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January 5, 2009

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

Re: Docket No. FDA-2008-D-0525: Draft Guidance for Industry on New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products

Dear Sir or Madam:

These comments on the Food and Drug Administration's (FDA's) September 30, 2008 draft "Guidance for Industry: New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products" are respectfully submitted on behalf of the Medical Imaging Contrast Agent Association (MICAA). MICAA is a trade association of companies involved in the research, development, manufacturing and distribution of medical imaging drug products in the United States.

As explained below, MICAA generally agrees with the approach adopted by FDA in the Draft Guidance. However, we have several suggestions for clarifications and additions to the document.

I. CONSISTENCY IN CLINICAL DATA REQUIREMENTS

An essential principle reflected throughout the Draft Guidance is that, regardless which type of application is used to establish a new contrast indication (i.e., NDA, BLA, PMA, or 510(k)), which label adds the new indication (i.e., imaging device label or drug label), or which Center takes the lead in review (i.e., CDER or CDRH), the type of scientific information required to substantiate the new indication should be the same. MICAA agrees with this principle. New indication claims that are similar for a device and a contrast agent should be supported by similar data. Relaxing the requirements for demonstrating safety and effectiveness simply because a new contrast indication is sought

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by a device sponsor rather than a drug sponsor would undermine confidence in FDA's premarket approval process, and could result in new contrast imaging procedures with questionable effectiveness, utility, or risk/benefit justification. MICAA also agrees that FDA's Guidance on Developing Medical Imaging Drug and Biological Products sets forth the appropriate considerations for both device and drug sponsors who wish to develop data to support a new contrast indication, and we support the Draft Guidance's recommendations in this regard (see Draft Guidance page 5, lines 41-43; page 12, lines 322-29).

II. CIRCUMSTANCES WHERE CHANGES IN DRUG LABELING ARE NOT REQUIRED

The Draft Guidance would permit the addition of a new contrast indication to the labeling of an imaging device without a corresponding change in the drug label where "the device technology does not alter the drug and when the drug use is otherwise consistent with its approved labeling." Draft Guidance page 9, lines 208-09. The Draft Guidance appears to require that, in order for the new drug use to be "consistent with its approved labeling," (1) the drug must be used at its approved formulation, dose, rate, and route of administration, and (2) the new contrast indication must be "consistent with the drug's approved indication" (see, e.g., Draft Guidance page 9, lines 223-28).

MICAA agrees with the first requirement, since a difference between the device and drug labeling in these essential characteristics and conditions for use would be confusing to practitioners. However, with regard to the second requirement, the Draft Guidance is not sufficiently clear as to what is meant by a device indication that is "consistent with the drug's approved indication." One example provided in the Draft Guidance is that of device software that allows for new quantitative angiographic imaging using an imaging drug already approved generally for angiographic imaging (Draft Guidance page 9, lines 209-14). These two indications are no doubt consistent. However, in a discussion of types of marketing submissions, another example is provided of a new contrast indication for breast cancer screening or diagnosis using an imaging drug that is not approved for imaging that area of the body (see Draft Guidance page 14, lines 410-12). For these widely divergent indications, the Draft Guidance leaves open the possibility that the new device indication is sufficiently "consistent" not to require revision of the drug labeling (Draft Guidance page 14, note 17). Because consistency in indications is described as a key factor in FDA's decision whether to permit a new contrast indication without corresponding changes to the drug labeling, it is important that the Draft Guidance clarify what "consistent indications" means, either by example or otherwise.

III. REVISION OF DRUG LABELING

The Draft Guidance provides that, where a new contrast indication is added to an imaging device, "holders of the already marketed imaging drug or biological product should generally submit an efficacy or labeling supplement, as appropriate, to add labeling for the new indication initially developed under a device application." Draft Guidance page 5, lines 47-50 (emphasis added). The document later states that, "if FDA approves or clears a new contrast indication in a device submission, the NDA/BLA holder may submit a labeling supplement or add the indication to the imaging drug." Draft Guidance page 14, lines 429-31(emphasis added). Yet another statement provides that, if FDA approves or clears a new indication in a device application, differences between the drug labeling and statements about the drug in the new device labeling "should not be understood to permit or require the drug sponsor to change its labeling based on statements in the device labeling." Draft Guidance page 9, note 8 (emphasis added).

These statements are inconsistent with each other and generate uncertainty whether, based on a new indication initially approved for a device, a drug sponsor "should" change its label, "may" change its label, or is even "permitted" to change its label. The basic approach of the Draft Guidance is that, under certain circumstances described in the Guidance, a new contrast indication may be added to a device without requiring revision of the drug labeling. FDA should reconcile the above statements and clarify that, unless FDA has determined that a new contrast indication for a device requires revision of the corresponding drug label, the drug sponsor may, but is not required to, submit a supplement to add the new indication to the drug label.

