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BY FACSIMILE/CONFIRMATION COPY BY MAIL

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 98D-0785: Revised Draft Guidance for Industry on
Developing Medical Imaging Drugs and Biologics (June 2000)

Dear Sir or Madam:

These comments on Food and Drug Administration's (FDA's) June 19, 2000 revised draft "Guidance for Industry: Developing Medical Imaging Drugs and Biologics" (hereinafter the "Draft Guidance") are submitted jointly by the Committee on Health Care of the Council on Radionuclides and Radiopharmaceuticals (CORAR) and by the Medical Imaging Contrast Agent Association (MICAA). CORAR is an industry association of manufacturers of radiopharmaceuticals, radionuclides, radiochemicals, and other radioactive products primarily used in medicine and life research. MICAA is a trade association of companies involved in the research, development, manufacturing and distribution of medical imaging drug products in the United States.

Preliminarily, both CORAR and MICAA appreciate of the efforts FDA has made to work with the medical imaging drug industry and the medical community to develop this guidance. We are pleased that, in developing the revised draft, FDA has taken into account a number of the comments offered by the two associations on the previous draft of this guidance. Of course, we continue to hold the views expressed in our prior comments that were not adopted by FDA, but those views are not repeated in this submission.

98D-0785

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The comments in this submission are grouped according to the section of the Draft Guidance to which they pertain.

SECTION III. INDICATIONS FOR MEDICAL IMAGING DRUGS

B. Functional, Physiological, or Biochemical Assessment

Page 6: In the discussion of function, physiological, or biochemical assessment indications, the Draft Guidance states that “promotional materials based on this labeled indication should not imply that the product can be used to detect or assess disease or pathology, such as tumor or abscesses.” CORAR and MICAA are deeply concerned that this statement appears to preclude any imaging agent from obtaining a functional, physiological, or biochemical assessment indication for imaging tumors, and that all agents indicated for tumor imaging would necessarily be subject to the requirements applicable to disease or pathology detection or assessment indications under Section IV.D.3 of the Draft Guidance.

Fluorodeoxyglucose F-18 (FDG) provides an example of this problem. FDA has found that the data in the literature support the use of FDG in PET imaging for assessment of “abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnosis of cancer.” See FDA, PET Drug Applications — Content and Format for NDAs and ANDAs, attachment II, Sample Formats – Labeling for Ammonia N 13 Injection, Fludeoxyglucose F 18 Injection [18F] FDG, and Sodium Fluoride F 18 Injection (Draft) (hereinafter “Labeling Guidance”), Mar. 2, 2000, at 18; 65 Fed. Reg. 12999, 13002 (Mar. 10, 2000). FDA developed this broad indication despite the fact that the literature FDA reviewed did not study this agent in all types of tumors. The use of FDG described by FDA in the proposed labeling would appear to meet the definition in the Draft Guidance of a functional, physiological, or biochemical assessment indication. The agent is “used to detect either a reduction or magnification of a normal functional, physiological, or biochemical process” – glucose metabolism. Draft Guidance at 5. It is used where disturbance of this process is “common to several diseases or conditions and [the agent is] not diagnostic for any particular disease or condition.” Id. However, under the Guidance, it appears that the indication proposed by FDA could not be a functional, physiological, or biochemical assessment indication because it contains a reference to tumors generally.

CORAR and MICAA request clarification on whether FDA intends to preclude FDG and all other radiopharmaceutical and other imaging agents intended to image tumors from pursuing a functional, physiological, or biochemical assessment indication. If so, CORAR and MICAA would strongly object to such an interpretation. Section 122(a)(2) of the Food

and Drug Administration set forth a special rule under which the indications for radiopharmaceuticals may, in appropriate cases, refer to manifestations (such as biochemical, physiological, anatomic, or pathological processes) of disease common to one or more disease states. The legislative history of that provision explained that “radiopharmaceutical diagnostic and monitoring agents may, under appropriate circumstances, be approved for use on the basis of their effectiveness in showing how a disease or process has developed, is developing, or is progressing.” S. Rep. No. 43, 105th Cong., 1st Sess. (1997) at 39. FDA’s implementing regulation specifies that, “where a diagnostic radiopharmaceutical is not intended to provide disease-specific information, the proposed indications for use may refer to a biochemical, physiological, anatomical or pathological process or to more than one disease or condition.” 21 C.F.R. § 315.4(b).

