October 12, 1999

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Dockets Management Branch
HFA-305
Food and Drug Administration
5600 Fishers Lane
Rm 1061
Rockville, Maryland 20852

Re: 21 CFR 212 (Docket No. 99N-4063)
Current Good Manufacturing Practices for Positron Emission Tomography Drug Products; Preliminary Draft Regulations; Availability

Gentlemen:

I would like to take the opportunity to submit the following comments with regards to above noted item as it appeared in the *Federal Register (FR 51274-75; Vol. 64, No.183, September 22, 1999)* and as posted to the FDA Web-site.

To begin with, I have been a practicing nuclear pharmacist for almost 20 years, having been involved in clinic practice settings, commercial centralized nuclear pharmacy, and basic radiopharmaceutical research within several university settings. Currently, I am employed by the University of Kansas Medical Center to assist them in the establishment of their new PET cyclotron/pharmacy, an area that I will eventually manage once it is up and operational (perhaps around February-March 2000). As such, I am sending these comments in as an individual and not as an official position of the University of Kansas Medical Center.

At the outset, let me say that by not having a companion draft compliance guide to coincide with the draft language in 21 CFR 212, I found it hard to know exactly in which direction the FDA might lean in terms of interrupting intent, etc. for many statements contained within the draft of 21 CFR 212. I notice that terminology that has traditionally appeared within GMP's in the past, has now changed, yet it is not immediately clear if FDA's intent for compliance remains the same.

Many of my colleagues tell me that the discussion (or debate depending on one's point of view) on what constitutes "compounding" versus "manufacturing" is over. Yes, it is true that Congress's Food and Drug Administration Modernization Act of 1997 left language regarding positron-emission tomography (PET) radiopharmaceuticals lying outside of the other opinions/language contained within this document with respect to drug compounding. However, I would like to point out that there are over 20 states that have adopted new State Pharmacy Practice Acts in the past few years. Within these documents is contained language that supports the professional practice of compounding, defines "collaborative practice agreements" in terms of exercising professional judgement when there exists a physician-pharmacist-patient triad relationship, and more. Concomitantly, many State Boards of Pharmacy are currently adopting or have already adopted rule language to support the intent and advances that state legislatures have granted the practice of pharmacy within their domains. Thus, the preparation or compounding of PET radiopharmaceuticals remains firm in my mind, and minds of many others, as part of the practice of pharmacy. The preparation of PET radiopharmaceuticals remains a professional function which falls within the realm of drug compounding and defined and enforced by state pharmacy law/state pharmacy practice acts across the country. Thus PET becomes an area within pharmacy that, where

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applicable/appropriate, remains a part of pharmacy and a state right's issue. Any attempt to label the preparation of PET radiopharmaceuticals as an act of manufacturing is incongruent with trends that are clearly established and expanding at the state level within pharmacy practice across the country today.

Having said this, I wonder how can we propose a term of "Compounded positron emission tomography (PET) drug" in this draft of 21 CFR 212, where the very intent of the document as a whole is to apply manufacturing GMPs to an area of practice that is anything but manufacturing?

In an attempt to be "flexible", much of the document appears to be left for interpretation, and ultimately demands that what could be taken as "acceptable limits" fall well outside of the purview and/or reach of many PET cyclotron operations today. For example, the definition of "Component" is so far reaching that literally any item used within the PET pharmacy, right down to the soap involved in the cleaning of glassware, could be construed to come under this definition. This definition needs to be more narrowly defined to include just those agents, chemicals, etc that are directly involved in the preparation of a PET radiopharmaceutical. The indirect aspect contained in this definition would be a classic example of over-kill.