IV. HOW DRUG LABELING SHOULD BE REVISED

In circumstances where a drug sponsor does seek to revise its label to conform to a new contrast indication that was initially added to the imaging device labeling, the Draft Guidance is not clear what type of submission should be made. The document refers to an "efficacy or labeling supplement, as appropriate" (Draft Guidance page 5, lines 47-50), but provides no guidance on when one or the other would be appropriate. The final Guidance should answer the following questions:

- When would a labeling supplement be sufficient?
- When would an efficacy supplement be required?

- If an efficacy supplement is required, must it contain new studies conducted by the drug sponsor, or is it sufficient to refer to studies already conducted by the device sponsor in support of the latter's new contrast indication? The Guidance should provide that, if an efficacy supplement is required, a section 505(b)(2) supplement would be the appropriate submission. Such a supplement would rely on the studies conducted by the device sponsor to demonstrate safety and effectiveness of the drug for the new indication.

- What changes should be made to the drug labeling – i.e., add the new indication only, or add the device sponsor's clinical study data as well? MICAA believes that the new information in both the device and drug labeling should be consistent in content. Therefore, relevant details from the device sponsor's supporting clinical study and other data should be added to the drug labeling.

V. OFF-LABEL INQUIRIES

Where a new contrast indication is added to the labeling of an imaging device without a conforming change to the drug labeling, practitioners might direct inquiries about the new indication to the drug manufacturer. The Guidance should make clear that the drug manufacturer is permitted to respond to such inquiries as long as they are unsolicited and the inquiries and responses are documented, in accordance with longstanding FDA policy permitting sponsors to respond to unsolicited requests for off-label information.

VI. PHARMACOVIGILENCE OBLIGATIONS

In situations where a new contrast indication is added to the labeling of an imaging device but the labeling of the contrast agent is not revised, the pharmacovigilence obligations of the drug sponsor may be unclear. For example, FDA regulations define an "unexpected adverse drug experience" as "[a]ny adverse drug experience that is not listed in the current labeling for the drug product." 21 C.F.R. § 314.80(a). The new use of the contrast that is described in the device labeling may generate adverse events that are not described in the current drug labeling, even though they might be described in the revised device labeling. If such an adverse event were reported to the drug manufacturer, it is uncertain whether the drug sponsor would be responsible for submitting a 15-day Alert report for serious and unexpected adverse events under 21 C.F.R. sections 314.80(c)(1) and (d). The Guidance should clarify the drug sponsor's obligations in this regard.

VII. DESCRIPTION OF IMAGING DRUG CHARACTERISTICS

In describing characteristics of imaging drugs, the Draft Guidance states that, "[i]n addition to these general properties, these imaging drugs are formulated to interact with the body to facilitate imaging." Draft Guidance page 7, lines 148-49. Because certain imaging drugs have insignificant biochemical interaction with body tissue, MICAA suggests that the phrase "these imaging drugs" be changed to "some imaging drugs".

* * *

MICAA appreciates the opportunity to comment on FDA regulation of combination products.

Sincerely,

Alan Kirschenbaum
Counsel to the Medical Imaging Agent
Contrast Association

Guidance for Industry:
New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit written or electronic comments on the draft guidance by 90-days after publication in the *Federal Register.*

Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*. Submit electronic comments to http://www.regulations.gov.

For questions regarding this draft document contact Patricia Y. Love, MD in the Office of Combination Products (OCP) at 301-437-1934.

U.S. Department of Health and Human Services
Food and Drug Administration

Office of Combination Products (OCP) in Office of Commissioner
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)

September 2008

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry:

New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products

Additional copies are available from:
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U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP) in Office of the Commissioner
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Center for Drug Evaluation and Research (CDER)

September 2008

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Guidance for Industry[1]
New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

FDA intends this guidance to assist developers[2] of medical imaging devices and imaging drug/biological products that provide image contrast enhancement. Particularly this guidance focuses on approaches in developing new contrast indications for imaging devices for use with already approved imaging drug or biological products. FDA intends for the recommendations in this guidance to promote timely and effective review of, and consistent and appropriate regulation and labeling for imaging drugs and devices.

This document supplements existing guidance developed by the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Center for Biological Evaluation and Research (CBER), and the Office of Combination Products (OCP).

This guidance does not address the specific scientific or technical content to provide in a regulatory submission to demonstrate safety and effectiveness of an imaging product(s) for specific indications.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[1] This guidance has been prepared by Office of Combination Products, in the Office of the Commissioner, in conjunction with the Center for Devices and Radiological Health and the Center for Drug Evaluation and Research.

[2] For purposes of this document, the term developer includes manufacturers, sponsors, and other holders of marketing applications for medical imaging device, drug, or biological products.

II. PURPOSE

This document describes a process that allows either the imaging drug or imaging device developers to seek approval of medical imaging contrast indications using an already marketed imaging drug or biological product, including radiopharmaceuticals.

