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2001 '03 JUN 19 P2:18

June 18, 2003

BY FEDERAL EXPRESS

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Re: Docket No. 98D-0785: Revised Draft Guidance for Industry on Developing Medical Imaging Drugs and Biologics (May 2003)

Dear Sir or Madam:

These comments on Food and Drug Administration's (FDA's) May 2003 draft "Guidance for Industry: Developing Medical Imaging Drugs and Biologics" (hereinafter the "Draft Guidance") are submitted jointly by the Committee on Health Care of the Council on Radionuclides and Radiopharmaceuticals (CORAR) and by the Medical Imaging Contrast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.

The comments in this submission are grouped according to the part and section of the Draft Guidance to which they pertain.

98D-0785 C25

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I. PART 1

A. Non-Clinical Studies

1. Repeat dose toxicity studies for contrast agents (page 6, lines 195-196)

FDA's former draft of this guidance, which was issued in June 2000, provided that, for contrast agents, "long-term, repeat-dose toxicity studies in animals usually can be eliminated."[1] The new draft contains the same statement, but adds parenthetically that products with a long residence time (e.g., > 90 days) are an exception. This exception should be revised. A residence time of greater than 90 days does not necessarily require long-term, repeat dose studies, because the total exposure associated with a single-dose, even if it has a long residence time, is typically much less than that associated with repeated doses. We recommend that the above-cited sentence be amended as follows:

- Long-term (i.e., greater than 3 months), repeat-dose toxicity studies in animals usually can be omitted. If the medical imaging drug has a long residence time (e.g., > 90 days), we recommend that the sponsor consult with the review division on whether repeat dose toxicity studies can be omitted.

2. Rodent carcinogenicity studies for contrast agents (page 6, lines 198-99)

Like the June 2000 Draft Guidance,[2] the new draft provides that long-term rodent carcinogenicity studies usually can be omitted for contrast agents. However, the new draft adds a recommendation that the sponsor submit a waiver request. Because contrast agents are not used chronically, long-term carcinogenicity studies will rarely be appropriate. However, MICAA does not object to the recommendation to submit a waiver request, provided that FDA provides timely responses to such requests. An untimely response by FDA to a waiver request could make it difficult for a sponsor to plan and implement its nonclinical testing program on schedule. Accordingly, we suggest that the provision identified above be amended as follows:

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1 FDA, Guidance for Industry: Developing Medical Imaging Drugs and Biological Products [Draft], June 2000 (hereinafter "June 2000 Draft Guidance"), at 44.

2 June 2000 Draft Guidance at 44.

- Long-term rodent carcinogenicity studies usually can be omitted. We recommend that a justified waiver request be submitted. FDA will respond to a waiver request within 60 days of its receipt.

3. Expanded acute single-dose toxicity studies for non-biologicals (page 7)

Like the June 2000 Draft Guidance, the new Draft Guidance recommends that expanded acute single-dose studies be performed before Phase 1. The June 2000 draft additionally provided that, if short-term repeated-dose studies have already been completed, non-expanded, single-dose studies may be sufficient.[3] The latter statement reflects a recognition that, in this situation, expanded acute single-dose studies are redundant in light of the short-term repeat-dose studies. However, this statement has (perhaps inadvertently) been omitted from the new draft. We recommend that it be included in the current draft.

B. Clinical Safety Assessments

1. Duration of clinical monitoring for Group 2 drugs (page 11, lines 344-46)

With respect to Group 2 medical imaging drugs, the Draft Guidance recommends that "the duration of clinical monitoring be sufficient to identify possible effects that may lag behind those predicted by pharmacokinetic analyses." Since the former effects are, by definition, unpredicted, it is unclear how a sponsor should determine an appropriate duration for clinical monitoring. CORAR and MICAA request FDA's guidance on this point.

2. Adverse events causing switch to Group 2 (page 13, lines 443-48)

The Draft Guidance states that, for a Group 1 medical imaging drug,

> [i]dentification of any adverse event during initial human use could be considered significant, particularly if those adverse events were not predicted from the effects observed in animals. If adverse events occur at any time during human studies, we recommend that the medical imaging agent be reconsidered as a Group 2 medical imaging agent.

