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

Re: Docket No. 1998D-0785: Guidance for Industry: Developing  
Medical Imaging Drug and Biological Products (June 2004)

Dear Sir or Madam:

These comments on the Food and Drug Administration's (FDA's) June 2004 "Guidance for Industry: Developing Medical Imaging Drug and Biological Products" (hereinafter the "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.

The comments in this submission are grouped according to the pertinent part of the three-part Guidance.

98D-0785

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I. PART 1 – CONDUCTING SAFETY ASSESSMENTS

A. Safety Assessments For Contrast Agents (page 4, lines 132-36)

In the section on medical imaging agent characteristics relating to safety, the Guidance contains the following text, which did not appear in any of the draft versions of the Guidance:<sup>1</sup>

In general, nonradiolabeled contrast agents pose safety issues similar to therapeutic drugs because of the inherently large amounts needed for administration. Therefore nonradiolabeled drugs generally should be treated like therapeutic agents for the purpose of conducting clinical safety assessments.

These statements would effectively preclude Group 1 status for contrast agents, since therapeutic agents, of course, are not eligible for Group 1 status. This interpretation appears to be confirmed in Section IV(A), which describes the criteria for Group 1 designation. While the discussion of the criteria for Group 1 in the 2003 draft guidance referred to the “dose” or the “dose and dosage” of the medical imaging agent,<sup>2</sup> the final Guidance has substituted in each instance the term “mass dose” – a term that, under the definition in the Glossary, applies exclusively to radiopharmaceuticals.<sup>3</sup>

While the Group 1/Group 2 mechanism was intended, in part, to implement FDA’s regulation on in vivo radiopharmaceuticals used for diagnosis or monitoring,<sup>4</sup> FDA staff clearly indicated at the 1999 public meetings on the Guidance that the Group 1/Group 2 designation procedure would extend, not only to radiopharmaceuticals, but also to contrast agents. Consistent with these discussions, the 2003 draft guidance contained nothing that barred contrast agents as a class from obtaining Group 1 status.

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<sup>1</sup> See, e.g., FDA, “Guidance for Industry: Medical Imaging Drug and Biological Products” (May 2003) (Draft).

<sup>2</sup> Id. (Part 1) at 11 (lines 367, 374, and note 19); 12 (lines 379, 385, and 393), 13 (lines 427 and 430); and 14 (line 460).

<sup>3</sup> Guidance (Part 1) at 11 (line 388 and note 18); 12 (lines 395, 401, and 412); 13 (lines 446, 450, and 452); and 14 (line 487).

<sup>4</sup> 21 C.F.R. §§ 315.6(c)(2) and 601.35(c)(2).

CORAR and MICAA strenuously object to FDA's exclusion of contrast agents from eligibility for Group 1 designation. In the first place, it is not necessarily true that contrast agents are administered in "inherently large amounts." For example, ultrasound contrast agents are administered in quantities of 1 to 10 mL. Moreover, while it would be difficult in many cases for a contrast agent to meet the safety margin test for Group 1 status, certain contrast agents may be able to demonstrate eligibility based on extensive prior use without an identified safety issue. Contrast agents share with radiopharmaceuticals some of the safety characteristics that permit a more focused safety evaluation – for example, they are typically used in a single dose, and generally have limited adverse pharmacological effect and are cleared rapidly from the body as compared with therapeutic drugs. We see no reason (nor does the Guidance explain) why contrast agents should be excluded a priori as a class from the Group 1/Group 2 designation procedure.

B. Demonstrating Group 1 Status Through Literature (page 14, lines 490-92)

In the section of the Guidance that discusses how Group 1 status may be demonstrated based on prior clinical use without a safety signal, FDA has added a new statement that "[l]iterature may be of limited value in establishing the clinical safety of a drug because most published studies focus on efficacy, with little or no description of any safety assessments."

We believe that this statement unduly discourages the use of literature in providing evidence of safety in prior clinical use. Some articles reporting on clinical studies may contain an adequate description of the safety assessments used in the trial. Moreover, in certain cases a compound that has been marketed by another sponsor, either as a ligand in a radiopharmaceutical or as a therapeutic drug, is proposed by a new sponsor for use with a new radionuclide for diagnostic purposes.<sup>5</sup> In such cases, there may be reports in the literature analyzing the post-marketing adverse event data for the marketed compound, which would be relevant to the clinical use criteria for Group 1.

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<sup>5</sup> At the public meeting on January 25, 1999, FDA staff recognized that, with respect to radiopharmaceuticals, Group 1 status could be based on a history of prior clinical use, not necessarily of the radiopharmaceutical itself, but of a therapeutic compound that is a pharmacophore or is used as a ligand. See Transcript, Open Meeting With CORAR on FDA's Draft "Guidance For Industry: Developing Medical Imaging Drugs and Biologicals," Jan. 25, 1999, at 48-49.

We request that the above language be deleted, or revised along the following lines: “Published literature may be of value in establishing the clinical safety of a drug where the description of safety assessments is adequate or when the article otherwise provides data pertinent to the safety profile of the agent under investigation.”

C. Waiver of Nonclinical Safety Assessments (page 5, lines 179-81)

The Guidance states that, “[i]f you determine that nonclinical pharmacology or toxicology studies are not needed, we are prepared to grant a waiver under 21 CFR 312.10 if you provide adequate justification.” If the Agency has any information about particular circumstances in which such waivers might be granted (beyond the general requirements in section 312.10), we request that such information be added to the Guidance.