1. Device developers should generally submit a marketing application to add a new indication for using an already approved imaging drug under the circumstances described in this guidance.
   a. The data to establish these indications in a device application should include information developed in accordance with FDA existing guidance on Developing Medical Imaging Drug and Biological Products.[3]
   b. For most types of indications as described in this guidance, when submitted to request marketing under a device application, the submission should be a Premarket Application (PMA).
2. Drug or biological product application holders of the already marketed imaging drug or biological product should generally submit an efficacy or labeling supplement, as appropriate, to add labeling for the new indication initially developed under a device application.
3. Device application holders may continue their current practice to request approval or clearance of labeling revisions for any new indications that may be initially approved in a supplement to the NDA for the imaging drug.
4. FDA expects to establish an internal intercenter imaging process to review and evaluate indications to ensure consistency in the development and review of clinical trials to establish the contrast indications that may be in either the drug or device labeling.

III. TERMINOLOGY

For purposes of this document, the following conventions apply.

- Imaging drug: The term imaging drug applies to drug and biological products including radiopharmaceuticals for use in medical imaging. In this guidance the term imaging drug is synonymous with the term contrast agent.
- Contrast indication: A contrast indication is a statement in the indication or intended use section of the labeling of either an imaging drug or imaging device using an imaging drug or biological product, including radiopharmaceuticals.

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[3] FDA guidance *Developing Imaging Drug and Biological Products, Part 1: Conducting Clinical Safety Assessments)* (Imaging Drug Guidance Part 1), http://www.fda.gov/cder/guidance/5742prt1.pdf ; *Part 2: Clinical Indications* (Imaging Drug Guidance Part 2); http://www.fda.gov/cder/guidance/5742prt2.pdf .; *Part 3: Design, Analysis and Interpretation of Clinical Studies* (Imaging Drug Guidance Part 3), http://www.fda.gov/cder/guidance/5742prt3.pdf

IV. SCOPE

As part of the Medical Device User Fee Amendments of 2007 (MDUFA) Commitment for the Performance Goals and Procedures, FDA agreed to develop guidance for medical imaging devices with "contrast agents or radiopharmaceuticals." Specifically, item I.N of the commitment letter states: "*FDA will, after consultation with affected parties, develop a guidance document intended to ensure timely and effective review of, and consistent and appropriate postmarket regulation and labeling recommendations for, diagnostic imaging devices used with imaging contrast agents and/or radiopharmaceuticals approved for the same or different indications. Draft guidance will be published by the end of FY 2008, and will be subject to a 90-day comment period. FDA will issue a final guidance within one year of the close of the public comment period.*" This document fulfills FDA's commitment to issue draft guidance by the end of FY 2008.

In preparing this document, FDA received stakeholder comments which included comments from sponsors of imaging drug or biological products used for contrast, manufacturers of imaging devices, and trade organizations such as Advamed, MITA, MICAA, and CORAR. These comments generally provided important insights and information that FDA used in developing this guidance. Certain issues raised by commenters, however, are outside the scope of this guidance. In particular, several comments concerned the effect of the drug exclusivity provisions of the Act on approval of contrast indications involving the use of a device and drug or biological product together. Although this guidance does not provide an in-depth discussion of those provisions, we note that these provisions apply to submissions under section 505(c)(3)(E) and 505(j)(5)(F) of the Act and do not authorize the agency to withhold approvals or clearances of applications other than drug applications during the exclusivity period.

Commenters also identified several specific indications for possible guidance development; e.g., myocardial perfusion or breast cancer imaging. Each specific indication would constitute a separate guidance and, thus, is also beyond the scope of this guidance.

V. BACKGROUND

Medical imaging is a rapidly developing area with the potential to provide novel diagnostic information to guide patient management or to facilitate delivery of diagnostic or therapeutic products to previously inaccessible areas of the body. Medical imaging technologies are also keys to several critical path methodologies (e.g., biomarkers, surrogate markers, personalized medical decision making).

Most medical imaging relies solely on device technology such as ultrasound (US), computerized tomography (CT), magnetic resonance imaging (MRI) and traditional radiology (x-ray) techniques. For example, many diagnostic US examinations are performed without administration of an imaging drug to the patient, using only the US device by itself. Some types of imaging technologies and certain technologies used in

