Guidance for Industry:

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

DRAFT GUIDANCE

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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.

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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

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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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.

[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.

[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

imaging of specific anatomic areas or tissues of the body rely on the administration of an imaging drug or biological product to enhance the image. For example, CT and MRI examinations may be performed both without and with an imaging drug. In such images, the imaging drug may improve the visualization of tissues, organs, and physiologic processes in part by increasing the relative difference of imaging signal intensities in adjacent regions of the body. Typically, when contrast is used, the images are taken both without and then with the imaging drug to provide contrast. For other imaging technologies such as radiopharmaceutical imaging (SPECT or PET),[4] in order to produce an image it is necessary to simultaneously use the imaging device and the radiopharmaceutical imaging drug (i.e., a useable image can not be produced by the device alone). Medical imaging devices are marketed under the device provisions of the Act. Medical imaging drugs and biological products are marketed under the drug and biological provisions of the Act.

Most imaging drugs are modality specific and chemically distinct from one another.[5] For example,

- X-ray and CT imaging drugs are iodine-containing compounds that in part are specifically designed to absorb x-rays;
- MRI imaging drugs contain paramagnetic metallic ions, most commonly gadolinium, iron or manganese. These imaging drugs are designed in part to alter the magnetic properties of body tissue;
- US imaging drugs typically consist of a gas contained within a lipid or protein shell (i.e., microbubbles or related microparticles). These products are designed in part to reflect sound waves; and,
- Radiopharmaceutical imaging drugs contain in part a radionuclide that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons.

In addition to these general properties, these imaging drugs are formulated to interact with the body to facilitate imaging. For example, some imaging drugs bind to receptors, interact with a metabolic pathway, cross abnormal blood brain barriers, or are engulfed by macrophages.

FDA existing guidance identifies imaging drug contrast indications in four broad indication areas:[6]

1) Structural delineation,
2) Disease or pathology detection or assessment,
3) Functional, physiological or biochemical assessment, and
4) Diagnostic or patient management.

[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

[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.

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.

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] A manufacturer of an imaging device who intends to develop a new contrast indication for use with a class of imaging drugs would submit a device application to CDRH. During the review process, CDRH will consult with CDER on issues including, but not limited to, the scientific/technical, risk/benefit, labeling, potential interaction issues for the drug or drug class, possible number of marketing applications.[10]

In some instances, the use of a diagnostic imaging device and imaging drug may constitute a combination product under 21 C.F.R. 3.2(e)(3).[11] For example, certain dedicated imaging drug-device products may constitute a combination product; e.g., a specific imaging drug to bind receptors for imaging with a dedicated software algorithm. Although a detailed discussion of how FDA applies combination product authorities is beyond the scope of this guidance, if a manufacturer has a combination product, the lead center determination, as with other products, will be in accordance with the primary mode of action regulations in 21 CFR 3.4.[12] Developers of a specific drug-device imaging product may wish to contact FDA to discuss whether a request for designation would be useful.[13]

As described further in this document Section IX, *Interaction with FDA and the Review Process,* for developers of an imaging device wishing to add a new contrast indication for a class of imaging drugs, the supportive clinical study should proceed under the investigational device exemption (IDE) regulations with a submission to CDRH. For imaging drug developers wishing to add a new contrast indication, the supportive clinical trials should proceed under the IND regulations with a submission to CDER. For a combination product, the submission should be sent to the lead center as determined by the product specific primary mode of action. Typically, the type of investigational application for a combination product is that of the lead center (e.g., an IND for CDER and IDE for CDRH).

B. Considerations for Data Necessary to Support Approval of the New Contrast Indication for Use

As noted in this document Section IV, *Scope,* there are four large categories of imaging contrast indications. In existing FDA guidance documents, the Agency provides

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[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.

[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.

patient population.[15] It may be necessary to determine how the device should be used with imaging drugs that have different dosing requirements. These data should be obtained in early studies, before determining the pivotal trial design to establish imaging drug dosing or device energy differences that should be in labeling to ensure safety and effectiveness. Generally such trial designs should study the members of the class, not one drug. Alternatively, imaging device developers may consider establishing an indication for only one member of imaging drug class. If only one drug is studied, the indication would be drug specific.

2. Imaging Device Class Considerations

Imaging devices typically have similar indications or intended uses. When developing a new contrast indication under a drug application, the devices evolve and often evolve quickly. There may be differences in the settings that can be adjusted or those that are locked for safety. For imaging drug manufacturers considering a new contrast indication for a class of devices, FDA recommends considerations of clinical trial designs that study the similarities and differences in the class of marketed imaging devices that are most appropriate for the new indication. Also, consider what imaging device changes have occurred since your imaging drug was first approved. For the new contrast indication, FDA also recommends considering trial designs that encompass both the most recently marketed imaging devices as well as those that are most widely available. If the new indication depends on a unique imaging device, then the indication should be device-specific.

C. Considerations on the Type of Marketing Submission to Provide When Using a Device Application Alone

Under the principles set forth in this document Section VI, *Review Principles*, FDA believes certain new imaging contrast indications can be reviewed in a device submission alone when they entail only device modifications and when a change in the approved drug labeling would not be necessary. As described below, when a device sponsor seeks to develop a contrast indication using an approved drug, the submission may be a PMA or 510(k).