Under all of these authorities, an agent like FDG that is used in the diagnosis of tumors generally because of its effectiveness in imaging abnormal processes common to many tumor types, and that is not claimed to detect or diagnose a specific type of tumor, should be permitted to pursue a functional, physiological, or biochemical assessment indication. We do not believe there is any logic supporting the preclusion of any reference to tumors generally from such an indication, particularly in cases where the measurement involves mechanisms that also occur in non-tumor tissue (such as FDG and glycolysis).

Note that FDA also considers FDG approvable in PET imaging “in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function.” Labeling Guidance at 18. This indication clearly falls within the Draft Guidance’s description of a functional, physiological, or biochemical assessment indication. It would be inconsistent for FDA to permit a functional, physiological, or biochemical assessment indication for FDG relating to the heart but not relating to tumors, where the drug functions in the same way for both pathological groups.

SECTION IV. DEMONSTRATING EFFICACY FOR MEDICAL IMAGING AGENTS

A. Clinical Usefulness

Page 9: The Draft Guidance explains that, where knowledge about a variable under study provides for an established clinical benefit, clinical usefulness can be documented by a “critical and thorough analysis of the medical literature and any historical precedents.” CORAR and MICAA request FDA to further clarify the degree and types of literature analysis that would be acceptable.

C. Defined Clinical Setting

The Draft Guidance states that “[a] defined clinical setting should reflect the circumstances and conditions under which the medical imaging agent is intended to be used. . . . In some cases, an appropriately designed trial may be able to include several clinical settings.” Draft Guidance at 11. In a subsequent discussion of disease or pathology detection or assessment indications, the Draft Guidance states that “pooling of efficacy data across defined clinical settings may be of limited value, and the medical imaging agent should be separately evaluated in sufficient numbers of patients in one or more settings.” *Id.* at 16. We believe that the Guidance should provide more clarity on what constitutes a defined clinical setting, and when data relating to different clinical settings may be pooled.

As an illustration, the Draft Guidance explains that “pooling of efficacy data obtained with a medical imaging agent from patients being evaluated for early, localized malignancy (one clinical setting) with data from patients with advanced metastatic malignancy (another clinical setting) may be of limited value because the diagnostic performance of the agent may differ in these settings.” *Id.* at 16. In this example, it is unclear what criteria should separate the clinical setting of localized malignancy from the clinical setting of advanced metastatic malignancy. Conceivably, one could distinguish clinical settings based on the number of metastases – e.g., 0 in the former setting and >2 in the latter; 1 in the former and >5 in the latter, etc. However, these criteria would be arbitrary in the case of an agent that behaves similarly regardless of the number of metastases. There would be little reason to conduct separate tests on separate subject populations for such arbitrarily determined clinical settings, or to discourage pooling of data.

FDA appeared to follow a pooling approach in its treatment of FDG. FDA apparently pooled the data from 16 studies reported in the literature on the use of FDG in breast, non-small cell lung, liver, thyroid, pancreatic, colorectal, and other types of cancer, and developed from these data a broad indication for the assessment of “abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with existing diagnosis of cancer.” See 65 Fed. Reg. at 13002, FDA, Labeling Guidance at 18. It is uncertain whether FDA considered each of these studies to be a defined clinical setting and all of the patients within each study to be within a single defined clinical setting. If so, it appears that FDA considered that the data from these settings could be pooled to establish a broad indication covering all of the settings and additional ones (e.g., additional types of cancer). We would like clarification whether this was the case.