D. Switch from Group 1 to Group 2 (page 13, lines 464-67)

The Guidance provides that, if adverse events occur at any time during human studies of a Group 1 agent, FDA will conduct a risk assessment to determine whether the agent should be redesignated as Group 2. The Guidance also describes the factors that will be examined in such an assessment. We anticipate that the sponsor will often have information that is pertinent to such an assessment. Accordingly, the Guidance should provide that FDA will notify a sponsor when the Agency is conducting such an assessment, and provide the sponsor with an opportunity (for example, through a meeting) to offer input before a decision whether to redesignate is made.

E. Reduced Safety Monitoring for Group 1 Drugs (page 10, lines 334-36)

The Guidance recommends “that standard clinical safety evaluations be performed in all clinical investigations of medical imaging agents, but we suggest that, for Group 1 agents, reduced human safety monitoring may be appropriate in subsequent human trials.” The reference to “all clinical investigations,” and then to “subsequent” human trials appears to be a drafting error. We believe “subsequent human trials” was intended to refer to human trials subsequent to the Group 1 designation. If so, this should be clarified.

F. Timing of Non-Clinical Studies (page 7)

The text of footnote (c) appears below the table on page 7, but the corresponding footnote is missing in the table.

## II. PART 2 – CLINICAL INDICATIONS

### A. Clinical Usefulness (pages 12-14)

The final Guidance contains confusing and potentially conflicting statements concerning whether drugs intended for structure delineation or disease or pathology detection, and some drugs intended for functional, physiological, or biochemical assessment, require a showing of clinical usefulness in addition to accuracy and safety. On one hand, the Guidance states that a test for structure delineation and disease or pathology detection is “of well-established value,” as are many functional, physiological, or biochemical assessments (e.g., ejection fraction, renal function, myocardial wall motion).<sup>6</sup> These statements strongly suggest that the sponsor need not re-demonstrate such value. The Guidance also provides that a test that delineates normal structures, or distinguishes between normal and abnormal anatomy, can “*speak for itself* with respect to the clinical value and will not require additional information substantiating clinical usefulness.”<sup>7</sup> Again, this appears to be a clear statement that such a product need not demonstrate clinical usefulness. Similar statements in other Parts of the Guidance appear to support this notion.<sup>8</sup>

On the other hand, the clinical usefulness section of the Guidance does not exclude these types of claims from the requirement of at least a literature justification. That section explains that clinical usefulness can generally be established through direct demonstration in clinical studies and/or by reference to historical data. “[W]hen the measure is well established as useful in the medical literature, the clinical benefit does not need be re-established.”<sup>9</sup> However, the Guidance goes on to explain that, even where the clinical benefit of a drug for early disease detection can be inferred because treatment is available, clinical usefulness is to be documented by a critical and thorough analysis of the medical literature and historical precedents.<sup>10</sup> One possible interpretation of this paragraph, read in

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<sup>6</sup> Guidance (Part 2) at 10, lines 345-53.

<sup>7</sup> Final Guidance (Part 2) at 6, lines 148-50 (emphasis in the original).

<sup>8</sup> See, e.g., Guidance (Part 2) at 11, lines 423-25 (“If the comparator test is well established as clinically useful (such as ejection fraction), we think it could be sufficient to demonstrate the value of the new test.”).

<sup>9</sup> Guidance (Part 2) at 13, lines 445-58.

<sup>10</sup> Guidance (Part 2) at 13, lines 452-58.

its entirety, is that, even for a drug intended for structure delineation (which should “speak for itself” with respect to clinical value<sup>11</sup>), or a drug intended for disease detection (which is of “well-established value”<sup>12</sup>), or a functional assessment where there are established methods of seeking similar information (for which “the clinical usefulness of the indication need not be reestablished”<sup>13</sup>), the sponsor is required to provide a critical and thorough analysis of the medical literature.

If this is FDA’s intent, CORAR and MICAA fail to see the justification for this requirement. An agent that assists in the early detection of colon polyps, breast cancer, Alzheimer’s disease, or any other disease that benefits from early treatment is of self-evident clinical usefulness. Similarly, an agent that images and measures ejection fraction should no longer require a critical and thorough literature analysis of why this is clinically useful. We understand that the law requires sponsors to demonstrate that an agent’s benefits justify the risks.<sup>14</sup> However, this requirement does not prevent the benefits from being presumed when they have been well-established in the past. FDA should not require sponsors to expend time and resources to prove the obvious, either through literature analysis or clinical studies.

B. Structure Delineation Indication (page 6, lines 182-84)

The Guidance states that an agent’s ability to outline abnormal anatomy may also be supportive of a disease detection indication in a specific population. “If the sponsor can demonstrate that use of the agent provides clinical benefit in this population, a disease detection indication might be appropriate.” CORAR and MICAA request clarification on what level of clinical benefit would be necessary to “convert” a structural indication to a disease detection indication.

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<sup>11</sup> Guidance (Part 2) at 6, lines 148-50.

<sup>12</sup> Guidance (Part 2) at 10, line 346.

<sup>13</sup> See Guidance (Part 2) at 10, line 349-50.

<sup>14</sup> Guidance (Part 2) at 12, lines 417-19.

III. DESIGN, ANALYSIS, AND INTERPRETATION OF CLINICAL STUDIES

A. Use of Comparator (page 24, lines 866-71)

The Guidance recommends that, if a test agent is being developed as an advance over an approved drug, a direct, concurrent comparison to the approved comparator should be performed, typically in the same patient, and that a truth standard should also be used. There may be instances in which the use by a single patient of both a radiopharmaceutical test agent and a comparator radiopharmaceutical would result in an unacceptable radiation exposure, particularly where the truth standard is also a nuclear medicine test. In such instances, FDA should permit the sponsor to use study designs that would still compare the study drug to a comparator, but would not require subjects to receive both the test drug and the comparator.

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CORAR and MICAA appreciate this opportunity to comment on the new Guidance.

Respectfully submitted,



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AMK/vam

cc: George Q. Mills