



ACADEMY OF MOLECULAR IMAGING

www.ami-imaging.org

ami@mednet.ucla.edu

0436 6 15 1636

December 19, 2005

Box 951735
Los Angeles, CA
90095-1735
310.267.2614
Fax: 310.267.2617

President
President-Elect
Secretary
Treasurer
Immediate Past President

The Honorable Andrew C. von Eschenbach, M.D.
Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Re: Docket No. 2004N-0439

Proposed rule for the Food and Drug Administration
regarding Current Good Manufacturing Practice for
Positron Emission Tomography

Dear Dr. von Eschenbach:

The Academy of Molecular Imaging (AMI) appreciates the opportunity to comment on the proposed rule on Current Good Manufacturing Practices (CGMP) for Positron Emission Tomography (PET) Drugs, as published on September 20, 2005.

AMI applauds several aspects of the proposed rule, and appreciates the judicious manner in which FDA has undertaken this rulemaking. The Center for Drug Evaluation and Research (CDER) should be commended for its conscientious collaboration with AMI and the PET community since the enactment of section 121 of the Food and Drug Administration Modernization Act of 1997 (FDAMA),¹ including its public meetings, and its development and refinement of the 1999 preliminary draft regulations¹ and 2002 preliminary draft proposed rule.¹

AMI remains concerned, however, that subjecting hospitals and research institutions to the same inspection regime as large commercial producers would be unduly onerous, requiring those institutions to shift limited resources away from health care delivery and research in order to satisfy regulatory obligations that are not warranted by clinical or safety considerations.¹ AMI would welcome the opportunity to assist FDA in developing inspection guidelines that help to mitigate this risk and to

¹ Public Law 105-115. Section 121 of FDAMA specifically requires FDA, in establishing PET CGMPs, to "consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists licensed to make or use positron emission tomography drugs."

¹ 64 Fed. Reg. 51274 (September 21, 1999).

¹ 67 Fed. Reg. 15344 (April 1, 2002).

¹ The proposed rule's compliance cost estimates (e.g. \$2.42 million one-time costs and \$2 million in annual costs per hospital or corporate facility) are of particular concern.

2004N-0439

C 8

ensure that the agency's requirements and enforcement strategies "take due account of any relevant differences between not-for-profit institutions that compound the drugs for their patients and commercial manufacturers of the drugs," as required by law.¹

AMI Applauds Several Features of the Proposed Rule

AMI wishes to express its strong support for the following aspects of the proposed rule:

- The incorporation into the proposed rule of principles and definitions in the United States Pharmacopoeia (USP) general chapter on PET drug compounding that "largely reflect the consensus views of the PET community and FDA on how to properly produce PET drug products."
- The exclusion of PET drugs from the requirements of 21 C.F.R. 210 and 211, and the regulation of investigational and research PET drugs under Chapter 823 of the USP, rather than the more specific requirements set forth in proposed part 212. AMI agrees that "it is appropriate to have less detailed CGMP requirements for investigational and research PET drugs to allow more flexibility during the development of these drugs" and that "many investigational PET drugs may not have commercial potential."²
- The clarification that the CGMP requirements under proposed part 212 apply solely to PET drug products "marketed under an approved new drug application (NDA) or an approved abbreviated new drug application (ANDA)." At present, AMI understands that such products are limited to ammonia N 13 injection, fludeoxyglucose F 18 injection (FDG F 18), and sodium fluoride F 18 injection.
- The assurance that, while the FDA retains authority under section 704 to inspect facilities producing investigational or research PET drugs, such inspections would be conducted only for cause, such as "a potential safety concern related to the production of an investigational or research PET drug."
- The exclusion under proposed section § 202.1 of intermediates, or chemical precursors, used in the synthesis and production of PET drugs, from CGMP requirements. AMI notes particularly that § 212.40(c)(1)(i) clarifies that finished-product testing and reliance upon supplier certificates of analysis (COA) is appropriate to ensure "that the correct components have been used (e.g., production of F18 FDG)."
- The limitation of potentially burdensome building and air-quality requirements in relation to aseptic processing and quality control for PET drug production facilities.

¹ Section 121(c)(1)(B) of FDAMA.

² CDER Draft Guidance, "PET Drug Products – Current Good Manufacturing Practice (CGMP)" September 2005, available at <http://www.fda.gov/cder/guidance/5425dft2.htm>.

Remaining Challenges of CGMP Implementation

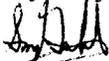
With respect to the statutory requirement to account for "any relevant differences between not-for-profit institutions that compound PET drugs for their patients and commercial manufacturers of such drugs," AMI is concerned that the proposed rule fails to acknowledge that the "size, scope and complexity of... production operations" it notes that lead to "CGMP differences" also are an important reflection of the differences between not-for-profit and commercial institutions that compound PET drugs. AMI is concerned that, in failing to draw this distinction in an express, formal manner, the proposed rule may compel not-for-profit hospitals and research institutions to divert resources away from research, health care delivery and patient services in order to meet their CGMP compliance obligations. The result would be to impose imprecise requirements that are ungrounded in clinical or safety considerations on small or not-for-profit institutions, and to disproportionately compromise their ability to serve patients and innovate. This is precisely the outcome that Congress sought to avoid in 1997.

AMI would welcome the opportunity to assist FDA in developing an approach to facility inspection that reflects the enormous variation among PET drug production facilities. Although the proposed rule correctly observes that the distinction between commercial and not-for-profit institutions may not always be entirely categorical, there nevertheless remain important differences between these two classes of producers. In particular, most production facilities housed at hospitals and research facilities are very modest operations, producing only limited doses of PET drugs for their own clinical use. Moreover, these institutions do not profit from such production, and may lack the resources to satisfy onerous inspection requirements. As the FDA fashions an inspection strategy, its discretion should be guided by these important factors and relevant questions, such as: How large is the facility? What is its volume of production? Does it operate on a for-profit or not-for-profit basis? Does it produce PET drugs only for use at its home institution, or also for commercial distribution?

Most importantly, AMI urges that under part 212, as a matter of enforcement discretion and practical implementation, FDA only inspect not-for-profit facilities that produce PET drugs for their own clinical use only when the agency has cause to suspect that drug safety or quality has been compromised. By adopting the same policy with respect to not-for-profit producers that it currently applies to investigational and research PET drugs, the FDA would assure that its limited resources are only spent when the agency is made aware of "a potential safety concern related to the production of" a PET drug product.

AMI applauds FDA's conscientious work on the proposed rule, and welcomes the opportunity to continue its collaboration with agency staff on these issues and to develop an appropriate CGMP inspection strategy protective of public health and innovation.

Very truly yours,



Sanjiv S. Gambhir, MD, PhD
President
Academy of Molecular Imaging