The suggestion at page 16 of the Draft Guidance (cited above) that patients with different types of cancer, and even patients at different stages of one type of cancer, constitute separate clinical settings, and that data ordinarily should not be pooled across settings, appears inconsistent with FDA's approach to FDG. Although the Draft Guidance briefly states that, "in some cases an appropriately designed trial may be able to include several clinical settings" (p. 11), CORAR and MICAA urge FDA to provide further guidance on when studies can include several clinical settings, what kinds of criteria separate one clinical setting from another, and when data can appropriately be pooled – particularly for cancer diagnostics. CORAR and MICAA strongly urge FDA not to apply the defined clinical setting principle in a manner that will unnecessarily increase the numbers of studies required for approval and thus delay the availability of new cancer diagnostics to patients and physicians.

SECTION V. GENERAL CONSIDERATIONS IN THE CLINICAL
EVALUATION OF MEDICAL IMAGING AGENTS

A. Phase 1 Studies

Page 18: This section of the Draft Guidance provides that "[p]harmacokinetic evaluations should address the absorption, distribution, metabolism, and excretion of all components of the formulation and any metabolites." (Emphasis added.) CORAR and MICAA believe that for ingredients that are generally recognized as safe, it is sufficient to identify them as such and that no further pharmacokinetic data are necessary. We recommend that FDA include a clarifying statement to this effect in the relevant paragraph.

B. Phase 2 Studies

Page 19: We recommend adding the following sentence at the end of the third paragraph under this section: "Patient preparation conditions -- for example, hydration, thyroid blocking, and the use of laxatives to clear the bowel -- should be clearly defined in the protocol."

SECTION VI. ADDITIONAL CONSIDERATIONS IN THE CLINICAL
EVALUATION OF EFFICACY

A. Selecting Subjects

Page 21: The Draft Guidance states that the pretest odds and probabilities of disease should be estimated for all subjects before any trial results are available, and the estimated

pretest odds and probabilities should be compared with the pretest odds and probabilities actually observed in the studies. CORAR and MICAA request FDA to describe acceptable methods and provide examples of the use and presentation of pretest odds. With regard to pretest probability, we request guidance on how this data may be presented, quantitated, and used in the labeling, and whether the entire range of pretest probabilities must be included in every pivotal study.

B. Imaging Conditions and Image Evaluations

Pages 25-26: The bullet-point list of information to be included in the case report form includes technical characteristics and technical performance of the imaging equipment. This information should be maintained at the investigation site, but it is unnecessary to include it in the case report form. In addition, the bullet-point list should be revised to add “the actual administered dose (in the case of a radiopharmaceutical, as measured by a radionuclide dose calibrator),” and “adverse events.”

Page 26-29: The Draft Guidance provides that image evaluations for the demonstration of efficacy generally should be fully blinded or blinded to outcome, and that these two kinds of evaluations can be performed through sequential unblinding. The Draft Guidance explains that “sequential unblinding might be used to provide incremental information under a variety of conditions that may occur in routine clinical practice (e.g., when no clinical information is available, when limited clinical information is available, and when a substantial amount of information is available).” Draft Guidance at 28. CORAR and MICAA assume from this discussion that the results obtained from all phases of the sequential unblinding (e.g., fully blinded, blinded to outcome, and other types of evaluations) may be communicated in the product labeling, since it is apparent that, where sponsors have obtained performance data corresponding to varying degrees of clinical information that physicians might encounter, this information would be valuable to physicians. We request FDA to make explicit in section VI.B.7 that the product labeling may include the results from fully blinded evaluations, evaluations blinded to outcome, and other types of evaluation where additional clinical information is provided to readers.

Page 31: In the discussion concerning assessment of inter-reader and intra-reader variability, FDA should clarify how this data will be handled for different blinded readers and discuss methods to perform inter- and intra-reader assessments. Diagnostic confidence should also be considered in this section.

