the sudden FDA interest in RDRC's, especially since human subjects are not being harmed?

This is a very interesting question to me. Could it be that there are so few radiopharmaceutical INDs due to FDA's escalating cost and dysfunctionality that the FDA bureaucrats have little to do? Could it be that the bureaucrats want to control the PET research being performed under RDRC because at least they would look busy? Could it be that having tried in vain to destroy PET, FDA sees one more avenue to do terrible harm to PET research activities? As PET projects become the major RDRC projects, is the FDA desire to control and kill just too overwhelming to resist? I don't know what the reason is, but it isn't good. The recent tripling of the RDRC personnel is a bad omen. There wasn't really enough work for one person; why do we need three? It sounds a lot like FDA wants to triple the bureaucracy. That should be crushed.

### **Summary**

I have argued that FDA never had the statutory activity to regulate non-drug metabolic tracers, and that the RDRC regulation in its present form should be ended. I have also argued that given the extreme dangers of having FDA regulate PET molecular imaging probes and other radiopharmaceuticals, it makes sense to have a type of RDRC mechanism for PET and all other radiopharmaceuticals that excludes FDA oversight and determination of safety and efficacy. To this end I would continue the RDRC, but make some changes to it, and institute an **independ-**