The definition of "Batch" appears equally confusing, but only in light of my falling back on previously offered explanations from FDA on what constitutes radiopharmaceutical compounding versus PET preparation. For example, radiopharmaceutical compounding of a traditional bone imaging agent, e.g., Tc-99m MDP, could involve a practice whereby there are "X" number of requests for patient doses submitted 24 hours in advance when an actual MDP reagent cold vial is labeled with Technetium-99m sodium pertechnetate. At the nuclear pharmacist's discretion, he/she may elect to add enough radioactivity to the cold vial to prepare not only the patient dose requests that came in advance, but have enough left over so any last minute add-ons or need for replacement doses (due to infiltration) are readily available. All this together has been deemed "compounding" within the scope of pharmacy practice. However, with regards to PET radiopharmaceuticals, explanations have been offered that requests for individual patient doses must be fielded at least 24 hours (or merely in advance) of initiating a cyclotron production run, and only enough material made to cover the advance orders for patient doses. If there is any PET radiopharmaceutical material left over, and a need arises to fill a request for a patient dose with a "Stat" dose, the act of doing so violates opinions of what is compounding and so results in an act of manufacturing. I fail to see the difference between these scenarios. Thus, within the definition of "Batch", what is meant by a "single manufacturing order". What you are really saying is that there are several patient dose requests and that there is a need to "compound" a given run/batch of a PET radiopharmaceutical (i.e., F-18 FDG). For individuals who have dual targets on their cyclotron, in hopes of creating enough product to meet advance requests for patient doses, would the product coming off each target constitute a single or dual batch? Given any left over PET radiopharmaceutical (prepared from a single or dual target bombardment) which could be used to fill "stat" patient dose requests, does this constitute a single "batch" run? Or must a batch only constitute requests for patient doses that come into the PET pharmacy is advance of starting the cyclotron, with subject requests being addressed in a different light? Would this end up be considered a multiple batch run?

The draft 21 CFR 212 calls for the determination of "Percentage of Theoretical Yield". What is the point of having to calculate this number and what relevance does it hold in terms of any final product that is prepared (and subsequently passes) any established quality assurance parameters/tests. For example, within any given reagent vial of radiolabeled Tc-99m MDP, quality control testing using instant thin-layer chromatography will certainly inform you if the majority of the finished product is within the desired form, that is Tc-99m reduced to the +4 valence state and tagged to MDP. However, within any given vial of this product, and on any given day of prepared radiolabeling, if one cared to perform HPLC or other elaborate tests, they would find that there are varying amounts of subspecies such as Tc-99m (+5) MDP and Tc-99m (+3) MDP. While present in extremely minute amounts, these are of little concern clinically in terms of the outcome of actual patient testing. There would be little point having to ascertain the theoretical percentage yield of these intermediates. Therefore, the same logic applies to the preparation of F-18 FDG, N-13 Ammonia, etc. What will be gained by requiring this calculation to be made? If there is a problem that results in lower yields of finished product, that end point will be the final determinant.

Wasting time on any other calculation that, in the end, will lend nothing to the final outcome (one way or the other) is pointless.

There is the stated requirement in the draft to provide a lot number, control number or batch number. I have no particular problem with this. Yet, I would like to point out to the FDA that within the scope of good pharmacy practice, there is required by state pharmacy law a unique prescription number on all prescriptions, or medication order requests (in actual practice, there is a difference between the two). I would like to think that FDA would yield to the requirements of state boards of pharmacy in terms of labeling requirements for prescriptions/medication order requests for PET radiopharmaceuticals. As such, state pharmacy law also has begun to require placement of an expiration date on drugs dispensed under a prescription/medication order. Granted, the issue of expiration dating is a mute point with many PET radiopharmaceuticals given the unique nature of their short physical half-life. Yet, I raise this point to indicate that there may not be a need to re-invent the wheel or try and supercede state pharmacy law in ways where the health, safety and welfare of the public is already under adequate scrutiny.

In the proposed definition of "Production", the words compounding and manufacturing are used together. I do not see a proposed definition for "manufacturing" within the draft of 10 CFR 212, but do see an attempt to describe that the preparation of PET radiopharmaceuticals is an act of "compounding". If the FDA is conceding that the preparation of PET radiopharmaceuticals is an act of compounding, then what is the point for the elaborate concerns of applying GMPs to an area that is already defined within the scope of pharmacy practice?

