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February 23, 2007

BY E-MAIL

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2007N-0005; Prescription Drug User Fee Act

Dear Sir or Madam:

The Council on Radionuclides and Radiopharmaceuticals ("CORAR") submits these comments in response to the Food and Drug Administration's ("FDA's") request for comment on the Agency's proposed recommendations for the reauthorization of the Prescription Drug User Fee Act ("PDUFA") for Fiscal Years ("FY") 2008 to 2012 (so-called "PDUFA IV").[1] CORAR is an association of 17 companies that manufacture and distribute radiopharmaceuticals, sealed sources, and radionuclides primarily for use in medicine and life science research. These comments supplement CORAR's public statement on the same issues at FDA's February 16, 2007 public meeting on PDUFA IV.

CORAR advocates that, in PDUFA IV, FDA and Congress address certain user fees issues unique to sponsors seeking approval of "human drug applications" for Positron Emission Tomography ("PET") drug products. As explained below, because of the inherent characteristics of PET drugs, some PET drug sponsors might need to identify a large number of "prescription drug establishments" in a marketing application. Because FDA annually assesses establishment user fees for each manufacturing establishment identified in an approved "human drug application," some PET drug manufacturers, absent

1 See FDA, Notice of Public Meeting, Prescription Drug User Fee Act, 72 Fed. Reg. 1743 (Jan. 16, 2007).

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relief, would be unfairly burdened with multiple establishment fees totaling millions of dollars annually.

CORAR first raised this issue in an August 2005 citizen petition, and asked FDA to administratively establish a "class waiver" under which PET drugs manufacturers would be exempt from multiple establishment user fees, and be subject, at most, to a single establishment fee for each approved "human drug application."[2] FDA has not substantively responded to CORAR's citizen petition. FDA's PDUFA IV proposal does not address issues specific to PET drugs. CORAR advocates an amendment to the Federal Food, Drug, and Cosmetic Act ("FDC Act") addressing this issue.

I. BACKGROUND ON PET DRUG DISTRIBUTION

PET drugs are produced by tagging (i.e., "labeling") a substrate compound with a positron emitting isotope, which is produced in cyclotrons (i.e., devices that accelerate protons or deuterons to the high energies needed for a nuclear reaction to occur). Once injected, the isotope travels through a patient's bloodstream and is distributed in certain tissues. Using a PET camera, nuclear physicians measure the different rates at which the isotope emits positrons, based, for example, on the different ways in which different types of tissue metabolize the drug's substrate, and thereby produce computerized images of biochemical processes and tissue structures within the body.

Physicians use the resulting images to diagnose, stage, and monitor diseases (e.g., focal epilepsy, certain cardiac diseases, dementias, and lung, breast, prostate, and colorectal cancer). In addition, PET as a biomarker is an important tool in FDA's Critical Path Initiative and in the quest for personalized medicine. For example, a Biomarkers Consortium consisting of representatives from the National Institutes of Health, FDA, and the Pharmaceutical Research and Manufacturers of America is engaged in a project to qualify one PET drug – fluorodeoxyglucose ("FDG") – as a biomarker for non-Hodgkin's lymphoma. Their objective is to demonstrate the ability of FDG-PET to gauge a particular patient's response to therapy or when to switch therapies to provide the best chance for curing or managing the cancer.

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[2] See CORAR, Citizen Petition, FDA Docket No. 2005P-0358, (Aug. 31, 2005) *available at* http://www.fda.gov/ohrms/dockets/dockets/05p0358/05p-0358-cp00001-01-vol1.pdf.

Because the radioactive half-lives of positron-emitting isotopes used in PET drugs are short (e.g., from several minutes to a few hours), the drugs must be used soon after they are prepared. Accordingly, PET drugs are prepared by PET drug facilities only as needed and in close proximity to the medical facilities where they are used. Their necessarily decentralized and relatively small-scale preparation distinguishes PET drugs from other diagnostic and therapeutic drugs, which typically have long shelf-lives and therefore can be manufactured in large quantities at centralized facilities and easily distributed over long distances for commercial use.

Until recently, FDA generally did not regulate providers of PET drugs as conventional pharmaceutical manufacturers, but instead considered the preparation of PET drugs for dispensing under a prescription to fall within the practice of pharmacy. By extension, PET drug providers, like other pharmacies engaged in drug compounding, were not required to comply with the regulatory requirements imposed on conventional drug manufacturers. PET drug providers, for example, have not had to obtain FDA approval of a marketing application before marketing their drugs, register their facilities as drug establishments, or comply with current Good Manufacturing Practices ("cGMPs").

In the early 1990s, as PET drug production expanded, FDA became increasingly convinced of the need for heightened regulation of PET drugs. FDA announced in 1995 that it would henceforth regulate PET drugs as "new drugs" subject to the New Drug Application ("NDA") requirements of the FDC Act.[3] FDA's initiative to change its regulatory approach to PET drugs was superseded by amendments to the FDC Act contained in the FDA Modernization Act of 1997 ("FDAMA"). These amendments placed a moratorium on FDA's regulation of PET products as "new drugs" until FDA establishes procedures by which PET drugs are to be approved under the FDC Act's new drug approval process, and establishes appropriate PET drug cGMPs.[4] During this moratorium, FDA has encouraged PET centers to voluntarily submit marketing applications for approval.