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[3] June 2000 Draft Guidance at 46.

This statement suggests that any adverse events associated with a Group 1 drug will result in redesignation as Group 2. This statement is overbroad. Adverse events occur in virtually every clinical trial – even in the placebo group of a placebo-controlled trial. If FDA's statement is taken literally, every Group 1 drug will be redesignated as Group 2. Moreover, many adverse events – e.g., an unpleasant taste in the mouth or a mild headache – may have no clinical significance and do not warrant an increase in the level of safety monitoring that would result from a switch to Group 2.

Simply put, the above statement would effectively eliminate Group 1. We recommend that a change from Group 1 to Group 2 be considered when there is a significant number of adverse events that are reportable under 21 C.F.R. § 312.32 – i.e., that are serious and unexpected and associated with the use of the drug. This is a standard that is well established and well understood, and would be adequate to signal that closer safety monitoring is required.

3. Group designation procedure (page 14, lines 471-73)

The Draft Guidance recommends that sponsors seeking a Group 1 designation for a drug should submit a written request for designation to the review division during the pre-clinical phase, phase 1 or phase 2 (Draft Guidance, Part 1, at 14, lines 471-73), and that standard clinical safety evaluations be performed "until FDA notifies you that it considers your drug to be in Group 1." Id. at 10, lines 316-18. However, the Guidance establishes no deadline for FDA to notify sponsors. Absent a deadline, FDA could take an unlimited time to respond to a designation request, during which period the sponsor would have to continue designing and conducting studies using standard safety monitoring. Delayed designations would undermine the utility of the Group 1 classification scheme. Accordingly, we urge FDA to add the following sentence at the end of Section IV.C (page 14, line 473): "Within 60 days after the receipt of the request, the division will issue a letter informing the sponsor whether the drug has been determined to be a Group 1 or a Group 2 medical imaging drug."

II. PART 2

A. Indications

1. Distinction between structural delineation and disease detection claims (page 5, lines 166-68)

The Draft Guidance provides examples of agents that distinguish between normal and abnormal anatomic structure, then states that, "[i]n the preceding examples, the agent's ability to outline abnormal anatomy approaches a disease detection indication . . . . If that is the goal of the clinical use, a disease detection indication should be sought." This discussion threatens to blur the distinction between these two types of claims, and suggests that FDA might consider many structure delineation claims to be disease detection claims. A claim that a drug is effective in distinguishing abnormal structures does not mean that the drug can detect a specific disease. Even if a drug has potential for both uses, the indication is determined by the labeling sought by the sponsor. We recommend that the above discussion be revised as follows:

> In the preceding examples, the agent's ability to outline abnormal anatomy ~~approaches~~ might also support a disease detection indication (Section III.B.). If that is the ~~goal of clinical use~~ use intended by the sponsor, a disease detection indication should be sought.

2. Functional, physiological, or biological assessment in previously-diagnosed patients (page 6, lines 217-220)

The Draft Guidance states that "[t]he indication *functional, biochemical, or biological assessment* is appropriate for patients in whom the diagnosis is already established and when evaluations of functional, physiological, or biochemical aspects of a tissue, organ, or body region would provide new information that has a clinically useful effect on management" (underscoring added). While this statement is true as far as it goes, it might be construed to imply that this type of indication is appropriate only for previously-diagnosed patients. Functional, physiological, or biological assessments are often used in patients who are suspected of having a disease or condition, to assist in arriving at a diagnosis. For example, an assessment of left ventricular function may be useful regardless whether the condition that has caused the abnormality in left ventricular function is known.

At the very least, the statement should be clarified by inserting ", among others," before "patients" in line 217.

3. Studies supporting patient management indications (page 7, lines 243-45)

The Draft Guidance recommends that, to obtain a diagnostic or therapeutic patient management indication, "adequate and well-controlled investigations [should] demonstrate that patient management decisions or outcomes are, in fact, improved by use of the medical imaging agent." CORAR and MICAA request that FDA provide examples of possible designs of studies to demonstrate improved patient management decisions or outcomes.