119 imaging of specific anatomic areas or tissues of the body rely on the administration of an
120 imaging drug or biological product to enhance the image. For example, CT and MRI
121 examinations may be performed both without and with an imaging drug. In such images,
122 the imaging drug may improve the visualization of tissues, organs, and physiologic
123 processes in part by increasing the relative difference of imaging signal intensities in
124 adjacent regions of the body. Typically, when contrast is used, the images are taken both
125 without and then with the imaging drug to provide contrast. For other imaging
126 technologies such as radiopharmaceutical imaging (SPECT or PET),[4] in order to produce
127 an image it is necessary to simultaneously use the imaging device and the
128 radiopharmaceutical imaging drug (i.e., a useable image can not be produced by the device
129 alone). Medical imaging devices are marketed under the device provisions of the Act.
130 Medical imaging drugs and biological products are marketed under the drug and biological
131 provisions of the Act.
132
133 Most imaging drugs are modality specific and chemically distinct from one another.[5] For
134 example,
135
136 • X-ray and CT imaging drugs are iodine-containing compounds that in part are
137 specifically designed to absorb x-rays;
138 • MRI imaging drugs contain paramagnetic metallic ions, most commonly
139 gadolinium, iron or manganese. These imaging drugs are designed in part to alter
140 the magnetic properties of body tissue;
141 • US imaging drugs typically consist of a gas contained within a lipid or protein shell
142 (i.e., microbubbles or related microparticles). These products are designed in part
143 to reflect sound waves; and,
144 • Radiopharmaceutical imaging drugs contain in part a radionuclide that exhibits
145 spontaneous disintegration of unstable nuclei with the emission of nuclear particles
146 or photons.
147
148 In addition to these general properties, these imaging drugs are formulated to interact with
149 the body to facilitate imaging. For example, some imaging drugs bind to receptors,
150 interact with a metabolic pathway, cross abnormal blood brain barriers, or are engulfed by
151 macrophages.
152
153 FDA existing guidance identifies imaging drug contrast indications in four broad
154 indication areas:[6]
155 1) Structural delineation,
156 2) Disease or pathology detection or assessment,
157 3) Functional, physiological or biochemical assessment, and
158 4) Diagnostic or patient management.
159

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[4] SPECT = single photon emission computerized tomography; PET = positron emission computerized tomography

[5] For purposes of this document, the term imaging drug applies to both drug and biological products including radiopharmaceuticals

[6] Imaging Drug Guidance, Part 2.

When an imaging drug is intended to be used with a legally marketed device, the labeling of the drug typically describes the approved imaging contrast indication(s) with specificity. For example, an imaging drug for disease or pathology detection might be labeled as follows: *Drug [X] is indicated for use in MRI to provide contrast enhancement and facilitate visualization of lesions with [z] abnormality in [specific organ] in patients who have [m] characteristics*. The degree of specificity in the labeling of imaging devices has been less consistent. In some instances, imaging device labeling refers to the approved imaging drug or drug class. In other instances, the labeling identifies the use with an imaging drug but does not refer to the drug class. In still other instances, the use with an imaging drug is implicit in the design of the device software but does not explicitly appear in the labeling.

Imaging device software and hardware engineering technologies that utilize imaging drugs evolve rapidly (i.e., once or twice a year) and typically out-pace development of new imaging drugs or new indications for already approved imaging drugs. Device advancements may create an opportunity for a new indication using an approved imaging drug without any change to its dose, rate, or route of administration. For example, if a drug that is approved for use in imaging the lung is systemically distributed in the body, new device software may allow the drug to be used in imaging the liver. If the drug and device manufacturer do not cooperate to seek approval for the new indication in the drug labeling, the pathway to market for the new device technology may be unclear.

This guidance describes principles under which either a drug or device developer can seek marketing approval of new contrast indications using an already marketed imaging drug. In developing these principles, FDA considered the scientific and technical issues that may occur when using a class of drugs and class of devices together, approaches to leverage prior Agency decisions, approaches to ensure consistency of information regardless of the submission being used to establish new contrast indications, and approaches to ensure the consistency of the regulatory vehicle for submission under the drug, biological, or device provisions being used to establish similar types of contrast indications. FDA intends for these principles to promote:

- The ability of the imaging device applicants to add certain new imaging contrast indications for use of the device with the already approved imaging drugs without having modification of labeling for both the device and the drug;
- Consistency in the type of scientific or technical information submitted to establish a new indication for use regardless of the type of marketing submission; i.e., NDA, BLA, PMA, premarket notification (510(k) submission (to the extent permissible under the different regulatory authorities); and
- Comparability in labeling format and content (to the extent permissible under the different regulatory authorities).

VI. REVIEW PRINCIPLES

FDA believes that, under the appropriate circumstances, the labeling of the imaging device can provide sufficient information about a new contrast indication using an approved imaging drug. This may occur when the device technology does not alter the drug and when the drug use is otherwise consistent with its approved labeling. For example, if the device software allows for new quantitative angiographic imaging using an imaging drug already approved generally for angiographic imaging, when the drug is administered in accordance with the drug's approved labeling, and when the drug labeling does not need revision, the Agency believes that in most instances a device submission alone should suffice.[7] On the other hand, when the new yet consistent contrast indication may cause the drug and device to interact in a manner that affects the safety or effectiveness of the product(s), the drug and device labels should generally align closely.