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3 See FDA, Notice, Regulation of Position Emission Tomography Radiopharmaceutical Drug Products; Guidance; Public Workshop, 60 Fed. Reg. 10,594, 10,595 (Feb. 27, 1995).

4 See FDAMA § 121.

II. THE ESTABLISHMENT USER FEE PROBLEM

FDA collects three types of user fees for a drug product that is the subject of a "human drug application:" (1) a one-time application fee; (2) an annual establishment fee; and (3) an annual product fee.[5] Establishment fees are assessed for "each prescription drug establishment listed in [an] approved human drug application as an establishment that manufactures the prescription drug product named in the application."[6] Each establishment is "assessed only one fee per establishment, notwithstanding the number of prescription drug products manufactured at the establishment."[7] The Fiscal Year 2007 establishment fee is $313,100 and will likely rise in coming years.[8]

PET drug sponsors that voluntarily submit to FDA a "human drug application" during the moratorium on the Agency's regulation of PET products as "new drugs" are subject to PDUFA user fees, unless otherwise exempted by the statute.[9] Once the moratorium ends, all PET drugs that are the subject of a "human drug application" will be subject to PDUFA user fees.

Because of the unusual characteristics of PET drugs, the assessment of establishment user fees, in particular, will significantly and unfairly burden commercial PET drug manufacturers. Due to the short half-lives of PET drugs, a commercial manufacturer that supplies PET drugs nationally, or even regionally, requires multiple manufacturing establishments located throughout the United States or the region (as the case may be). Each of these establishments must be identified in any marketing application submitted to FDA. Because establishment fees are assessed annually for manufacturing establishments

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5 The term "human drug application" is defined to mean "full" 505(b)(1) NDAs and 505(b)(2) applications for either a new chemical entity or a new "indication for a use" of a previously approved drug product. FDC Act § 735(1). Under FDA's PDUFA IV proposal, the definition of "human drug application" would be "simplified" so that it no longer distinguishes between 505(b)(1) and 505(b)(2) applications. See 72 Fed. Reg. at 1747.

6 FDC Act § 736(a)(2)(A)(ii).

7 Id. at § 736(a)(2)(A)(ii).

8 See FDA, Notice, Establishment of Prescription Drug User Fee Rates for Fiscal Year 2007, 71 Fed. Reg. 43,780 (Aug. 2, 2006).

9 For example, the sponsor of a designated "orphan drug" is excepted from paying only the application fee. See FDC Act § 736(a)(1)(E).

identified in an approved "human drug application," commercial PET drug applicants would be assessed multiple establishment fees.[10] For example, one PET drug manufacturer operates 44 cyclotron facilities nationwide. If these were all used to manufacture and supply a particular PET drug covered under an approved NDA, this company could have to pay over $13 million annually in establishment fees (based on Fiscal Year 2007 user fee rates).

Large annual assessments would place a significant financial burden on certain PET drug manufacturers. Indeed, annual company revenues for some PET drugs would not even cover the $13 million in annual establishment fees in the above example, much less recover the costs of development, production, and marketing or provide a profit. The PET drug market is miniscule compared to the market for many therapeutic drugs; yet, absent relief, some PET drug sponsors will be burdened with much higher fees than multi-billion dollar therapeutic drug products. Under these circumstances, it will be financially unfeasible for multi-cyclotron PET producers to devote resources to investigating, developing, and commercializing novel PET agents. Even if such a company did undertake to develop and commercialize a PET drug, it might have to do so using only a limited number of PET establishments to avoid an exorbitant annual fee burden, leaving some geographical areas without access to a potentially valuable drug.

Although academic medical centers, which typically have one cyclotron, will still be able to develop and seek FDA approval for new PET agents without being burdened with multiple establishment fees, these PET centers are ill-equipped to commercialize novel PET drugs nationally or even regionally. Ultimately, unless there is some relief from establishment fees, patient access to valuable PET diagnostic agents will be severely limited.

III. LEGISLATIVE SOLUTION

To address the clear but unintended inequity that exists under current law with respect to PET drugs, CORAR proposes that the FDC Act be amended to limit establishment fees to one annual fee per "human drug application." In addition, many PET drugs are produced by not-for-profit academic medical centers with one cyclotron for use within the same institution. Such PET drug producers should be eligible for additional relief. CORAR proposes a total exemption from annual establishment fees for a PET drug

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10 FDC Act § 736(a)(2)(A).

sponsor that (i) is, or is affiliated with, a not-for-profit medical center that has only one cyclotron, and (ii) certifies annually to FDA that greater than 95 percent of the doses of the PET drug produced by the sponsor are for use within the medical center.

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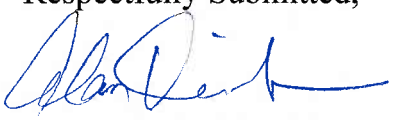
CORAR appreciates the opportunity to comment on FDA's PDUFA IV proposal, and looks forward to working with FDA and Congress to craft legislative language that will treat PET drug manufacturers equitably and fairly so that consumers will continue to have access to these innovative and life-saving diagnostics.

Respectfully Submitted,



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