B. Clinical Usefulness

1. Screening indication (page 5-6, lines 191-93)

The Draft Guidance states that "[a]n indication of detection of disease or pathology in an asymptomatic population (a screening indication) may be appropriate if the sensitivity of the imaging modality is high enough and the rate of false positives is low enough." CORAR and MICAA request that FDA provide examples, factors to consider, or other guidance on how to determine when sensitivity is high enough, and the false positive rate low enough, to support a screening indication.

2. Clinical usefulness for structure delineation and disease detection indications (pages 10-11, Section IV.B)

The clinical trials section (Section IV) of the Draft Guidance begins with a preliminary discussion of clinical usefulness, which explains that

> [i]n some cases, a test that provides accurate information in describing a clinical condition is of well-established value. Generally, this is true for indications for structure delineation and disease or pathology detection or assessment. In many cases, there will be established methods of seeking similar information and the only issue is comparing the accuracy of the new and old method.[4]

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[4] Draft Guidance, Part 2, at 8, lines 299-301.

(Emphasis added.) CORAR and MICAA agree that the clinical usefulness of agents shown to be effective for structure delineation and detection of disease or pathology is generally well-established, and should not have to be established anew by the sponsor.

With respect to disease detection agents, this view was also expressed by FDA in the June 2000 draft, which explained that clinical usefulness of an agent used to detect disease could be inferred where treatment options are available for the disease (e.g., for an agent used for early detection of breast cancer).[5] However, the discussion of clinical usefulness in Section IV.B of the new Draft Guidance appears to impose additional burdens on sponsors seeking approval for such agents. Section IV.B recommends that, even for agents intended for disease detection where treatment is available for the disease, the sponsor must document clinical usefulness "by a critical and thorough analysis of the medical literature and any historical precedents." (Draft Guidance, Part 2, at 10, lines 394-95) We believe that the approach of the June 2000 Draft was correct: neither clinical studies nor a review of the literature or historical precedents is necessary to demonstrate the clinical usefulness of an agent that has been shown to accurately and reliably detect a disease for which treatment is available. The clinical usefulness of such an agent can be inferred. For example, the clinical usefulness of an agent that accurately and reliably detects breast cancer in its early stages is obvious, and a requirement for the sponsor to critically and thoroughly analyze the literature and historical precedents would be an unnecessary burden.

Similarly, with regard to agents for structure delineation, the Draft Guidance correctly explains that "[o]rdinarily, the ability to locate and outline normal structures or distinguish between normal and abnormal anatomy can *speak for itself* with respect to the clinical value of the information and will not require additional information substantiating clinical usefulness."[6] Yet, once again, the discussion of clinical usefulness in section IV.B. appears to generally impose on all medical imaging drugs, without differentiation, the obligation to show clinical usefulness either by direct demonstration in clinical studies or by reference to historical data. See Draft Guidance, Part 2, at 10.

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5 June 2000 Draft Guidance at 9; see also id. at 10 (for a disease detection indication, identification with sufficient validity and reliability of a disease or condition is adequate to demonstrate clinical usefulness if it is reasonable to infer that the test results lead to more appropriate management).

6 Draft Guidance, Part 2, at 4, lines 135-37 (emphasis in the original).

In order to ensure that the clinical usefulness section (IV.B) is interpreted consistently with other portions of the Guidance, the third and fourth paragraphs of Section IV.B should make clear that the recommendations contained therein on how to show clinical usefulness (i.e., through clinical studies or by reference to historical data) generally do not apply to agents with indications for structure delineation and disease or pathology detection or assessment, as explained on pages 4 (lines 135-37) and 8 (lines 300-01) of the Guidance.

In addition, the first sentence of Section IV.B (lines 363-64) could be construed in a manner that is inconsistent with FDA's recommendations concerning clinical usefulness in other parts of the Guidance. That sentence states that "[d]efining clinical usefulness is important for medical imaging agents, even for agents with anticipated low toxicity rates . . . ." While it is true that medical imaging drugs should be clinically useful, clinical usefulness is frequently well-established, as explained elsewhere in the Guidance. The statement could be read to suggest that sponsors of all medical imaging drugs, regardless of indication and toxicity, must demonstrate clinical usefulness. This is contrary to the Guidance's discussions referred to above concerning structure delineation and disease and pathology detection claims. We recommend that this sentence be deleted.