The Agency notes that individual imaging indications may present unique or complex issues of safety or effectiveness that necessitate a review approach different from the one set forth below. Nonetheless, the agency expects to review most applications for imaging product indications involving a drug and a device under the following guidelines:

1. *When might only an imaging device application suffice?* When an imaging device or device modification enables the device to be used with an approved imaging drug (i.e., at its approved formulation, dose, rate, and route of administration) for a contrast indication that is consistent with the drug's approved indication, in most cases FDA expects to be able to make a review determination based on an original or supplemental submission from the device application holder alone. A favorable decision on the application would allow the imaging device sponsor to add the contrast indication to the device labeling without the need for a conforming change to the imaging drug labeling.[8]

2. *When might only an imaging drug application suffice?* When an imaging drug modification (i.e., formulation, dosage, rate, or route of administration) enables the drug to be used with an approved or cleared imaging device for a new indication, the NDA/BLA holder should submit a supplement to FDA to request approval for such change. For example, an NDA is most appropriate for a drug reformulation to allow enhanced biodistribution to a new area, but using the same imaging software. In most instances, FDA expects to review an NDA submission to add such an indication to the drug labeling without the need for a device submission or conforming labeling to the imaging device.

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[7] During the comment period, industry is welcome to provide other suggestions of what they believe might be a consistent indication

[8] If FDA approves or clears a new indication in a device application, differences (if any) between the drug labeling and statements about the drug in the new device labeling should not be understood to permit or require the drug sponsor to change its labeling based on statements in the device labeling.

3. *When might both an imaging drug and device application be most appropriate?*

   Generally there are two circumstances when both an NDA/BLA and a device application should be provided to request approval of a new indication for using the imaging drug and the imaging device together.

   a. When an imaging device modification also necessitates a change in the imaging drug formulation, dosage, rate, or route of administration for the same imaging indication or for a new indication, FDA will generally need to review both a drug and device submission to ensure labeling conformity. For example, if a change in device design provides for enhanced imaging at lower doses of the drug, to ensure appropriate drug safety, FDA may determine that the drug dosing information should be in both the imaging drug and device labels.

   b. When an imaging drug modification (i.e., formulation, dosage, rate, or route of administration) also necessitates a change in the approved imaging device performance characteristics, specifications, or design for its labeled imaging indication or for a new indication for use, FDA will generally need to review both a drug and a device submission to request approval for the new indication and labeling changes.

Regardless of which label (imaging device, drug or biological product) adds the new contrast indication, the safety and effectiveness of the new contrast indication should be established by data collected from appropriately designed clinical trials using both the drug and the device. The regulatory pathway does not affect the scientific and technical information that is most appropriate for establishing the safety and effectiveness of the new contrast indication. (For additional information please see section VII.B, *Considerations for Data Necessary to Support a New Contrast Indication for Use*). Further, the labeling of product(s) adding the new indications should reflect the essential information that establishes the contrast indication (e.g., the clinical study description, imaging device characteristics and settings, imaging drug dosing regimen, target organ).

VII. PREMARKET DEVELOPMENT CONSIDERATIONS

A. Determinations of Lead Center Responsible for Premarket Review

Most imaging devices and drugs approved for use with a class of drugs or class of devices do not meet the definition of a combination product under 21 CFR 3.2(e). For example, the imaging device or drug contrast indications refer respectively to a class of imaging drugs (gadolinium contrast) or a class of imaging devices (magnetic resonance imaging).[9]

[9] Although these class products do not meet the definition of a combination product, each is integral to the established indication and would be prescribed for the specific contrast indication.

286 A manufacturer of an imaging device who intends to develop a new contrast indication for
287 use with a class of imaging drugs would submit a device application to CDRH. During the
288 review process, CDRH will consult with CDER on issues including, but not limited to, the
289 scientific/technical, risk/benefit, labeling, potential interaction issues for the drug or drug
290 class, possible number of marketing applications.[10]
291
292 In some instances, the use of a diagnostic imaging device and imaging drug may constitute
293 a combination product under 21 C.F.R. 3.2(e)(3).[11] For example, certain dedicated
294 imaging drug-device products may constitute a combination product; e.g., a specific
295 imaging drug to bind receptors for imaging with a dedicated software algorithm. Although
296 a detailed discussion of how FDA applies combination product authorities is beyond the
297 scope of this guidance, if a manufacturer has a combination product, the lead center
298 determination, as with other products, will be in accordance with the primary mode of
299 action regulations in 21 CFR 3.4.[12] Developers of a specific drug-device imaging product
300 may wish to contact FDA to discuss whether a request for designation would be useful.[13]
301
302 As described further in this document Section IX, *Interaction with FDA and the Review*
303 *Process,* for developers of an imaging device wishing to add a new contrast indication for
304 a class of imaging drugs, the supportive clinical study should proceed under the
305 investigational device exemption (IDE) regulations with a submission to CDRH. For
306 imaging drug developers wishing to add a new contrast indication, the supportive clinical
307 trials should proceed under the IND regulations with a submission to CDER. For a
308 combination product, the submission should be sent to the lead center as determined by the
309 product specific primary mode of action. Typically, the type of investigational application
310 for a combination product is that of the lead center (e.g., an IND for CDER and IDE for
311 CDRH).
312
313 **B. Considerations for Data Necessary to Support Approval of the New**
314 **Contrast Indication for Use**
315
316
317 As noted in this document Section IV, *Scope,* there are four large categories of imaging
318 contrast indications. In existing FDA guidance documents, the Agency provides
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320

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[10] Imaging drug and biological products including radiopharmaceuticals are regulated in CDER.