Page 32: In section VI.B.11.a, the Draft Guidance encourages sponsors to incorporate analyses into the statistical analysis plan that are based on the intention-to-treat principle, but that are adapted to a diagnostic setting – e.g., “intention-to image” or

“intention-to-diagnose.” We request FDA to provide examples of the application of the intention-to-image and intention-to-diagnose principles.

SECTION IX. NONCLINICAL SAFETY ASSESSMENTS

B. Nonclinical Safety Assessments for Drug Products

Page 45: In the final paragraph of section B.2., the special safety considerations for diagnostic radiopharmaceuticals should include an analysis of particle size (for products containing particles) and an assessment of instability reflected in aggregation or precipitation.

Page 47: The Draft Guidance states that immunotoxicity studies should be completed before Phase 2. CORAR and MICAA assume that this requirement applies only to biologicals. This should be clarified in the guidance.

With regard to biologicals, comprehensive immunotoxicity testing is time consuming and expensive, and the corresponding benefit is minimal in certain cases. The bullet point relating to immunotoxicity testing should be revised to state:

- Immunotoxicity testing (for biologicals), if warranted. Immunotoxicity testing prior to phase 2 is necessary if evidence of a potentially clinically significant immunomodulatory effect has been noted in the previous nonclinical studies, or if the nonclinical profile of the imaging agent is consistent with generally accepted criteria for immunotoxicity testing.

Page 47: The Draft Guidance states that drug interaction studies should be completed no later than the end of phase 3. For contrast agents intended to be given in single administration, drug interaction studies should be required only when there is evidence to suggest that such an interaction is likely. In addition, drug interaction studies may not always be appropriate if the mechanism of action of a contrast agent is physical rather than biochemical. In order to be consistent with existing guidances of the Clinical Pharmacology Section of the Medical Policy Coordinating Committee of CDER, the “Drug interaction studies” bullet point should be revised to state, “Drug metabolism/drug interaction studies, if warranted.”

SECTION X. CLINICAL SAFETY ASSESSMENTS

A. Group 1 Medical Imaging Agents

Page 48: Section X.A of the Draft Guidance provides that a medical imaging agent can be classified as a Group 1 agent if, among other things, it “is not a diagnostic radiopharmaceutical containing a radionuclide that emits alpha or beta particles.” A footnote explains that this statement does not apply to pure positron emitting radiopharmaceuticals. Virtually all diagnostic radionuclides, including Tc-99m, Tl-201, Ga-67, I-123, have some degree of beta particle emission. See, e.g., G. Mariani et al., J. Nuc. Med., 2000, 41, 1519. Accordingly, this exclusion from Group 1 status should be deleted.

Page 50: The Draft Guidance provides that, in order for a medical imaging drug to obtain Group 1 designation based on safety margin criteria, the NOAEL in expanded-acute, single-dose toxicity studies in suitable animal species should be at least 100 times greater than the maximal dose and dosage to be used in human studies. Standard acute studies are sometimes conducted early in development, instead of expanded acute studies, to efficiently screen preclinical development candidates or to meet foreign regulatory criteria. The Draft Guidance recognizes that non-expanded single-dose toxicity studies may be sufficient if short-term repeated-dose toxicity studies have been completed. See Draft Guidance at 46. In such cases, Group 1 designation should be possible based on a 100x safety margin in the non-expanded single-dose toxicity studies, instead of an expanded acute study, provided that the safety margins specified in the Guidance have been achieved in safety pharmacology and short-term, repeated-dose toxicity studies.

Page 50: The Draft Guidance states that, to establish the safety margins required for Group 1 designation, the NOAELs should be “appropriately adjusted.” This term is defined to mean that dosage comparisons between animals and humans should be modified for factors such as body size (e.g., body surface area) and possible pharmacokinetic and toxicokinetic differences between animals and humans. The guidance does not explicitly recognize body mass (mg/kg, mmol/kg, etc.) as an appropriate basis for comparison. However, the information available for most contrast image agents suggests that comparison based on mass is appropriate. For a given modality, diagnostic doses tend to be similar across compounds and species. Most agents distribute into the extracellular and vascular spaces, with elimination generally by physical processes (usually glomerular filtration), which are dependent upon blood supply (usually renal). Since physiological volumes tend to allometrically scale across species according to body weight ($\sim aW^{1.0}$), comparison based on body weight mass, using standard interspecies scaling approaches, is justified. Accordingly, in the definition of “appropriately adjusted” on page 50 of the Draft

Guidance, the words "or body mass" should be added following "body size (e.g., body surface area)."