In the definition of "Quality Control", the intent here is so far reaching, that just about anything found in a pharmacy could be deemed lending itself in someway to the preparation of PET radiopharmaceuticals. A case could be made right down to the soap used in washing glassware, that in itself could be construed as being part of this definition. It concerns me that there are no apparent limits in terms of interpretation here. I would not want to have to "validate" the accuracy/integrity of soap used in cleaning glassware, if that glassware item is in some way used to help ready the performance of some quality control test procedure run on a PET radiopharmaceutical. Similarly, many other examples that are equally as far-reaching back in the scheme of things can be described. This is pointless over-kill again.

In the proposed definition of "Theoretical Yield", there may be some merit in having this calculation just as some might argue for the determination of "percentage of theoretical yield", yet the practicality of having to do this comes under question. Computer scenarios that control the production of a PET radiopharmaceutical will monitor the process from start to finish. I am not immediately aware that any of these computer programs provides the calculation that is being sought here for "Theoretical Yield" (or for "percentage of theoretical yield"). As previously noted, if a problem of less-than-optimal yield occurs, one would obviously know it. Having to make both of these "theoretical" calculations might help pinpoint a problem, but does absolutely nothing in terms of changing the obvious outcome. Such calculations could be "recommended", but to propose codifying them in regulatory language strikes me as another example of over-kill.

Within the scope of the proposed terms of "Validation" and "Verification", I am somewhat concerned as to how the FDA intends to require small PET operations to provide the kind of "dual reporting/verification" that it traditionally asks for within GMPs. If there is to be flexibility in terms of manpower, having the luxury of two persons present at all times during all aspects of a given PET preparation/production run is not realistic within the kind of operating budgets being offered to us by our institutions/companies. Is FDA mandating that there be a specific number of personnel present during each production run? If so, I certainly would not mind having someone inform me that at least two (2) people must be present - I'll never turn away an extra set of hands. Yet the reality is, that I will likely not get the luxury of an assistant until such time as it is deemed by "administration" that the volume of business warrants the hiring of additional personnel (in accordance with pre-conceived business plans). Will the FDA permit dual verification of procedures/steps used in the preparation and quality assurance testing of a PET radiopharmaceutical to be done well after the fact - not in real time observation/occurrence? Will the FDA permit small PET operations to have the same individual who was preparing the PET radiopharmaceutical also serve as the second co-signer/verifier in any validation/verification

requirements? And must the expectation/act of dual operator verification be done as the procedures/steps are being carried out, or accomplished hours later after a given production run is completed? Can this requirement be met using the same person or must there be actually two different individuals as signer/verifier?

When it is stated that current good manufacturing practices for PET include certain factors such as "personnel and resources", "quality control systems", and "equipment and facilities", what sort of requirements are to be associated with these areas? For example, within a stack monitoring system to measure the possible release of radioactive materials in effluents, will there be a set number of monitors and alarms that must be place, and any set expectations in terms of their location within a given system in a given facility? Will the FDA accept quality control testing of PET radiopharmaceutials to be limited to only gas spectrometry and thin-layer chromatography imaging, or must HLPC chromatography be included too (or replace one of the other two)? Similar questions can be raised within each of the above noted areas, and have already been alluded to thus far in this comment letter for one reason or another.

I am concerned about the intent and scope of language associated with "quality control unit" and the authority to examine and approve or reject components, containers, closures, in-process materials, etc. Again, the range for such statements appears to be extremely far-reaching. Within the scope of drug compounding, gelatin capsules do not undergo on-site testing/validation prior to use, yet within the scope of language appearing in this draft of 21 CFR 212, I see where gelatin capsules might be scrutinized. Without knowing what sort of limits, if any, FDA intends here, the general broad nature of this current draft language is again over-kill.

Within the scope of Subpart D - 212.30, I agree with the overall intent of the wording as it is stated. Yet, without the benefit of further interpretation from a corresponding draft FDA compliance guide, I believe that there could be far-reaching implications here that would make meeting the intent of such language difficult for many small PET operations. Note that pharmacists are totally opposed to paperwork, since the weight of it seems to be a part of what we do. The overall scope of this subpart, relative to intent within various defined terms, could make the administrative and prescriptive weight of compliance here overall burdensome.

Similarly, the same sort of concern can be expressed for Subpart E - 212.40, as noted above for Subpart D. Linking the scope of this subpart with what I see for the defined term of "component", "batch", etc could make the compliance of this subpart incredibly difficult.