[11] Section 3.2(e)(3) states: "A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose."

[12] Final rule for *Definition of the Primary Mode of Action of a Combination Product*, published August 25, 2005, Federal Register, http://www.fda.gov/OHRMS/DOCKETS/98fr/05-16527.pdf

[13] See FDA guidance for industry entitled *How to write a request for designation;* http://www.fda.gov/oc/combination/Guidance-How%20to%20Write%20an%20RFD.pdf

recommendations on what and how to submit device technology information on certain devices (e.g., US, MRI, SPECT, PET). FDA's Imaging Drug Guidance Parts 1, 2, and 3 provide detailed recommendations on the information needed to establish the safety and effectiveness of different types of contrast indications associated with imaging drug and biological products.. This set of documents includes information respectively on the following:

- Conducting Safety Assessments;
- Clinical Indications; and
- Design, Analysis, and Interpretation of Clinical Studies

Further, for the subset of imaging products that are combination products, the FDA guidance entitled *Early Development Considerations for Innovative Combination Products* provides information on how known information might be useful in product development. [14]

FDA recommends that manufacturers of imaging drug-device combination products or manufacturers of an imaging device for use with an imaging drug class consider these existing guidance documents as a starting point for development plans for their specific contrast indication. Because of the breadth, innovation and complexity of these imaging drug-device systems, there is no single clinical trial design that would be appropriate for all products or indications. However, FDA expects that the scientific and technical questions posed by a specific contrast indication, patient population, and set of products would be similar regardless of the center lead or type of marketing submission being used. Thus, most new contrast indications should include comparable documentation collected from appropriately designed clinical trials of the imaging drug-device as well as preclinical test results, and, when appropriate, device software or new technology validation.

1. Imaging Drug Class Considerations

When an imaging device manufacturer is considering a new contrast indication for a class of imaging drugs, in developing the clinical trial designs, the manufacturer should consider what is common and what is unique about the class of drugs. For example, each class of imaging drugs referenced in this document Section V, *Background,* (e.g., microbubbles, paramagnetic metallic ions linked to different chemicals, iodinated products, diagnostic radiopharmaceuticals added to drug products and monoclonal antibodies that target specific receptors) may have a common indication and certain general safety characteristics. Within a class, there also may be different doses, different risk profiles, or other unique labeling. Further, within a broad imaging class there may be different generations (e.g., changes in chelates, carriers, ligands, or other features of the imaging drug.)

In designing a trial for a class of FDA-approved imaging drugs, FDA recommends that the design(s) include features to address unique aspects of the class of imaging drugs. A sponsor should also consider what is different about the new indication or

[14] See http://www.fda.gov/oc/combination/innovative.pdf

365 patient population.[15] It may be necessary to determine how the device should be used
366 with imaging drugs that have different dosing requirements. These data should be
367 obtained in early studies, before determining the pivotal trial design to establish
368 imaging drug dosing or device energy differences that should be in labeling to ensure
369 safety and effectiveness. Generally such trial designs should study the members of the
370 class, not one drug. Alternatively, imaging device developers may consider
371 establishing an indication for only one member of imaging drug class. If only one
372 drug is studied, the indication would be drug specific.
373
374 2. Imaging Device Class Considerations
375
376 Imaging devices typically have similar indications or intended uses. When developing
377 a new contrast indication under a drug application, the devices evolve and often evolve
378 quickly. There may be differences in the settings that can be adjusted or those that are
379 locked for safety. For imaging drug manufacturers considering a new contrast
380 indication for a class of devices, FDA recommends considerations of clinical trial
381 designs that study the similarities and differences in the class of marketed imaging
382 devices that are most appropriate for the new indication. Also, consider what imaging
383 device changes have occurred since your imaging drug was first approved. For the
384 new contrast indication, FDA also recommends considering trial designs that
385 encompass both the most recently marketed imaging devices as well as those that are
386 most widely available. If the new indication depends on a unique imaging device, then
387 the indication should be device-specific.
388
389 **C. Considerations on the Type of Marketing Submission to Provide When**
390 **Using a Device Application Alone**
391
392
393 Under the principles set forth in this document Section VI, *Review Principles,* FDA
394 believes certain new imaging contrast indications can be reviewed in a device submission
395 alone when they entail only device modifications <u>and</u> when a change in the approved drug
396 labeling would not be necessary. As described below, when a device sponsor seeks to
397 develop a contrast indication using an approved drug, the submission may be a PMA or
398 510(k).
399
400 1. When is a PMA most appropriate?
401
402 FDA believes that approval of most proposed new contrast indications meeting the criteria
403 described in this document Section VI.1 (i.e., those arising from a change in the imaging

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[15] Most imaging drug classes (e.g., gadolinium, microbubbles, and radiopharmaceuticals) have a boxed warning regarding different types of serious adverse events. The clinical trial design for a new indication for an approved imaging drug should consider the relevance of the existing safety profile to the proposed new use. For example, conducting magnetic resonance imaging of the renal arteries using an approved drug that has known toxicity in patients with renal insufficiency raises new questions of safety and effectiveness because of the different risk population compared to that specified in the approved drug label for brain imaging.

