COMMENTARY

FDA RESPONDS TO MARCUS LETTER REQUESTING CLARIFICATION OF POLICIES

The following letter, dated June 10, 1988, was sent by Paula Botstein, MD, deputy director of the Food and Drug Administration's (FDA) Office of Drug Research and Review. The recipient, Carol Marcus, PhD, MD, director of the Nuclear Medicine Outpatient Clinic at Harbor-UCLA Medical Center, had written a letter to the Agency requesting clarification of a number of policies regarding radiochemicals, agents used in positron emission tomography (PET) and physician-sponsored INDs. That letter, directed to Robert Temple, MD, director of the Office of Drug Research and Review at the FDA, was mailed July 20, 1987, and reproduced in its entirety in Newsline *(Feb. 1988, p. 142).*

In discussing Dr. Botstein's reply, Dr. Marcus noted with approval that the FDA has now agreed to review physician-sponsored INDs that are for genuine research purposes, even though the product is being subjected to NDA review. Physician-sponsored INDs for the purpose of obtaining products for the normal practice of medicine, however, are not eligible for FDA review, if the Agency is reviewing an NDA for the product.

The biggest differences remain in the area of what constitutes the practice of pharmacy, which is regulated by the states, and what constitutes drug manufacturing, which is regulated by the FDA, according to Dr. Marcus. Despite these differences, Dr. Marcus is pleased that a dialog has begun. "It is most encouraging that the FDA is attempting to define its policy, because this gives us an opportunity to discuss specific details with them," she said.

Dear Dr. Marcus:

Dr. Temple has requested that I reply to your letter dated July 20, 1987 regarding particular issues which affect the radiopharmaceutical community.

Because our response may have a significant impact on this promising modality, we have attempted to approach these complex regulatory issues in a thoughtful and measured manner. We hope you will understand our delay in providing this response.

The Food, Drug, and Cosmetic Act (hereafter referred to as the Act) established extensive controls to assure that finished pharmaceuticals and components are safe and effective for their intended uses. A shipper or supplier may be liable to injunction and/or criminal prosecution if a new drug is distributed contrary to the provision of the Act. This is not a new position.

FDA has for many years regarded suppliers of chemicals for prescription compounding, or for other drug uses, as fully subject to regulation under the Act's drug labeling and preclearance requirements. Suppliers must register pursuant to Section 510, submit to inspection under Section 704 and meet the current good manufacturing practice requirements of Section 510(a)(2)(b). In addition, in the case of new drugs, the manufacturer of such chemicals must be approved in an NDA. These are legal requirements which we believe to be in the public interest.

As you have stated, for many years radiopharmacists have obtained radiochemicals to prepare unapproved radiopharmaceuticals for human administration. FDA has not sought to regulate under the new drug provisions of the Act this limited aspect of the practice of pharmacy, where a radiopharmacist, acting pursuant to a prescription order from a physician, compounds a radiopharmaceutical for clinical use within the institution with which he or she is affiliated.

The agency takes a different view with regard to sale of unapproved non-radioactive kits or similar ligands (not synthesized from components) for purposes of being labeled by radiopharmacists with radiochemicals. In this case, the radiopharmacist labels a commercially prepared "cold" kit or ligand, which was in all probability shipped in interstate commerce from the supplier with the *intent* of ultimately being used for diagnosis or treatment. An example of this is the labeling of cold MIBG with radioactive iodine-131 for adrenal scanning. The MIBG is a drug (a component for a finished product) that has not been compounded from its individual components by the radiopharmacist, but usually has been purchased from an outside source. Similarly, the iodine-131 being used for the labeling procedure is often supplied as a radiochemical. If the safety and effectiveness of such drugs have not been established in an approved NDA, IND should be submitted to the FDA to provide for the clinical use of the drug. I have enclosed for your information FDA's "Nuclear Pharmacy Guideline," which discusses in detail the Agency's approach to the practice of nuclear pharmacy.

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Similarly, a kit or ligand for PET imaging, because of its intended use, is not an intermediate but is rather a drug that is fully subject to FDA regulation. As you probably are aware, non-radioactive reagent kits or nuclide generators are regulated as drugs under the Act when used in the preparation of a radiopharmaceutical.

At this time, let me address some additional concerns you have raised regarding the FDA policy.

With respect to your belief that the Agency is "trespassing on the territory of other regulatory agencies," it is the FDA's ultimate responsibility to assure that any new drug, prepared for either diagnostic or therapeutic purposes, has been determined to be safe and effective for its stated purpose and is the subject of an approved NDA or an abbreviated NDA. Alternatively, the drug should be under active investigation (IND) involving controlled clinical trials to establish its safety and effectiveness. No other agency performs this task.

Regarding your remarks concerning National Laboratories, FDA does not set policy for the National Laboratories. Nothing in FDA's regulations would prohibit National Laboratories, or any one else, from submitting an IND or NDA in compliance with the requirements of the Act. Submissions have been made and are being made by National Laboratories under the new drug section of the Act.

Moreover, we do not believe that patients are being deprived of optimal care. As previously stated, the FDA has not sought to apply the new drug provision of the Act to the compounding of a radiopharmaceutical under limited circumstances consistent with the practice of pharmacy and medicine and we are aware that this practice has led to the initial development of new products and new uses of existing products. However, with regard to the distribution of kits or ligands for medical use, we have applied the new drug provisions of the Act. See FDA's "Nuclear Pharmacy Guideline," enclosed. Better quality safety and effectiveness data will be derived from studies conducted under the IND regulations and patient safety will be safeguarded. I am certain you will agree that patients receive optimal care when they receive drugs which have been approved on the basis of data generated from adequate and well-controlled scientific studies and have adequate prescribing information in their labeling. In addition, we welcome suppliers of unapproved radionuclides to work with the Agency so that these agents may become the subjects of NDA approvals and thus be more readily available to the entire community.