I am not certain what FDA means when it says "(1) At least one test must be conducted on each lot to verify the identity of each component"..."and then proceeds in the next paragraph (2) to say "each lot of each component and each container and closure...". Again, how far back in time does the intent of this statement go? An entire day could be spent verifying and validating that all "components" (as the proposed definition implies), and how all of this relates directly or indirectly to the finished PET radiopharmaceutical. Given the intent here, a small PET operation would never be in a position to prepare a second run of any given PET radiopharmaceutical, because the bulk of one's time would be spent performing QA tests and validations on all components, intermediates from the production process, etc. And, if one was to run their cyclotron using dual targetry, would the weight of these regulations fall upon the yield from each bombarded target as part of the same batch or from different batches (assuming of course you are making the same PET radiopharmaceutical from this dual process)?

Under Subpart F - 212.50, I agree with the general intent that it is important to refer to master formulas, batch records and record-keeping exercises. This is especially true for purposes of identifying situations where there is a product recall by some manufacturer for a "relevant" component that may be used as part of the overall PET production schema. This expectation would be no different than in any other area of pharmacy practice or general compounding practice. Yet, what concerns me would be the overall extent and scope of the intent here, since we are not privy yet to a companion draft compliance guide to offer more interpretation. There is little need to have to determine the "theoretical yield" and "percentage of theoretical yield", especially in terms of minimum and maximum limits. The reasons for this have already been stated.

As part of the overall process control monitoring procedures, I would surmise that FDA would not oppose any efforts to employ electronic record keeping as part of the daily operational perspectives of a PET center. In this light, there are several software packages available that have been employed within the scope of commercial centralized and hospital-based nuclear pharmacy practice for years. Sooner or later, someone will adapt one of these software programs to accommodate the record-keeping and dose dispensing needs associated with PET radiopharmaceuticals. What concerns me here is the proposed language by FDA to the extent that these software programs must also be validated and the extent and repetition that they may have to be re-validated. Will such validation also be on a batch-by-batch or lot-by-lot basis, and be perceived to be as far reaching as the definition of "components" seems to imply? Will there only be the need for initial validation of the software from the start, first time use, with no other re-testing done (except perhaps as part of an annual review process)? And since I have raised the specter, will there be annual review only of the overall production process in terms of meeting stated effectiveness for detecting potential problem situations, etc. Much in the same way that we only perform periodic calibration checks of radionuclide dose calibrators in a nuclear pharmacy (quarterly, unless the machine was sent out for repair/maintenance). There are other daily tests of a dose calibrator (e.g., constancy), but there is not a general repeating of possible equipment checks that can be performed. Thus the frequency of testing as will be called for in the overall process review/validation as implied in this draft document comes under concern.

Under Subpart G - 212.60, comment here might be reserved for when comment can be fielded with respect to the three draft manufacturing/chemistry model application documents posted to the FDA's Web-site as they pertain to F-18 FDG, N-13 Ammonia and F-18 Fluorine. I can see where FDA might (I would hope) permit the production of PET radiopharmaceuticals in keeping with the scope and intent of any monograph for that agent as it appears from the United States Pharmacopeial Convention, Inc. (USP), especially in terms of identity, strength, quality and purity. However, having seen the other draft model application documents, to which separate comments will be offered in more detail at the appropriate point in time, it concerns me the scope and intent that FDA is looking for here.

For example, within the draft model application for manufacturing/chemistry, etc for F-18 FDG, FDA has suggested a list of quality assurance tests that it would like see done, and offers some comment in terms of how a particular test is to be performed. For most of these examples listed in this document, what is being asked appears most reasonable. There is the stated expectation by FDA that radiochemical purity of F-18 itself to be no more than 2% from ideal norms, and FDA offers no insight in terms of how this determination is to be made. Rather the petitioner is asked to describe the process by which he/she will make this determination. If FDA is not certain how such a test can be performed, nor prepared to make suitable recommendations pertaining thereto, then it is pointless to place the burden on PET community to have to describe a test and associated procedures that FDA itself cannot provide in a prospective manner. Without sounding factitious, I am not looking for the Nobel Prize in Chemistry. I presume that Mass Spectroscopy might afford us with an answer to this question, where HPLC won't, but then given the size of the sample to be tested and the cost of the apparatus in which to perform the test, I must conclude what is the overall point. It is another example of over-kill (especially in the scope of average PET operations where budgets for equipment, supplies and personnel are indeed limited).