404 device alone that do not affect the imaging drug or require changes to drug labeling)
405 should be sought in a PMA. This particularly includes new contrast indications within the
406 categories of a) disease or pathology detection or assessment, b) functional, physiological
407 or biochemical assessment, or c) diagnostic or therapeutic patient management. The need
408 for a PMA reflects the new type of safety and effectiveness questions arising when the new
409 imaging drug-device indication is added to the device submission, particularly in the
410 absence of a concurrent NDA.[16] For example, a new contrast indication for breast cancer
411 screening or diagnosis using an imaging drug that is not approved for imaging that area of
412 the body may present new types of questions of safety and effectiveness.[17] FDA believes
413 the approach of reviewing a PMA for such a labeling change will promote greater
414 consistency pre- and post-market between the regulation of the imaging device and the
415 contrast drug.
416
417 2. When might a 510(k) be appropriate?
418
419 Although new indications for devices using imaging drugs are likely to raise new types of
420 safety and effectiveness questions that require review of a PMA, submission of a 510(k)
421 for the new indication might be appropriate. For example this might be acceptable if the
422 approved imaging drug and cleared imaging device are already indicated for the same or
423 consistent contrast indication.
424
425 3. What if my product is under an NDA or BLA?
426
427 Holders of an NDA or BLA for an imaging drug or biological product who seek to develop
428 new contrast indications that refer to devices should submit supplements to their
429 NDA/BLA in accordance with existing drug or biological product provisions. In addition,
430 if FDA approves or clears a new contrast indication in a device submission, the NDA/BLA
431 holder may submit a labeling supplement to add the indication to the imaging drug.
432

433 VIII. POSTMARKET CONSIDERATIONS

434
435 The holder of an approved device submission that includes a new contrast indication
436 should monitor changes to the marketed drug labeling as well as other changes to the drug.
437 In certain instances, FDA may require such monitoring or other postmarket surveillance
438 related to the drug upon approval or clearance of the device submission. Further to
439 enhance adverse event reporting, FDA expects that the application holder adding the new
440 contrast indication should submit to FDA any reports of adverse events related to the
441 indication in its labeling.[18]

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[16] Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury (See generally FD&C Act section 515; and Device Advice/PMA http://www.fda.gov/cdrh/devadvice/pma/)

[17] In considering such a new indication, FDA will also determine whether the imaging drug label revision is also appropriate.

[18] FDA intends to adopt regulations on adverse event reporting requirements for combination products. See 2007 Federal register, Vol. 72, No. 82, 22492.

442 **IX. INTERACTION WITH FDA AND THE REVIEW PROCESS**
443
444 Early communication and discussion between manufacturers and FDA concerning
445 potential new contrast indications should include concurrent discussion with the centers
446 and, as appropriate, OCP. Early dialogue allows manufacturers to obtain initial feedback
447 on the kinds of preclinical and clinical data that may be necessary to obtain approval of the
448 proposed new contrast indication. Such communication may identify critical issues for
449 product development and help to ensure an efficient development and approval process.
450 Further, early and frequent communication provides the opportunity for FDA to establish
451 its intercenter review team and to develop the appropriate scientific expertise to facilitate
452 timely and efficient reviews of any future submissions.
453
454 FDA strongly encourages any manufacturer who is considering medical imaging
455 development for use with a class of imaging products to contact the center that typically
456 regulates its product to request preliminary intercenter guidance.
457
458 CBER, CDER and CDRH provide guidance on milestone/collaboration meetings
459 throughout the development process and submission of investigational and marketing
460 applications. Pre-investigational (pre-IND and pre IDE) meetings are particularly useful
461 for discussing innovative products. Ideally the meeting background package should
462 provide a comprehensive discussion of the proposed contrast indication, the device
463 technology, a copy of the existing drug labeling, and outline of the type of clinical studies
464 being proposed. During ongoing development, pre-marketing submission meetings are
465 also helpful to discuss marketing application content, as well as the sequence and timing of
466 modular submissions or when more than one marketing submission will be provided for
467 the combination product. Guidance on how to arrange developmental meetings can be
468 obtained on the CDER,[19] CBER[20] and CDRH[21] websites.
469
470 The lead center should be contacted to schedule meetings in accordance with the
471 milestones applicable to the lead center. Lead center will consult or collaborate with other
472 centers or agency components in accordance with the scientific and technical issues in the
473 submission. As described further in this document Section VII.A, *Determination of Lead*
474 *Center Responsible for Premarket Review,* for device manufacturers who are considering
475 trials to add new contrast indications using a class of imaging drugs, the lead center is
476 CDRH. For a combination product, the lead center is determined by the primary mode of
477 action.[22]
478
479