3. "Both aspects of effectiveness" (page 11, line 416)

In explaining how clinical usefulness may be demonstrated for contrast agents, the Draft Guidance provides examples of two approaches to illustrate "how both aspects of effectiveness could be evaluated." However, it is unclear what the two aspects of effectiveness are that are referred to in this sentence. FDA should clarify this.

4. Demonstrating clinical usefulness where comparator is used (page 11, lines 423-25)

In describing one approach to establishing effectiveness and clinical usefulness of a medical imaging drug, the Draft Guidance suggests comparing a new test with an established comparator test, which could be either another test or a truth standard. The Guidance states, "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."

CORAR and MICAA agree with this principle. However, it is uncertain whether the term "well established" in the above-cited sentence would encompass a situation where the clinical usefulness of the comparator test was previously validated by the sponsor of

that test through clinical studies. If a new test is shown to be as effective or more effective than a previously approved comparator test, clinical usefulness of the new test should be inferred regardless whether the clinical usefulness of the comparator test has been well-established in the literature or was demonstrated directly by the sponsor of the comparative test. We recommend that the above sentence be amended as follows:

> If the comparator test has been well established in the literature as clinically useful (such as ejection fraction) or was directly demonstrated to be clinically useful by the sponsor of the comparative test, we think it could be sufficient to demonstrate the value of the new test.

5. Clinical "value" (Sections III and IV, passim)

In discussing clinical usefulness and effectiveness, Part 2 of Draft Guidance refers at various points to the "clinical value", or simply the "value", of a test. See, e.g., page 8, lines 298-314, and page 11, lines 419-43. It is unclear whether this term has a meaning that is different from clinical usefulness. If FDA intends the terms to be synonymous, we suggest that the term "usefulness", which is explained in some detail, be used in place of "value". If "value" is different from "usefulness", FDA should define the meaning of the former.

III. PART 3

1. Timing of completion of statistical analysis plan (page 8, lines 237-39)

The Draft Guidance states that the statistical analysis plan for each principal efficacy study should be part of the study protocol, and should be submitted to the protocol before images have been collected. This recommendation is inconsistent with International Conference on Harmonization E9 Statistical Principles for Clinical Trials, which provides that

> [t]he statistical analysis plan . . . may be written as a separate document to be completed after finalizing the protocol. In this document, a more technical and detailed elaboration of the principal features stated in the protocol may be included . . . . The plan should

> be reviewed and possibly updated as a result of the blind review of the data . . . and should be finalized before breaking the blind.[7]

We recommend that FDA revise its approach so that it is consistent with the ICH guideline. Accordingly, page 8, lines 236-239 of the Draft Guidance should be amended as follows:

> We recommend that sponsors submit a single ~~comprehensive~~ statistical analysis plan for each principal efficacy study. We recommend that ~~this~~ the principal features of the statistical analysis plan be part of the study protocol, ~~include~~ including the plan for the blinded image evaluations ~~and be~~. The statistical analysis plan should be finalized and submitted to the protocol and to the IND before ~~images have been collected~~ breaking the blind. [See Guidance for Industry: E9 Statistical Principles for Clinical Trials, at 27.]

2. Blinded imaging evaluations (pages 11-12, lines 396-99)

The Draft Guidance recommends that

> a *fully blinded image evaluation* or an *image evaluation blinded to outcome* by independent readers serve as the principal image evaluation for demonstration of efficacy. Such image evaluations can be performed through *sequential unblinding.*

(Emphasis in the original.) CORAR and MICAA request clarification that FDA is not recommending that sponsors necessarily use both a fully blinded evaluation and an evaluation blinded to outcome to demonstrate efficacy. As explained in the Guidance (lines 484-88), using both of these kinds of evaluations (i.e., through sequential unblinding) is a useful way of providing information about the use of the drug under conditions similar to those in the clinic. However, there are situations in which sequential unblinding is impractical or extremely burdensome because of the great number of images that need to be read in such a study. Ideally, the two sets of readings – fully blinded and blinded to outcome – are conducted by two different groups of readers, and these two groups should

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[7] FDA, Guidance for Industry: E9 Statistical Principles for Clinical Trials (Sept. 1998), at 27.

both be independent from the investigators. In a large study, it may be difficult to find sufficient numbers of physicians (in addition to the investigators) who have the time, expertise and skills necessary to perform the readings. In addition, the total time required for image readings in a sequential unblinding procedure is doubled in comparison to a fully blinded reading or a reading blinded to outcome. Depending on the size of the study, this may present difficulties in scheduling readings in radiology facilities, where availability is often limited in any event.