Within Subpart 212.61, the performance of sterility testing is important, and having FDA indicate that it will allow the pre-release of a PET radiopharmaceutical before such testing can begin is important. In many instances, PET radiopharmaceuticals are so short in their half-life that requiring sterility testing at all becomes a mute point. Should a PET radiopharmaceutical fail sterility testing, I agree that the facility to which the dose was sent needs to be notified, even any individual within the immediate area to which that PET radiopharmaceutical was shipped and used in a patient. I am not certain as to why only the physician must be notified of a sterility failure? Why cannot there not be an agent of physician (especially in situations where the physician may not be readily available)?

In general, for any other items as they appear in this draft of 21 CFR 212, if not specifically mentioned above, then let me state that that I believe there is suitable flexibility to accommodate PET radiopharmaceutical preparation, dispensing, quality assurance testing, distribution, and even "post-

marketing surveillance". All told, such language is not much different from that which are stated in existing good nuclear pharmacy practice guidelines, available from the American Pharmaceutical Association, a document that I have followed throughout my professional career.

The bulk of my comments here today could be summarized as pertaining to areas of the document in which some additional interpretation and/or guidance in terms of what FDA is looking for is warranted. I am all in favor of taking a somewhat lenient approach to the document and thus draft regulatory language that appears to offer flexibility to meet the needs of small PET operations from those of a much larger commercial concern. I agree that it is unrealistic to expect small PET operations, making fewer than 20 individual patient doses to meet the full weight of GMPs as they are applied to large-scale drug manufacturer preparing hundreds of thousands of drug units daily. However, in an effort to be "fair", the current draft 21 CFR 212 leaves far to many open ended concepts which can easily lead to significant variation and inconsistency in interpretation - perhaps nationally or regionally from an FDA perspective.

Individual nuclear pharmacists or radiochemists, working in concert to prepare fewer than 10-20 PET radiopharmaceuticals per day (and often all of the same type of drug, namely F-18 FDG), are not operating on the same level as a major drug manufacturer. I agree that there needs to be some level of scrutiny and application of GMP principles. But without making suitable allowance for differences in scope of practice and/or size of operation, with regards to GMPs as applied to small PET operations versus major drug manufacturers, ultimately this would prove incredibly burdensome to the PET community at present given its obvious limitations of manpower, resources, etc. Instead of practitioner and regulatory working together in order to bring forward a modality/technology that can hold incredible promise for patient care, we might end up achieving just the opposite - working to effectively to squelch any benefits we hope to gain from PET in medical practice. I don't believe that this is what any of us, practitioner or regulator wants in terms of addressing the needs of patients today and for the future.

The work that FDA has demonstrated in this draft document is a good step forward in trying to recognize the difference from large-scale drug manufacturer to small local provider of a unique radiopharmaceutical that comes under the practice of pharmacy. And by many rights should be regulated by appropriate state agencies with guidance from FDA (much is the same way that the FD&C Act is used in guidance by state boards of pharmacy). I sincerely hope that the next iteration of the draft of 21 CFR 212 will demonstrate an even greater appreciation and awareness for the difference between full-scale drug manufacturers and small, regional PET operations.

One thing is clear, when the final documents come out, there will indeed need to be a meaningful education period in place between FDA and the PET community as a whole. Education coupled with patience in terms of bringing the PET community up to speed with whatever form GMPs that is ultimately handed down to it. I hope that this education process will not only involve local/regional FDA field inspectors working with the PET community, but also having the FDA work with organized groups in medicine and pharmacy (perhaps even academic institutions pertaining thereto), so that utilization of existing meeting forums can occur. This will enable, in the long run, PET practitioners to receive consistent ongoing instruction and training with regards to expectations, etc emanating from FDA.

Sincerely,

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