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[19] See http://www.fda.gov/cder/guidance/3683fnl.pdf.
[20] See http://www.fda.gov/cber/gdlns/ind052501.htm.
[21] See http://www.fda.gov/cdrh/devadvice/ide/approval.html , and, *Early Collaboration Meetings Under the FDA Modernization Act, Final Guidance for Industry and CDRH Staff*; http://www.fda.gov/cdrh/ode/guidance/310.html
[22] When the imaging drug and device meet the definition of a combination product, the labeling principles in this document would not affect the lead center assignment based on the primary mode of action. The principles affect only which label should contain the new information.

480 OCP is available formally or informally to address jurisdictional, developmental,
481 premarket review, cross-labeling, and postmarket regulatory consistency issues. Also,
482 OCP is available to provide similar guidance for products that do not meet the definition of
483 a combination product, but raise similar questions. During product development, protocol
484 design, submission coordination, and labeling, the reviewing centers intend to
485 consult/collaborate in making these assessments, as appropriate. FDA further intends to
486 rely on its existing *SOPP for Intercenter Consultative and Collaborative Review Process*[23]
487 to promote timely and effective review.
488
489 As appropriate, OCP will assist in developing additional focused procedures for the
490 imaging review divisions/branches. This will provide for an Intercenter Imaging Team to
491 review clinical protocols, labeling, considerations on the number or type of marketing
492 applications, and other practices to ensure consistency of developmental approaches and
493 relevance of results to submit under either the drug, biological, or device provisions. This
494 would include, but is not limited to, the scientific/technical, risk/benefit, labeling, or
495 potential interaction issues for the drug or drug class with the device(s). FDA expects that
496 such intercenter procedures will promote consistency in labeling and acceptability of new
497 indications requested based on prior agency determinations regardless of the regulatory
498 provisions used for approval or clearance.
499
500
501 **X. HOW MAY I OBTAIN MORE INFORMATION?**
502
503 OCP is available as a resource to developers and review staff throughout the lifecycle
504 (assignment, development, premarket review and postmarket regulation) of a combination
505 product. The Office can be reached at (301) 427-1934 or by email at
506 combination@fda.gov . In addition, the Office maintains an updated list of FDA guidance
507 documents that developers may find helpful in the development of their products. The
508 guidance is available at the Office's Internet Website at
509 http://www.fda.gov/oc/combination .
510
511 In addition each center maintains a guidance webpage that provides comprehensive
512 information on the types of products or constituent parts regulated in the center. The
513 CDER Guidance webpage is accessible at http://www.fda.gov/cder/guidance/index.htm .
514 The CDRH Guidance web page is accessible at http://www.fda.gov/cdrh/guidance.html
515 and the device advice webpage is accessible at http://www.fda.gov/cdrh/devadvice/ . The
516 CBER Guidance web page is accessible at http://www.fda.gov/cber/guidelines.htm .
517
518 Selected specific guidance documents that may be useful for imaging drugs and imaging
519 devices include, but are not limited to, the following.
520
521 • Applications under section 505(b)(2);
522 http://www.fda.gov/cder/guidance/2853dft.pdf

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[23] Standard Operating Procedures and Policies: *Intercenter Consultative and Collaborative Review Process*; http://www.fda.gov/oc/combination/consultative.html

- Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices; http://www.fda.gov/cdrh/ode/guidance/793.pdf
- Early Development Considerations for Innovative Combination Products; http://www.fda.gov/oc/combination/innovative.pdf
- Exploratory IND studies; http://www.fda.gov/cder/guidance/7086fnl.pdf
- FDA Radiological Health Program: Ultrasound Imaging; http://www.fda.gov/cdrh/radhealth/products/ultrasound-imaging.html
- Guideline for Master Files; http://www.fda.gov/cder/guidance/dmf.htm
- FDA guidance *Developing Imaging Drug and Biological Products, Part 1: Conducting Clinical Safety Assessments,* http://www.fda.gov/cder/guidance/5742prt1.pdf ; *Part 2: Clinical Indications*; http://www.fda.gov/cder/guidance/5742prt2.pdf ; *Part 3: Design, Analysis and Interpretation of Clinical Studies,* http://www.fda.gov/cder/guidance/5742prt3.pdf
- Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review http://www.fda.gov/cdrh/modact/evidence.html ;

XI. GLOSSARY

- Combination product; 21 C.F.R. 3.2(e)

  "(1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

  (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

  (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, contrast indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or

  (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect."

563 • Contrast indication: A contrast indication is a statement in the indication or
564 intended use section of the labeling of either an imaging drug or imaging device
565 using an imaging drug or biological product
566
567
568 • Imaging drug: The term imaging drug applies to drug and biological products
569 including radiopharmaceuticals for use in medical imaging. This is consistent with
570 or includes the term contrast agent.
571