In order to make clear that the sponsor may, but is not required to, conduct both fully blinded evaluations and evaluations blinded to outcome, we recommend that the above-cited language be replaced by the following:

> We recommend that a *fully blinded image evaluation* or an *image evaluation blinded to outcome* by independent readers serve as the principal image evaluations for demonstration of efficacy. Alternatively, both types of evaluations may be used. If both types are used, the ~~Such~~ image evaluations can be performed through *sequential unblinding.*

3. Disclosing inclusion and exclusion criteria to blinded readers (page 12, lines 439-41)

In discussing fully blinded image evaluations, the Draft Guidance recommends that, "in some cases," general inclusion and exclusion criteria for patient enrollment not be provided to the readers. CORAR and MICAA request FDA to provide examples of cases in which inclusion and exclusion criteria should not be provided to the readers.

4. Separate image evaluations (page 19, lines 696-716)

Example 1 in the Draft Guidance section on separate image evaluations discusses how separate image evaluations (unpaired and paired) should be performed in a comparative study designed to show that the diagnostic performance of a new medical imaging agent is superior to that of the approved agent and can replace the approved agent. CORAR and MICAA request clarification on whether this discussion would also apply to a study designed to show equivalence (non-inferiority) to the comparator.

5. Comparison to an approved agent (page 23, lines 855-58)

The Draft Guidance recommends that, where a test agent is being compared to an approved drug, "information from both test and comparator images be compared not only to one another but also to an independent truth standard." In our view, the use of an independent truth standard in addition to a comparator is not always appropriate. Some tests that have been used in the past as gold standards have become outmoded and are no longer the standard of care. For example, contrast venography is no longer commonly performed in the U.S., but FDA has nevertheless advocated the use of this procedure as a gold standard for imaging of deep vein thrombosis.

In other instances, the procedure historically used as a gold standard is more invasive than the comparator and therefore exposes investigational subjects to additional risks. An example of this is an x-ray procedure that is used as the gold standard for an investigational MRI contrast agent that is compared to an approved MRI agent. The x-ray procedure not only exposes the patient to radiation but also often involves the insertion of a catheter to deliver the contrast, and the doses of the x-ray contrast are typically higher than those of the MRI contrast agents, exposing the subject to a higher risk of adverse effects. The use of such a gold standard, at best, makes it more difficult to recruit subjects, and, at worst, may be unethical.

While a truth standard is usually appropriate, we advocate an approach to determining the truth standard that is more flexible than that currently reflected in the Draft Guidance. Section IV.D.1 of the Guidance ("Comparison to an Agent or Modality Approved for a Similar Indication") should be amended to recommend that the truth standard be determined taking into account the current standard of practice, patient safety, and the risk versus benefit to the patient. The Guidance should expressly acknowledge that the use of a gold standard may be inappropriate in certain cases – for example, where a previously accepted gold standard is no longer the standard of care, or poses risks greater than those of the comparator agent. In such cases, an appropriate truth standard should be discussed and agreed upon between the sponsor and the division, rather than being rigidly imposed on the sponsor by FDA.

* * *

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

Respectfully submitted,

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and Radiopharmaceuticals and
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June 18, 2003

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 (May 2003)

Dear Sir or Madam:

Please submit the attached comments to docket no. 98D-0785. These comments are intended to replace comments that were filed in the same docket earlier this afternoon by our firm. The only difference between the attached comments and the previous version is the correction of a minor typographical error on the first page.

Thank you.

Sincerely,

Alan M. Kirschenbaum

AMK/vam
Enclosure

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