For your information, the FDA has recently explicitly relaxed its regulations regarding investigators of additional unlabeled uses of approved drugs, including radiopharmaceuticals. Please be advised that no IND need be submitted for such uses, if the following conditions [see final rule published in the *Federal Register* of March 19, 1987] are met:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
2. the investigation is not intended to support a significant change in the advertising for the product;
3. the investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product; and,
4. the investigation is conducted in compliance with the requirements for institutional review, informed consent and promotion and sale of investigational drugs.

In addition, an IND is not required when a physician uses an already approved drug for an unlabeled indication within the practice of medicine, which the Agency has consistently viewed as including the use of marketed drugs for unlabeled indications in the "day to day" treatment of patients.

Radiopharmaceuticals for PET Imaging

Many of the staff at FDA, particularly those in our Division of Oncology and Radiopharmaceutical Drug Products, have spent substantial effort in exploring the various aspects of the regulations of radiopharmaceuticals for PET imaging. The clinical use of PET imaging carries a great potential for the radiopharmaceutical community and for the patients served. It also raises complex medical, legal, regulatory, compliance and management issues.

For example, although PET centers are customarily located in clinical institutional settings, these centers are similar in many respects to drug manufacturing sites. Reconciling the implications that emerge just from this situation alone makes it apparent that serious consideration must be given to devising, within the Act and regulations, means of regulation that assure safe and effective PET imaging agents without placing an undue burden on either the PET center or the FDA.

PET is not a new modality, but sufficient assurance of individual product uniformity from site to site and over time at the same site appears lacking. However it is achieved, such assurance is, of course, important in consistently ob-

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taining the anticipated effect of PET radiopharmaceuticals in patients. Were such a goal obtainable, it would be reasonable to expect, within regulatory limitations, that the amount of clinical safety and effectiveness data for each drug product among PET centers would necessarily be reduced substantially.

We are approaching the regulation of PET with an open mind and with due regard for its special nature and role in the development of new products. We intend to be flexible and creative in our approach.

Physician-Sponsored INDs and Outside Review of INDs

The most efficient mechanism to get a drug through the NDA approval process is for the commercial sponsor to conduct an appropriate number of adequate and well-controlled clinical studies which are of proper design to yield data upon which the Agency may base an approval. As newer radiopharmaceutical agents have evolved, we have urged the sponsors to proceed in this more focused direction.

An important aspect of this approach includes a commitment on the part of the sponsor to limit the number of certain kinds of physician-sponsored INDs beyond those for studies deemed adequate and necessary for NDA approval. Sponsors of individual INDs may want the drug for various reasons. These principally include (1) using the drug in clinical practice without really evaluating the drug or collecting safety and effectiveness data, (2) using the drug as a specific research tool typically in a funded research investigation in an area of interest which is different from that of the commercial sponsor, and (3) evaluating the performance of the drug in a manner substantially different from the approach and setting chosen by the commercial sponsor. The last two types of INDs will collect important data, although these data may not be directly or readily applicable for use by the sponsor in the original NDA submission.

The first type of physician-sponsored IND mentioned is less useful with regard to drug approval. Such an IND expends resources, usually does not provide usable data and may contribute to delayed approval. Thus, in an attempt to hasten the approval process we have discouraged commercial IND sponsors from freely providing a drug which is under clinical trials to additional practitioners, particularly for use under such individual physician-sponsored INDs.

The American College of Nuclear Physicians expressed themselves on this matter by recommending that widespread distribution of drugs under INDs with cost recovery be avoided. They stated their concern on this issue and on a related issue to Dr. Frank Young, Commissioner of Food and Drugs, when they met with the FDA in August 1986:

> *"Prohibit Commercialization of an IND"*—The widespread distribution of an IND pharmaceutical, with cost recovery, should be eliminated. This widespread distribution decreases the incentive to obtain an NDA approval. A limit on IND studies would also stimulate the timely performance of adequate and well controlled studies, and thus lead to a more rapid response during the review process." (*ACNP/Scanner,* Volume XII, No. 7 September 1986).

Additionally, FDA has sometimes suggested for firms, as a further means of increasing the focus and hastening approval, that they limit the number of initial indications for use of the drug. Firms are encouraged to plan and implement studies on additional indications to be submitted for supplemental approval after the drug is approved for marketing.

It should be understood that we are restricting our remarks regarding physician-sponsored INDs to cases in which a commercial sponsor is actively seeking approval for marketing the drug. FDA is certainly supportive of the concept of physician-sponsored INDs in general.

Development of a new drug can be made more burdensome by submission of a large number of INDs, the number being more of a problem than the amount of clinical data contained in the INDs. This is because in most of the INDs submitted, the physician sponsor is simply using the drug in the clinical practice of medicine. In those INDs, the amount of medical data to review is minimal and is not a significant burden on the FDA medical reviewer. I cannot agree with your suggestion that the review of such INDs is an appropriate task to share with an outside peer review group. The types of physician-sponsored INDs that would be candidates for an outside peer review group generally are not numerous enough to constitute a significant burden on the FDA medical review staff.

I thank you for your interest and concern for the nuclear medicine community. Please excuse our delay in responding, but our intent was to provide as comprehensive a response as possible to your concerns. We believe that the Agency and the community can continue to work together to resolve differences and solve problems.

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