1. When is a PMA most appropriate?

FDA believes that approval of most proposed new contrast indications meeting the criteria described in this document Section VI.1 (i.e., those arising from a change in the imaging device alone that do not affect the imaging drug or require changes to drug

[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.

labeling) should be sought in a PMA. This particularly includes new contrast indications within the categories of a) disease or pathology detection or assessment, b) functional, physiological or biochemical assessment, or c) diagnostic or therapeutic patient management. The need for a PMA reflects the new type of safety and effectiveness questions arising when the new imaging drug-device indication is added to the device submission, particularly in the absence of a concurrent NDA.[16] For example, 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 may present new types of questions of safety and effectiveness.[17] FDA believes the approach of reviewing a PMA for such a labeling change will promote greater consistency pre- and post-market between the regulation of the imaging device and the contrast drug.

2. When might a 510(k) be appropriate?

Although new indications for devices using imaging drugs are likely to raise new types of safety and effectiveness questions that require review of a PMA, submission of a 510(k) for the new indication might be appropriate. For example this might be acceptable if the approved imaging drug and cleared imaging device are already indicated for the same or consistent contrast indication.

3. What if my product is under an NDA or BLA?

Holders of an NDA or BLA for an imaging drug or biological product who seek to develop new contrast indications that refer to devices should submit supplements to their NDA/BLA in accordance with existing drug or biological product provisions. In addition, if FDA approves or clears a new contrast indication in a device submission, the NDA/BLA holder may submit a labeling supplement to add the indication to the imaging drug.

VIII. POSTMARKET CONSIDERATIONS

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

IX. INTERACTION WITH FDA AND THE REVIEW PROCESS

Early communication and discussion between manufacturers and FDA concerning potential new contrast indications should include concurrent discussion with the centers and, as appropriate, OCP. Early dialogue allows manufacturers to obtain initial feedback on the kinds of preclinical and clinical data that may be necessary to obtain approval of the proposed new contrast indication. Such communication may identify critical issues for product development and help to ensure an efficient development and approval process. Further, early and frequent communication provides the opportunity for FDA to establish its intercenter review team and to develop the appropriate scientific expertise to facilitate timely and efficient reviews of any future submissions.

FDA strongly encourages any manufacturer who is considering medical imaging development for use with a class of imaging products to contact the center that typically regulates its product to request preliminary intercenter guidance.

CBER, CDER and CDRH provide guidance on milestone/collaboration meetings throughout the development process and submission of investigational and marketing applications. Pre-investigational (pre-IND and pre IDE) meetings are particularly useful for discussing innovative products. Ideally the meeting background package should provide a comprehensive discussion of the proposed contrast indication, the device technology, a copy of the existing drug labeling, and outline of the type of clinical studies being proposed. During ongoing development, pre-marketing submission meetings are also helpful to discuss marketing application content, as well as the sequence and timing of modular submissions or when more than one marketing submission will be provided for the combination product. Guidance on how to arrange developmental meetings can be obtained on the CDER,[19] CBER[20] and CDRH[21] websites.

The lead center should be contacted to schedule meetings in accordance with the milestones applicable to the lead center. Lead center will consult or collaborate with other centers or agency components in accordance with the scientific and technical issues in the submission. As described further in this document Section VII.A, *Determination of Lead Center Responsible for Premarket Review,* for device manufacturers who are considering trials to add new contrast indications using a class of imaging drugs, the lead center is CDRH. For a combination product, the lead center is determined by the primary mode of action.[22]

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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.

OCP is available formally or informally to address jurisdictional, developmental, premarket review, cross-labeling, and postmarket regulatory consistency issues. Also, OCP is available to provide similar guidance for products that do not meet the definition of a combination product, but raise similar questions. During product development, protocol design, submission coordination, and labeling, the reviewing centers intend to consult/collaborate in making these assessments, as appropriate. FDA further intends to rely on its existing *SOPP for Intercenter Consultative and Collaborative Review Process*[23] to promote timely and effective review.

As appropriate, OCP will assist in developing additional focused procedures for the imaging review divisions/branches. This will provide for an Intercenter Imaging Team to review clinical protocols, labeling, considerations on the number or type of marketing applications, and other practices to ensure consistency of developmental approaches and relevance of results to submit under either the drug, biological, or device provisions. This would include, but is not limited to, the scientific/technical, risk/benefit, labeling, or potential interaction issues for the drug or drug class with the device(s). FDA expects that such intercenter procedures will promote consistency in labeling and acceptability of new indications requested based on prior agency determinations regardless of the regulatory provisions used for approval or clearance.

X. HOW MAY I OBTAIN MORE INFORMATION?

OCP is available as a resource to developers and review staff throughout the lifecycle (assignment, development, premarket review and postmarket regulation) of a combination product. The Office can be reached at (301) 427-1934 or by email at combination@fda.gov. In addition, the Office maintains an updated list of FDA guidance documents that developers may find helpful in the development of their products. The guidance is available at the Office's Internet Website at http://www.fda.gov/oc/combination.

In addition each center maintains a guidance webpage that provides comprehensive information on the types of products or constituent parts regulated in the center. The CDER Guidance webpage is accessible at http://www.fda.gov/cder/guidance/index.htm. The CDRH Guidance web page is accessible at http://www.fda.gov/cdrh/guidance.html and the device advice webpage is accessible at http://www.fda.gov/cdrh/devadvice/. The CBER Guidance web page is accessible at http://www.fda.gov/cber/guidelines.htm.

Selected specific guidance documents that may be useful for imaging drugs and imaging devices include, but are not limited to, the following.

- Applications under section 505(b)(2); http://www.fda.gov/cder/guidance/2853dft.pdf

[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."

- 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

- Imaging drug: The term imaging drug applies to drug and biological products including radiopharmaceuticals for use in medical imaging. This is consistent with or includes the term contrast agent.