During the past several months, Dr. Earl Meyers, Acting Director of the Division of Oncology and Radiopharmaceuticals at the FDA, and Dr. Bryant Jones of the same division have given several talks that have done much to clarify the position of the FDA on regulation of radiopharmaceuticals. Since a clear understanding of this position is of the utmost importance to all of us who use—or manufacture—radiopharmaceuticals, I have summarized here some of the FDA's statements.

As it is now stated, the Federal Food, Drug and Cosmetic Act as amended in 1962 and the New Drug Regulations govern the use of *all* investigational and new drugs *including* those with a radioactive component (whether reactor produced, accelerator produced or naturally occurring) because all radioactive products used as drugs fall within the definition of drugs under the Act. According to Dr. Meyers, "It is the responsibility and policy of the Food and Drug Administration to enforce the Federal Food, Drug and Cosmetic Act in the interest of consumer protection with respect to radiopharmaceuticals as well as other drugs."

Exempted from the Act for the time being are reactor-produced isotopes for investigational use if they are shipped in conformance with AEC regulations. As you know, the AEC and FDA have been working toward an agreement under which FDA would assume the same control over investigational radioisotopes as it exercises over other investigational drugs.

But although reactor-produced radioisotopes are now exempt from FDA control, "the exemption does not apply to accelerator-produced isotopes, to naturally occurring isotopes, to cold-drug substances used in conjunction with an investigational isotope use nor does it relieve any person or firm from the obligation of obtaining an approved New Drug Application before distribution of the drug for other than investigational purposes." For example, under the present regulation as exempted, the FDA says that a manufacturer should have an approved NDA before he undertakes commercial distribution. According to Dr. Jones, this latter requirement is not being universally applied at the moment because a firm may sell radiopharmaceuticals under the AEC regulations while in the investigational stage.

But perhaps the most serious oversight not recognized by investigators, according to Dr. Jones, "is that every institution or facility operating under a broad license from the AEC, which is developing new procedures and clinical methods, is in violation of the New Drug Regulations because it is using new chemicals and compounds which are new drugs in their own right." For example, while ^{99m}Tc sodium pertechnetate obtained from a generator can be considered exempt as long as it is shipped and used in conformity with the AEC regulations, if it is reacted to form a sulfur or rhenium colloid, it no longer falls under the AEC regulations. Any investigator, the FDA says, using these materials should have an IND on file with the FDA or be a participating investigator covered by a properly sponsored and filed IND.

The investigational drug regulations pertaining to clinical pharmacology phases of a drug test let one submit a general outline of these phases as the claim for exemption. The FDA has developed the following simplified procedures particularly for the physician-investigator who sponsors an investigational drug

including its use solely as a research tool. He should meet this requirement by submitting a notice to FDA of:

1. His intent to use the compound or compounds proposed for study;
2. Identification of the compound or compounds together with the facts that satisfy him that the agent may be justifiably administered to man;
3. The purpose of the use and the general program of the activity proposed;
4. And appropriate background information, including a brief statement of the investigator's scientific training and experience and the nature of the facilities available to him.

It is not necessary that these requests for exemption be lengthy and comprehensive. However, such things as the patient-consent provision and the requirement for reporting adverse reactions still apply.

Once the IND has been filed with the FDA, an investigator can proceed with his study without waiting for approval. In the past, the FDA has come under considerable attack for its IND regulation by scientists who feel that it tends to curtail investigation and discourage good people from entering the investigational new drug field. The FDA feels this point is unjustified because, "a program can hardly be called restrictive which asks only that the government be informed of research activity as it is proposed and as it is conducted. It is a great protection to patients and physicians alike to have an interested agency alert to the dangers of drug research and ready and able to act."

Once the pharmacological and clinical studies have been completed and the sponsor believes the new drug is safe and effective for the purposes for which it is recommended, he submits a new drug application (NDA). The material in the application is reviewed and evaluated by medical officers, pharmacologists and chemists, and FDA has 180 days in which to act on the application. If it is approved, the drug may go on the market. If not, the applicant is notified of the reasons so he may correct the deficiencies.

Just what constitutes a "new drug" has also been a matter of question. Dr. Jones says, "One of the general misconceptions is that a drug is old because it has been around for a long time. A drug may be 'new' without necessarily being a new substance. For example, if aspirin tablets were labeled or promoted as a seasickness remedy, they would be considered a 'new drug'." This "new use" concept applies to radiopharmaceuticals as well as other drugs.

"Basically, the intent of the law in controlling new drugs," Dr. Meyers says, "is to ensure that adequate safety and effectiveness testing of new drugs has been accomplished before marketing. The Act and the New Drug Regulations essentially prescribe principles which have been recognized by the medical profession for many years governing experimentation on man."

In summing up the FDA position, Dr. Jones says, "We at the FDA feel that radiopharmaceuticals should be handled in the same manner as are other drugs and that the radiation only constitutes an additional hazard. . . . We look forward to the *further notice* in the Federal Register which will remove reactor-produced radiopharmaceuticals from the exemption of the New Drug Regulations."

MERRILL A. BENDER
Roswell Park Memorial Institute