Page 51: The Draft Guidance contains a new section that addresses situations where the formulation used in nonclinical safety studies is different from that intended for marketing. This section appropriately recognizes that optimization of the formulation may occur after some pharmacology and toxicology studies have already been completed. CORAR and MICAA request that FDA provide guidelines in this section for determining when bridging pharmacology/toxicology studies should be conducted, as well as basic criteria for acceptable bridging studies.

C. Radiation Safety Assessment for All Diagnostic Radiopharmaceuticals

Page 53: The first paragraph of Section X.C. states that "[t]he radiation doses of diagnostic radiopharmaceuticals should be kept as low as reasonably achievable (ALARA)." ALARA is an well established principle applied in the radiation protection field for workers handling radioactivity. However, it has no relevance to the medical use of radiation. The ALARA principle is based on the premise that radiation workers receive no benefit from exposure, so the risk of exposure should be minimized to the greatest extent reasonably achievable. This is not the case in nuclear medicine, where the patient receives a benefit that counterbalances the risk. If ALARA were truly applied in nuclear medicine, the patient should never receive any radioactivity, since this is reasonably achievable.

A more reasonable approach to radiation dosimetry is to adjust the dose of a diagnostic radiopharmaceutical to maximize the benefit-to-risk ratio. Indeed, this is the approach proposed by FDA in the first sentence of section X.C.3 (page 55). This ratio will vary not only on the severity of the patient's disease but also on the patient's age and other risk factors. Because ALARA is inappropriate in the context of nuclear medicine, the above-cited sentence should be deleted from the Draft Guidance.

Page 54: The concluding sentence of section X.C.1 states that safety hazards for patients and health care workers during and after the administration "of the radiolabeled antibody" should be identified, evaluated, and managed appropriately. The word "the" should be changed to "a," since many diagnostic radiopharmaceuticals will not contain a radiolabeled antibody.

Page 54: Section C.1.2.d of the guidance states that the calculation of radiation dose should include "[t]he radiation dose from the radionuclide, including the free radionuclide and any daughter products generated by decay of the radionuclide." Radiocontaminants other than decay products should also be taken into account. Accordingly, we suggest that this item be revised to state, "The radiation dose from the radionuclide, including the free

radionuclide, any daughter products generated by decay of the radionuclide, and any radiocontaminants.”

Page 55: Section X.C.3.f states that the calculations of dose estimates should “include the radiation exposure contributed by other diagnostic procedures such as roentgenograms or nuclear medicine scans that are part of the study.” Such sources of radiation exposure are not relevant to the radiopharmaceutical under study since they do not result from the radiopharmaceutical. Moreover, it is impractical for a sponsor to take into account the exposure from other diagnostic procedures, since these will vary from institution to institution depending on the equipment and the use thereof. Accordingly, this item should be deleted from the list of requirements for dose estimate calculations.

* * *

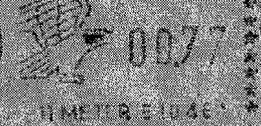
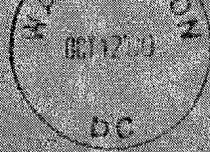
CORAR and MICAA appreciate this opportunity to comment on the revised Draft Guidance. Representatives of both associations would be available at any time to answer any questions concerning the above comments.

Sincerely,



Alan M. Kirschenbaum
Counsel to the Council on Radionuclides
and Radiopharmaceuticals and
The Medical Imaging Contrast Agent
Association

AMK/dmb
Attachment



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