the product's interaction with a biochemical process in the body. For example, the product may be substituted for glucose in anaerobic glycolysis, theoretically localizing in ischemic tissues where glucose metabolism is the predominant energy source (epileptic foci, acute vascular insufficiency states).

The manufacture of PET radiopharmaceuticals consists of a process that takes place within a few hours. A target material is irradiated by a cyclotron; chemical synthesis takes place in a programmed, automated apparatus; and the final solution is compounded and filled. The biological distribution of a PET radiopharmaceutical in the body is monitored by a positron tomograph, or PET scanner, which detects the photons emitted as a result of the radioactive decay of the PET radiopharmaceutical.

PET manufacturing procedures differ in a number of important ways from those associated with the manufacture of conventional drug products:

• Because of the short half-lives of PET radiopharmaceuticals (some of which are only minutes long), PET facilities generally manufacture the products in response to daily demand for a relatively small number of patients.

 Manufacturing is typically done on a small scale and only a few lots are produced each day. Thus, the daily production of a PET facility is normally handled by few employees, sometimes by one production operator and a parttime support person.
PET radiopharmaceuticals must be

• PET radiopharmaceuticals must be administered to patients in a short period of time because of the brief halflives of the products. Any prolonged manufacturing time or testing or release delays would reduce the useful clinical life of the product.

• Unlike most pharmaceuticals, PET radiopharmaceuticals usually do not enter a general drug distribution chain. An entire lot (one vial) is usually distributed directly from the PET facility to a single medical department, to a physician for administration to patients, to a radiopharmacy for dispensing, or to another site close to the PET facility. The receiving facilities are in a geographic proximity that will allow for receipt and use within the product's half-life parameters.

The agency believes that there are fundamental principles of the CGMP regulations that need to be applied to drug manufacturing processes, including those for PET radiopharmaceuticals, to ensure the safety and efficacy of the finished products. However, as just noted, certain features are unique to the manufacture of PET products. Part 211 (21 CFR part 211), which is primarily directed to the regulation of conventional drug products, contains requirements and specific language which might result in unsafe handling of PET radiopharmaceuticals, are inapplicable or inappropriate, or which otherwise do not enhance drug product quality in the manufacture of PET radiopharmaceuticals.

FDA is therefore proposing to amend its regulations to permit manufacturers of PET radiopharmaceuticals to apply to the agency for approval of an exception or alternative to the requirements of part 211 as they apply to the manufacture of PET radiopharmaceuticals. A request for an exception or alternative must contain either an explanation why compliance with a particular requirement of the CGMP regulations is unnecessary or cannot be achieved, or a description of alternative procedures or controls that satisfy the purpose of the CGMP requirement. Both of these must include all necessary supporting data. Alternatively, the request may include other information justifying an exception or alternative. The request for an exception or alternative may be approved by the agency if it is determined that the requestor's compliance with the CGMP requirement is unnecessary to provide suitable assurance that the drug meets the requirements of the act as to safety and it has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess, or if compliance with the requirement cannot be achieved. In addition, the request for an exception or alternative may be approved if the requestor's alternative procedures or controls satisfy the purpose of the CGMP requirement, or if the requestor's submission otherwise justifies an exception or alternative. The agency may withdraw approval of an exception or alternative if it finds, on the basis of new information, that the criteria for approval are no longer met. Such withdrawal will be accomplished by providing written notice, and the reasons for the action, to the original requestor.

The agency will also periodically provide guidance to the industry on the application of the CGMP regulations to PET radiopharmaceuticals.

Elsewhere in this issue of the Federal Register, FDA is publishing: (1) A notice of availability of a draft guideline to assist persons in determining whether certain manufacturing practices, procedures, and facilities used for PET radiopharmaceuticals are in compliance with FDA's CGMP regulations; and (2) a notice of a public workshop and FDA guidance on the regulation of PET radiopharmaceuticals.

FDA is requesting written comments within 30 days after the date of publication of this proposed rule. In addition, FDA is proposing that any final rule that may publish as a result of this proposal become effective on its date of publication in the Federal Register. The proposed rule would permit manufacturers of PET radiopharmaceuticals to apply to FDA for approval of an exception or alternative to the requirements of the CGMP regulations. Accordingly, the proposed rule, if finalized, is a substantive rule which, in the discretion of the agency, grants or recognizes an exemption or relieves a restriction. (See 5 U.S.C. 553(d)(1) and 21 CFR 10.40(c)(4)(i).) In addition, the Commissioner of Food and Drugs finds good cause under 21 CFR 10.40(a)(2) for providing 30 days for comments instead of 60 days and under 5 U.S.C. 553(d)(3) and 21 CFR 10.40(c)(4)(ii) for making a final rule based on this proposal effective upon its publication in the Federal Register. The manufacturing process for PET radiopharmaceuticals is sufficiently different from that of other regulated products that application of certain CGMP requirements to PET radiopharmaceuticals is impractical. Because PET radiopharmaceuticals are already in use, a longer comment period or a later effective date may delay FDA approval or hinder appropriate application of CGMP regulations to PET radiopharmaceuticals, that are necessary to protect the integrity of the drug manufacturing process.

II. Request for Comments

Interested persons may, on or before March 29, 1995, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

III. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment