

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

*Additional copies are available from:
Office of Combination Products, HFG-3
Office of the Commissioner
Food and Drug Administration
15800 Crabbs Branch Way
Rockville, MD 20855
(Tel) 301-427-1934
(Fax) 301-427-1935
<http://www.fda.gov/oc/combination>*

**U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP) in Office of the Commissioner
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)**

December 2009

TABLE OF CONTENTS

I.	INTRODUCTION.....	3
II.	SCOPE	4
III.	TERMINOLOGY	4
IV.	BACKGROUND	5
V.	GENERAL PRINCIPLES	6
VI.	WHAT TYPE OF MARKETING SUBMISSION TO PROVIDE.....	10
VII.	ILLUSTRATIONS FOR WHEN A DEVICE SUBMISSION (510(K) OR PMA) IS SUFFICIENT AND AN NDA SUBMISSION IS NOT NECESSARY	12
VIII.	ILLUSTRATIONS FOR WHEN BOTH A DEVICE SUBMISSION AND AN NDA SUBMISSION MAY BE NECESSARY FOR A DEVICE MODIFICATION	14
IX.	CONSIDERATIONS FOR HOLDERS OF IMAGING DRUG APPLICATIONS..	17
X.	PREMARKET DEVELOPMENT CONSIDERATIONS.....	18
XI.	POSTMARKET CONSIDERATIONS.....	20
XII.	INTERACTION WITH FDA AND THE REVIEW PROCESS	20
XIII.	HOW MAY I OBTAIN MORE INFORMATION?	22
	APPENDIX 1 - MEDICAL IMAGING PRODUCT LABELING CONVENTIONS.....	23
	APPENDIX 2 – TYPE OF MEDICAL IMAGING PRODUCTS	24

Guidance for Industry¹

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

This guidance represents 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 developers² of medical imaging devices and imaging drug/biological products (hereinafter more generally referred to as drugs or drug products) that provide image contrast enhancement in determining:

- When the imaging device developer may add certain new imaging contrast indications to its device for use with already approved imaging drugs without a need for a modification of the drug labeling;
- When the imaging drug developer may add certain new imaging contrast indications to its drug for use with already approved imaging devices without a need for a modification of the device labeling, and
- What type of marketing submission(s)³ the imaging drug or imaging device developer should submit to FDA to request approval/clearance to add a new imaging contrast indication.

FDA intends for the principles in this guidance to promote timely and effective premarket review of, and to promote consistent, appropriate regulation and labeling for imaging drugs and devices. These principles are intended to: 1) promote consistency in the type of scientific or technical information submitted to establish a new imaging contrast indication for use regardless of the type of marketing submission, and 2) to promote compatibility in labeling indication statements.

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.

³ For purposes of this document, the term submission and application are used interchangeably and apply to drug, device, and biological product marketing applications or premarket notifications.

Contains Nonbinding Recommendations

This document supplements existing guidance referred to later in this document 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 or substantial equivalence 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.

II. SCOPE

As part of the Medical Device User Fee Amendments of 2007 (MDUFA) Commitment for the Performance Goals and Procedures, in the September 27, 2007 Agreement letter,⁴ FDA agreed to develop guidance for medical imaging devices used with “contrast agents or radiopharmaceuticals.” Specifically, item I.N of the commitment letter states the *“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.”* Draft guidance was published on September 30, 2008; the comment period closed on January 5, 2009. FDA held meetings with imaging industry stakeholders in July 2008 and August 2009. This document fulfills FDA’s commitment to issue the final guidance called for by the commitment letter.

III. TERMINOLOGY

For purposes of this document, the following conventions apply.

- Imaging drug: Imaging drugs are drugs and biological products (including radiopharmaceuticals) intended for use in medical imaging. This description is generally consistent with the term contrast agent.

⁴ <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/UCM109102.pdf>

Contains Nonbinding Recommendations

- **Indication statement:** Indication statement, for the purposes of this document, is synonymous with the definition of *Indication and Usage* under 21 CFR 201.57 and the definition of *Indications for Use* under 21 CFR 814.20(b)(3)(i).⁵ The approved indication is included in the FDA approval letters and accompanying labeling for NDAs, BLAs, and PMAs.⁶ The indication is stated in the Indication for Use Statement form that accompanies the premarket notification 510(k) clearance letter. FDA expects that other sections of the labeling would clarify but not expand the use beyond the indication statement.⁷
- **Imaging contrast indication:** Imaging contrast indication is a statement in the indication section of the imaging drug labeling that describes the use of the drug. Generally, when an imaging drug is intended to be used with a specific imaging device, the imaging contrast indication also appears in the device labeling.

Existing FDA guidance identifies imaging drug contrast indications in four broad indication areas.⁸ For additional information see section VI.B *Considerations for When an NDA is Appropriate*.

IV. BACKGROUND

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

Most medical imaging depends solely on the device technology to produce and display images; e.g., ultrasound (US), computerized tomography (CT), magnetic resonance imaging (MRI), and traditional radiology (x-ray) techniques. However, imaging drugs are sometimes used in conjunction with these imaging devices to provide image

⁵ 21 CFR 201.57 (c)(2) *Indications and usage*. “This [labeling] section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.” 21 CFR 814.20(b)(3)(i) *Indications for Use* “A general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.”

⁶ NDA (new drug application), BLA (biologics license application), PMA (premarket approval application). For purposes of this document references to an NDA includes BLA submissions.

⁷ For purposes of this document, the indication statement is distinct from the sponsor’s intended use summary provided in a 510(k) notification under 21 CFR 807.92(a)(5).

⁸ FDA Guidance for Industry, *Developing Medical Imaging Drug and Biological Products: Part 2, Clinical Indications*;
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071603.pdf>

Contains Nonbinding Recommendations

enhancement. For example, for CT and MRI, the addition of an 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.

For other imaging technologies such as radiopharmaceutical imaging (SPECT or PET),⁹ the device alone cannot produce a usable image. Therefore, in order to produce and display a usable image, it is necessary to administer an imaging drug to the patient before using the imaging device. For additional background on the types of imaging products, see Appendix 2.

Although intended to be used together, technological advancements with imaging devices and imaging drugs generally may not proceed at the same rate. Historically, imaging device software and hardware engineering technologies that utilize imaging drugs evolve rapidly (i.e., changes occur 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 necessitating a change to the imaging drug's labeling; i.e. 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 might allow the identical drug to produce an image of the liver. However, if the drug and device manufacturer do not cooperate to seek approval to add the new liver imaging indication in the drug labeling, the pathway to market the new indication using the new device technology alone is often unclear. The purpose of this guidance is to describe the principles and provide examples under which drug or device developers can seek marketing approval/clearance to add new imaging contrast indications to the medical device using an already approved imaging drug.

In developing these principles, FDA considered the scientific and technical issues that may occur when using imaging drugs and devices together, approaches to leverage prior Agency decisions, approaches to ensure consistency of information regardless of the type of submission being used to establish new imaging contrast indications, and approaches to ensure the consistency of the regulatory vehicle for submission under the drug, biological product, or device provisions being used to establish similar types of imaging contrast indications.

V. GENERAL PRINCIPLES

To ensure the safe and effective use of both imaging drugs and imaging devices, FDA believes that, the imaging drug and imaging device labeling should be generally consistent. Within this context, however, under appropriate circumstances as described in this document, the labeling of the imaging device alone may be able to provide

⁹ SPECT stands for single photon emission computerized tomography; PET stands for positron emission computerized tomography.

Contains Nonbinding Recommendations

sufficient information about a new imaging contrast indication when using an imaging drug in accordance with its approved drug labeling. This instance may occur when the device technology does not change the drug characteristics and when the drug use is otherwise consistent with its approved imaging drug labeling.¹⁰ In other instances the imaging drug labeling may be able to provide sufficient information about a new imaging contrast indication using an imaging device in accordance with its approved device labeling. In determining consistency with approved labeling, FDA's considerations include, for example, labeling for the indication statement, dosing regimen (dose, rate, route of administration), conditions of use, patient population, and safety information. The Agency notes that individual imaging contrast indications may present unique or complex issues of safety or effectiveness that necessitate a review approach that varies from the one set forth below. Nonetheless, the agency expects to review most premarket applications for imaging product indications involving a drug and a device under the following approach to determine whether a submission should be provided for the imaging device, imaging drug, or for both imaging products.

1. Imaging device submission: When a new imaging device or device modification enables an approved imaging drug (i.e., at its approved formulation, dose, dosing regimen, rate, and route of administration) to be used for a new imaging contrast indication in a manner that is consistent with its approved indication, in most cases, FDA expects that a device submission from the device application holder alone would be sufficient to add the new imaging contrast indication to the device. The device submission would be either an original device application for a new device or supplemental device application for a modified device. Through this process, the imaging device developer would add the modified imaging contrast indication to the device labeling without the need for a change to the imaging drug labeling. For example, when new device software allows for the enhancement of the sensitivity and specificity of the same imaging site already identified in the approved imaging drug labeling, and the drug is administered in accordance with its approved labeling and the labeling does not need revision to ensure safety and effectiveness, the Agency believes in most instances a device submission and device labeling change alone should suffice.
2. Imaging drug submission: In contrast, when an imaging drug modification (i.e., formulation, dosage, rate, or route of administration) enables the currently approved/cleared imaging device to be used for a new indication for use without a change to the device, the NDA/BLA holder should submit a supplement to FDA to request approval for such a change. For example, an NDA submission would be most appropriate for a drug reformulation that allows enhanced biodistribution to a new area, but uses the same imaging software. In most instances, FDA expects a submission of an NDA submission to be sufficient to add such an indication to the drug labeling without the need for a submission of a device application or a labeling change to the imaging device.

¹⁰ Examples of imaging device - drug interactions that may affect the characteristics of the imaging drug include ultrasound rupture of microbubbles and light activation of molecules to release a singlet oxygen species. The safety and efficacy of these changes may vary depending on the different tissues being imaged.

Contains Nonbinding Recommendations

3. Imaging device and imaging drug submissions: In some instances, however, the device modification required to support the new imaging contrast indication may cause the drug and device to interact in a manner that affects the safety or effectiveness of the product(s), may change the imaging dosing, safety or effectiveness information, or may produce labeling inconsistencies. In such circumstances, FDA expects that both the drug and device labels would need to be revised to ensure the safe and effective use of both products for the new imaging contrast indication. If this is the case, the following principles would apply:
- When a new device or an imaging device modification necessitates a change in the imaging drug formulation, dosage, rate, or route of administration of the currently approved imaging indication, or when the new or modified device is for a new indication not in the approved drug labeling, FDA will generally expect a submission from the holders of both the drug and device applications to ensure labeling conformity. For example, if a change in device design provides for enhanced imaging at lower doses of the drug, FDA may determine the new drug dosing information should be included in both the imaging drug and device labels in order to help ensure that the drug will be used safely and effectively;
 - When an imaging drug modification (i.e., formulation, dosage, rate, or route of administration) necessitates a change in the approved imaging device performance characteristics, specifications, or design for its currently approved/cleared imaging indication or for a new indication for use, FDA will generally expect a submission of both a drug and a device application to add the new indication and to ensure labeling consistency. For example, an NDA supplement would be appropriate for a change in an ultrasound drug formulation to enhance drug stability for an existing indication; and a device submission would be appropriate for a corresponding change in the ultrasound device design to image the reformulated drug.

Regardless of which label (imaging device or imaging drug or both) adds the new imaging contrast indication, the safety and effectiveness of the new indication should be established by data collected from appropriately designed clinical trials using both the imaging drug and the imaging device. In general, FDA expects that the regulatory approval pathway (e.g., 510(k), PDP, PMA, PMA supplement, NDA, NDA efficacy supplement, NDA 505(b)(2), or NDA labeling supplement) should not affect the scientific and technical information that is most appropriate for establishing the safety and effectiveness of the new imaging contrast indication. (For additional information see Section IX, *Premarket Development Considerations*.) Further, the labeling of product(s) that adds the new indication statement should reflect the essential information that establish the imaging contrast indication; e.g., the clinical study description, imaging device characteristics and settings, imaging drug dosing regimen, target organ. By developing labeling that relies on consistent types of information, FDA intends to minimize the potential for misleading information across the imaging drug and device labels for similar indications.

A. Determination of Lead Center Responsible for Premarket Review

Most imaging devices and drugs approved for use with a class of imaging products do not meet the definition of a combination product under 21 CFR Part 3; e.g., when an imaging device is approved for use with a class of imaging drugs (e.g., gadolinium contrast) or when a drug is approved for use with a class of devices (e.g., MRI).¹¹ If an imaging device is not a combination product, a manufacturer of an imaging device who intends to develop a new imaging contrast indication for use with a class of imaging drugs should submit a device application to CDRH for review. 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.¹² Similarly, a manufacturer of an imaging drug who intends to develop a new imaging contrast indication for use with a class of devices should submit a drug application to CDER for review. CDER will consult with CDRH on all device related issues.

However, in some instances, the use of a certain diagnostic imaging device and imaging drug may constitute a combination product under 21 C.F.R. 3.2(e)(3).¹³ For example, a specific imaging drug used to bind receptors for imaging that uses a dedicated software algorithm may constitute a combination product. 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 will be in accordance with the primary mode of action regulatory provisions.¹⁴ Manufacturers of a specific drug-device imaging product may wish to contact FDA Office of Combination Products to discuss whether a request for designation would be useful.¹⁵

As described further in Section XI, *Interaction with FDA and the Review Process*, for the developer of an imaging device wishing to add a new imaging contrast indication for a class of imaging drugs, the supportive clinical trial(s) should be conducted under the Investigational Device Exemption regulations at 21 CFR 812 with a submission to CDRH. Similarly, for the developer of an imaging drug wishing to add new imaging contrast indications for a class of devices, the supportive clinical trials should proceed under the Investigational New Drug regulations at 21 CFR Part 312 with a submission to CDER. For a combination product, the submission should proceed under the lead center

¹¹ Although these class products do not meet the definition of a combination product at 21 CFR 3.2, the use of each product is integrally related to the approved indications and the products would be prescribed for use with each other.

¹² Imaging drug and biological products including radiopharmaceuticals are regulated in CDER.

¹³ 21 CFR 3.2(e)(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, 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.”

¹⁴ Final rule for *Definition of the Primary Mode of Action of a Combination Product*, published August 25, 2005, Federal Register, <http://edocket.access.gpo.gov/2005/pdf/05-16527.pdf>. See 21 CFR 3.4.

¹⁵ FDA guidance *How to write a request for designation*; <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126053.htm>

as determined by the product specific primary mode of action and typically the investigational application would be of the type administered by the lead center.

VI. WHAT TYPE OF MARKETING SUBMISSION TO PROVIDE

Under the concepts set forth in Section V *General Principles*, FDA believes certain new imaging contrast indications that are consistent with imaging drug labeling 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. In other circumstances both a device and drug marketing submission may be necessary.¹⁶ Therefore, when a device sponsor considers what type of submission(s) may be appropriate for their device change, there are two issues to consider: What type of device application should be submitted and when would a drug submission be appropriate? To assist in determining the type of device application to submit, CDRH previously issued two guidance documents that may be useful in determining the type of device application to submit when adding a new contrast imaging indication: a) *Guidance for Industry: General/Specific Intended Use (1998)* and b) *Deciding When to Submit a 510(k) for a Change to an Existing Device (1997)*. While neither is intended to apply to drug products or combination products, these guidance documents do provide starting point principles for determining whether a 510(k) or PMA is most appropriate.¹⁷ The following section VI.A applies these concepts to imaging devices. Section VI.B provides considerations for when a NDA is appropriate. Section VII and VIII provide further illustrations on the types of marketing submissions.

A. Considerations for the type of device submission: 510(k) or PMA

In determining whether a new device or a modified device is appropriate for review and clearance under a 510(k), FDA intends to assess whether the proposed device can be deemed substantially equivalent to a predicate device in accordance with 21 CFR 807.100(b), which states the following.

- “(1) The device has the same intended use as the predicate device; and
- (2) The device:
 - (i) Has the same technological characteristics as the predicate device; or
 - (ii)(A) Has different technological characteristics, such as a significant change in the materials, design, energy source, or other features of the device from those of the predicate device;

¹⁶ OCP is currently developing a guidance document for public review and comment that will address the factors FDA expects to consider in determining whether a single or multiple marketing applications should be submitted for a combination product.

¹⁷ FDA’s guidance on *Deciding When to submit a 510(k) for a Change to an Existing Device* states in the “Scope” section that the “guidance is not intended to apply, although it may, to combination products, such as drug/device or biologic/device combinations.” FDA’s *Guidance for Industry: General/Specific Intended Use (1998)* provides information on medical devices for purposes of determining substantial equivalence. It does not provide details on combination products under device applications or changes to add a drug use.

Contains Nonbinding Recommendations

(B) The data submitted establishes that the device is substantially equivalent to the predicate device and contains information, including clinical data if deemed necessary by the Commissioner, that demonstrates that the device is as safe and as effective as a legally marketed device; and
(C) Does not raise different questions of safety and effectiveness than the predicate device.”

Typically, FDA receives 510(k) submissions for: 1) adding the use of an approved imaging drug to the labeling of a 510(k) device that is cleared for use without an imaging drug, or 2) for using a new or modified device with an approved imaging drug for a new imaging contrast indication not provided in the drug labeling.

FDA’s first step in determining the appropriate type of device submission is to assess whether the sponsor’s selected predicate device is appropriate. If the proposed device has a different intended use from the intended use identified in the cleared predicate device, the proposed device will receive a not substantially equivalent (NSE) determination based on a new intended use, and, therefore, will be reviewed under a PMA or De Novo application.

Once an appropriate predicate device is considered acceptable by FDA, the decision on whether the proposed device may be substantially equivalent to the predicate device depends on the evaluation of the technologic characteristics and the evaluation of safety and effectiveness questions as illustrated in the CDRH 510(k) decision tree.¹⁸ FDA notes that since the imaging drug is part of the device indication, these questions should include questions related to the imaging drug. After the review is completed, if the proposed device is considered NSE to the predicate device due to questions of safety and effectiveness, the sponsor will be advised to submit a PMA or De Novo application.

After a determination about what type of device submission is appropriate, the developer should consider whether its proposed indication would be a new indication for the imaging drug or would create a labeling inconsistency for the drug. If so, then an NDA should be submitted along with the device application.

B. Considerations for When an NDA is appropriate.

Imaging drug indication differences are based on whether the indication is within the original imaging categories identified in Section V, *General Principles* and whether the conditions of use are the same. A determination of when an NDA submission should be provided depends on the consistency with the labeled indication and on the safety or effectiveness information (e.g., patient population, dose, dosing regimen, frequency of repeat studies, concomitant medication, and risk factors). Imaging drug indications do not expressly address the concept of general vs. specific indications as referenced above for determining the type of device submission; instead imaging drug indications are categorized as: 1) Structural delineation, 2) Disease or pathology detection or assessment,

¹⁸ Additional information is available under 510(k) Memorandum K-86-3 issued June 30, 1986; <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081383.htm>

Contains Nonbinding Recommendations

3) Functional, physiological or biochemical assessment, or 4) Diagnostic or patient management.¹⁹ As explained in the guidance document referenced below, any change from one category to another is considered a new indication. Device changes that would generally be inconsistent with an existing drug label and for which an NDA submission would be appropriate include changes such as the following:

- Change in drug imaging indication category (change from structural to disease or pathology detection),
- Change in patient population,
- Change in dose, rate, route, or dosing regimen,
- Change in safety profile, or
- Change in the device labeling that could introduce confusing or misleading information for healthcare providers when relying on the imaging device, imaging drug or both labels.

Therefore, the initial step in determining whether a device proposed change is consistent with the drug labeling is to carefully consider the approved indication of the drug. The appropriate type of submission may be an NDA efficacy or labeling supplement. (For additional information see Section IX, *Considerations for Holders of Imaging Drug Applications*.)

VII. ILLUSTRATIONS FOR WHEN A DEVICE SUBMISSION (510(K) OR PMA) IS SUFFICIENT AND AN NDA SUBMISSION IS NOT NECESSARY

As provided by the examples below, there are circumstances where the device proposed change is consistent with the existing drug indication and can be reviewed under a 510(k)/PMA alone. In such an instance, a submission of an NDA supplement to change the drug label would not be necessary before approving or clearing the device.

Scenario: Both the imaging device and one specific imaging drug (gadolinium) are cleared and approved, respectively, for contrast magnetic resonance angiography (MRA) of the aortoiliac region. The device developer submits a new 510(k) requesting clearance for its device modified by adding quantitative measurement to its existing software to increase the sensitivity/specificity detecting aortoiliac lesions with of 95% stenosis using the approved imaging drug. The approved imaging drug label's clinical trials section identifies the primary endpoint as a visual comparison of pre and post contrast images detecting lesions with > 50% stenosis.

¹⁹ FDA Guidance for Industry, *Developing Medical Imaging Drug and Biological Products: Part 2, Clinical Indications*;
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071603.pdf>

Contains Nonbinding Recommendations

1. Is 510(k) or PMA appropriate?

For purposes of this scenario, the sponsor's cleared MRA device for use with the approved aortoiliac imaging drug would be an acceptable predicate for the increased sensitivity and specificity of the lesion detection. However, the use of the MR device and specific gadolinium imaging drug to add specific quantification of aortoiliac lesions at 95% stenosis may raise different questions of safety and effectiveness (e.g., the validation of the sensitivity and specificity of a quantitative measure as compared to a visual display of qualitative data that would be subject to clinical interpretation). As such, the 510(k) may be found to be NSE.

2. Is an NDA supplement appropriate?

No, an NDA supplement would not be necessary. The gadolinium imaging drug is approved to evaluate aortoiliac occlusive disease in adults with known or suspected peripheral vascular disease. The approved labeling clinical trials section identifies the primary endpoint as a visual comparison of pre and post contrast images in order to detect lesions with > 50% stenosis. The device software increases the sensitivity/specificity of the visual detection or adds a computer assisted component to aid the detection to lesions that would be within the aortoiliac MRA imaging drug's indication. Therefore, the device modification would be consistent with the approved indication of the approved imaging drug.

The following additional examples further illustrate other device proposed labeling changes (regardless of device submission type) that are considered within the imaging drug indication and for which an NDA submission would not be necessary.

a. Imaging drug for Ultrasound (US):

An approved imaging drug (ultrasound microbubble) is indicated for structural delineation of the left ventricular endocardial border in patients with suboptimal non-contrast echocardiography. Assume that the device design is changed to add gating to increase the sensitivity and specificity of the LVO (left ventricular opacification) and border detection. The device change does not alter the approved drug indication; and therefore, an NDA supplement is not necessary. However, if the gating was to measure left ventricular ejection fraction, this use would not be consistent with the approved drug's indication.

b. Imaging drug for Computerized Tomography (CT):

Most imaging iodinated contrast drugs are indicated for CECT (contrast enhanced) imaging of the head and body, excretory urography, and peripheral venography. CT scans have evolved to Multidetector CT scanners. The addition of imaging iodinated contrast drug enhancement to the device

Contains Nonbinding Recommendations

labeling using Multidetector CT within same areas and dosing as approved in CECT would be considered within the approved imaging drug's indication.²⁰

c. Imaging Drug for MR – Body Indication:

According to the currently approved labeling, MR imaging gadolinium drugs with a “body” indication are considered as limited to the intrathoracic (excluding the heart), intraabdominal, and retroperitoneal regions. Device MR modifications for gadolinium enhancement to increase structural identification of masses within these regions (but not within specific organs) are considered to be within the approved drug imaging indication.

VIII. ILLUSTRATIONS FOR WHEN BOTH A DEVICE SUBMISSION AND AN NDA SUBMISSION MAY BE NECESSARY FOR A DEVICE MODIFICATION

As provided by the examples below, there are circumstances where the device proposed labeling change is inconsistent with the existing drug's indication and cannot be reviewed under a 510(k)/PMA alone. Therefore, a submission and approval of an NDA supplement to change the drug label would be necessary before or concurrent with approval or clearance of the device.

Scenario 1 - Ultrasound Contrast (US): The device is cleared for general US non-contrast imaging in several areas of the body and for contrast enhanced echocardiography using FDA approved US imaging drugs in accordance with their labeling. The imaging drug (microbubble) is approved for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The device has been modified and the sponsor submitted a 510(k) requesting clearance to add the use of the US imaging drug: 1) for the identification of myocardial perfusion defects, 2) for imaging low flow/smaller vessels in abdomen and peripheral vascular disease for the detection and assessment of aneurysms, plaque, and intimal thickness, and 3) to qualitatively assess tumors, monitor growth, vascularization & treatment effectiveness.

1. Is a 510(k) or PMA appropriate?

For the purposes of this scenario, the sponsor selected its own cleared US device as the predicate. FDA expects that the US device will have different technological characteristics when using the US imaging device and microbubble in different areas of the body (e.g., the wash-in/wash-out techniques to improve delineation of the LV border vs. rupture the microbubble for identification of the myocardial perfusion defects vs.

²⁰ FDA notes that imaging iodinated contrast drug labels do not specify the use of Multidetector CT.

Contains Nonbinding Recommendations

evaluation of peripheral vessels or aneurysms). These technological differences raise different safety and effectiveness questions as compared to the predicate device which include: interactions of the device megahertz energy that may rupture the microbubbles that may lead to adverse events, new clinical endpoints, new patient populations, and different benefits/risks ratio analysis. Also, the use of the US imaging drug for myocardial perfusion defects is a change from a cardiac general structural identification to a disease/pathology detection indication. The use in other areas of the body, and the use for aneurysms or intimal plaque measurements are substantially different indications with patient management implications. The quantitative assessment of tumor growth would raise different questions of safety and effectiveness for the new imaging endpoint correlation with disease outcomes. For these reasons, the 510(k) would be considered NSE.

2. Is an NDA supplement appropriate?

Yes, an NDA supplement would be appropriate because each of these proposed indications is different from the existing imaging drug indication as follows.

a. The US imaging drug is not approved for evaluation of cardiac/ myocardial perfusion. The existing US imaging drug indication is for the opacification of the left ventricle and visualization of the LV endocardial border (structural). A new use for myocardial perfusion imaging in patients with suspected or known coronary artery disease would represent a new functional or diagnostic indication even though it is in the same organ. New efficacy data would be needed to document image findings. New safety data would be needed using the different US wash-in/wash-out techniques and ultrasound mechanical index values to evaluate possible microsphere cavitations or rupture with associated arrhythmias.

b. As above, the existing US imaging drug indication does not include an evaluation of a vessel. Overall, the new evaluation of vascular structures, aneurysm, plaque or intimal thickness raises new safety and effectiveness (risk/benefit) questions related to demonstration that contrast US meaningfully enhances structure delineation disease/pathology detection or patient management (depending upon the endpoints) compared to non-contrast US. The clinical utility of certain endpoints (e.g. measurements of change in plaque or intimal thickness) would need verification. As such, this use would be considered as a new specific indication and not similar to the existing US imaging drug's indication.

c. Also, similar to the other indications in this scenario, the proposed use of the US imaging drug to qualitatively assess tumors, monitor growth, vascularization and treatment effectiveness is not part of the existing US LV endocardial border indication. This use would be a change from a structural to a functional, disease/pathology detection indication or a patient

Contains Nonbinding Recommendations

management indication (depending upon the endpoints). These proposed uses would all be new indications for which safety and effectiveness verification would be needed. An NDA supplement should be provided to establish the new indications and associated revisions to the imaging drug's labeling.

Scenario 2 - MR Contrast Breast imaging: The MR device is cleared for non-contrast breast imaging in patients with abnormal mammograms or non-palpable breast lesions. The device developer would like to submit a 510(k) requesting clearance for use of gadolinium imaging drugs to enhance breast imaging in the same patient population. At the time of submission, an FDA approved gadolinium imaging drug labeled for breast MR imaging does not exist.

1. Is a 510(k) or PMA appropriate?

For the purposes of this scenario, the sponsor selected its own cleared device as the predicate. Since the predicate device was cleared with the same indication as the proposed device, but without the use of the gadolinium imaging drug, it would be considered an acceptable predicate for a 510(k) submission. However, the 510(k) submission for the imaging device for use with the imaging drug could not be found substantially equivalent to the predicate until an imaging drug was concurrently approved for breast imaging.

2. Is an NDA supplement appropriate?

Yes, to date FDA has not approved a gadolinium imaging drug for breast contrast enhancement.²¹ Based on current practice standards, this use would likely be a change from structural imaging to a disease or pathology detection imaging drug indication. There would be new safety and effectiveness issues for this new indication. An NDA efficacy supplement would be expected.

Scenario 3 - Qualitative to Quantitative Imaging: The device is cleared for MR contrast imaging for qualitative structural identification of lesions in several areas of the body including the liver. An MR gadolinium imaging drug is approved for qualitative dynamic and hepatic phase imaging of focal liver lesions during a single imaging session. The device modification is to add software enhancements to add dynamic MR imaging of the liver to quantitatively assessment of tumors to monitor growth, vascularization, and treatment effectiveness.

1. Is a 510(k) or PMA appropriate?

For this scenario, the sponsor identified its cleared device as the predicate. However, the technological enhancements to add quantitative imaging are different from the original design and, as such, raise different questions of safety

²¹ Based on currently labeled gadolinium imaging drugs, the "body" indication statement is limited to the intrathoracic (excluding the heart), intraabdominal, and retroperitoneal regions. In this indication, specific organs are not part of the indication. Also, the breast is extrathoracic.

Contains Nonbinding Recommendations

and effectiveness for treatment response (e.g., the validation of the sensitivity and specificity of discrete quantitative measures of drug uptake to product specific diagnostic information such as lesion density, pattern, and configuration). For this reason, the 510(k) may be considered NSE.

2. Is an NDA supplement appropriate?

Yes, for the imaging drug (gadolinium) already approved for liver MR imaging, an NDA supplement should be submitted for the new indication. The approved MR gadolinium imaging drug is for T1-weighted magnetic resonance imaging (MRI) of the liver to detect and characterize lesions in adults with known or suspected focal liver disease. This indication is a mixed structural and pathology detection characterization (e.g., hepatocellular carcinoma, cholangiocarcinoma, metastasis, focal lymphoma, presence or absence of a lesion). However, the specific quantitation of tumors to monitor growth, vascularization & treatment effectiveness is a patient management indication that is not part of the approved imaging drug's indication. Presumably, the dynamic image involves kinetic measures and new end points that are used to make pathology/disease evaluations that would be considered as a new indication. An NDA efficacy supplement should be submitted to achieve imaging drug labeling for the new indication.

In all of the above scenarios, when the 510(k) is found to be NSE (not substantially equivalent) to a predicate, the submission should be a PMA. If the submitter would like FDA to consider a DeNovo petition, FDA recommends having a detailed discussion that includes consideration of what type of Special Controls Guidance could be developed to mitigate the risks of the device.

IX. CONSIDERATIONS FOR HOLDERS OF IMAGING DRUG APPLICATIONS

Holders of an NDA or BLA for an imaging drug or biological product who seek to develop new contrast indications that refer to information developed in a device submission should submit supplements to their NDA/BLA. In addition, if FDA approves or clears a new imaging contrast indication in a device submission (which did not require a change to the drug labeling), the NDA/BLA holder may nevertheless submit a labeling supplement to add the indication to the imaging drug. Furthermore,

- If the NDA holder wishes to request exclusivity, then an efficacy supplement should be submitted.²²
- When an NDA holder wishes to add clarifications to an imaging drug label and an NDA supplement is not otherwise needed, these labeling changes would be submitted as a labeling supplement.

²² Under 21 CFR 314.108, FDA may grant drug product exclusivity for studies not conducted or sponsored by the applicant. On a case-by-case basis, FDA will consider whether exclusivity may be appropriate when relying on studies submitted in the PMA/510(k).

Contains Nonbinding Recommendations

- If the NDA proposes a new indication, new dose, or new dose rate or route, that requires new device technology, then in parallel with the NDA efficacy supplement, the device sponsor would submit the appropriate device submission in accordance with the principles under Section VI, *What type of Device Marketing Submission to Provide*.

X. PREMARKET DEVELOPMENT CONSIDERATIONS

A. Considerations for Data Necessary to Support Approval of a New Imaging Contrast Indication

As noted in Section III. *Terminology*, there are four large categories of imaging contrast indications. Existing FDA guidance documents provide recommendations on what to include in a submission and how to submit device technology information on certain devices (ultrasound, MRI, SPECT, PET).²³ In other existing FDA guidance documents, the Agency also provides detailed recommendations on the data necessary to establish the safety and effectiveness of different types of imaging contrast indications associated with imaging drug and biological products (*Developing Medical Imaging Drug and Biological Products*, Part I, 1, 2 and 3).²⁴ 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 *Early Development Considerations for Innovative Combination Products* provides information on how known information might be useful in product development.²⁵

FDA recommends that manufacturers of imaging drug-device combination products or manufacturers of imaging devices for use with an imaging drug class consider these existing guidance documents as a starting point for development plans for their specific

²³ Emission Computed Tomography Devices and Accessories (SPECT and PET) and Nuclear Tomography Systems;

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM073797.pdf>; Magnetic Resonance Diagnostic Devices;

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073817.htm>

²⁴ FDA guidance *Developing Imaging Drug and Biological Products, Part 1: Conducting Clinical Safety Assessment*,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071600.pdf>; *Part 2: Clinical Indications*;

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071603.pdf>; *Part 3: Design, Analysis and Interpretation of Clinical Studies*,

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071604.pdf>

²⁵ *Early Development Considerations for Innovative Combination Products*;

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm>

Contains Nonbinding Recommendations

imaging 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 imaging 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 imaging 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.

FDA recognizes that the type and volume of data necessary to submit may vary in accordance with such factors as the indication, patient population, safety questions, and drug characteristics. When the dose, dosing regimen, rate and route of administration of the imaging drug is the same and the device does not interact with the drug, it is likely that FDA guidance *Developing Imaging Drug and Biological Products Part 3: Design, Analysis and Interpretation of Clinical Studies* will be the most relevant guidance. Further, in some instances the type of trial design may be tailored to focus on certain issues; e.g., electrophysiologic studies to evaluate effect of microbubble rupture on ventricular arrhythmia. Also, as appropriate, in some instances published literature or other public documents may be able to provide the information to establish an indication.

1. Imaging Drug Class Considerations

When an imaging device manufacturer is considering a new imaging contrast indication for a broad class of imaging drugs (e.g., gadolinium), 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 described in Section IV. *Background* (e.g., microbubbles, paramagnetic metallic ions linked to different chemicals, iodinated products, and 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 also there may be different doses, different risk profiles, or other unique labeling. Further, within a broad imaging class there may be different characteristics as the class evolves; e.g., changes in chelates, carriers, ligands, or other features of the imaging drug. As new generations of imaging drugs are approved, their indications may be different.

In designing a trial for a class of FDA approved drugs, FDA recommends that the design(s) include features to address differences as appropriate within the class of imaging drugs. Also, it would be important to consider what is different about the new indication or patient population.²⁶ It may be necessary to determine how the

²⁶ Most imaging drug classes (e.g., gadolinium, microbubbles, and radiopharmaceuticals) have a Black Box Warning regarding different types of serious adverse events. The clinical trial design should consider the relevance of the existing safety profile to the proposed new use. For example, magnetic resonance imaging of the renal arteries using an approved drug that has known toxicity in patients with renal insufficiency, the combined use raises new questions of safety and effectiveness of using the drug in a different risk population than that provided in the approved drug label for brain imaging.

Contains Nonbinding Recommendations

device should be used with imaging drugs that have different dosing requirements. These data should be established 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. Alternatively, imaging device developers may consider establishing an indication for only one imaging drug in a class.

2. Imaging Device Class Considerations

Imaging devices typically have similar indications or intended use. However, within an imaging drug class there may be differences that should be considered in developing the device settings to ensure consistent performance characteristics. Also, there may be device settings that should be preset and locked for safety and effectiveness. For imaging drug manufacturers considering a new imaging 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, it is important to consider what imaging device changes have occurred since your imaging drug was first approved. For the new imaging contrast indication, FDA also recommends considering trial designs that encompass both the most recently cleared/approved imaging devices as well as those that are most widely available.

XI. POSTMARKET CONSIDERATIONS

The holder of an approved device submission that includes the specific new imaging contrast indication should monitor the approved drug's 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.²⁷ Further, to enhance postmarket safety reporting, while many imaging device and imaging drugs do not meet the definition of a combination product, the reporting principles for combination products may be useful to sponsors whose labeling includes the use of a differently regulated product and who may receive reports about that differently regulated product.²⁸

XII. INTERACTION WITH FDA AND THE REVIEW PROCESS

Early communication and discussion between manufacturers and FDA 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 for their product and proposed new imaging contrast indication. Such

²⁷ 21 CFR Part 803, 814.82, 822.

²⁸ FDA published postmarket safety reporting requirements for combination products; *Federal Register*, Vol 74, No 189, October 1, 2009, page 50744.

Contains Nonbinding Recommendations

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 a 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 combination products.²⁹ Ideally the meeting background package should provide a comprehensive discussion of the proposed imaging 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,³⁰ CBER,³¹ and CDRH³² websites.

The manufacturer should contact the lead center to schedule meetings in accordance with the milestones applicable to the lead center. The lead center will consult with other centers or agency components as needed in accordance with the scientific and technical issues in the submission. As described further in Section V.A *Determination of Lead Center Responsible for Premarket Review*, for device manufacturers who are considering trials to add new imaging contrast indications using a class of imaging drugs, the lead center would be CDRH. For a combination product, the lead center is determined by the primary mode of action.³³

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 guidance for products that do not meet the definition of a combination product, but raise similar questions. During product development, protocol

²⁹ IND stands for investigational new drug application; IDE stands for investigational device exemption.

³⁰ See <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

³¹ See

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

³² See

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm> and, *Early Collaboration Meetings Under the FDA Modernization Act, Final Guidance for Industry and CDRH Staff*;

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm>

³³ 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.

Contains Nonbinding Recommendations

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*³⁴ to promote timely and effective review.

As appropriate, OCP will assist in developing additional focused procedures for the imaging review divisions/branches. These procedures should provide for an Intercenter Imaging Team to review clinical protocols, labeling and other practices to ensure consistency of developmental approaches and relevance of results to submit under either the drug, biological, or device provisions. The review 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.

XIII. 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/CombinationProducts/default.htm>.

In addition each center maintains a guidance webpage that provides comprehensive information on the types of products or constituent parts regulated in the center. For medical imaging drug products, the CDER Guidance webpage is accessible at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. The CDRH Guidance and Device Advice web page is accessible at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.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/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>
- Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices;
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072686.htm>

³⁴ Standard Operating Procedures and Policies: *Intercenter Consultative and Collaborative Review Process*; <http://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm119234.htm>

Contains Nonbinding Recommendations

- Early Development Considerations for Innovative Combination Products;
<http://www.fda.gov/oc/combination/innovative.pdf>
- Exploratory IND studies;
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm>
- FDA Radiological Health Program: Ultrasound Imaging;
[EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/ucm115357.htm](http://www.fda.gov/EmittingProducts/RadiationEmittingProductsandProcedures/MedicalImaging/ucm115357.htm)
- Guideline for Device Master Files;
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm>
- Guidline for Drug Master Files;
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122886.htm>
- FDA guidance *Developing Imaging Drug and Biological Products, Part 1: Conducting Clinical Safety Assessments*,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071600.pdf>; *Part 2: Clinical Indications*;
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071603.pdf>; *Part 3: Design, Analysis and Interpretation of Clinical Studies*,
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071604.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/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080183.htm>

APPENDIX 1 - MEDICAL IMAGING PRODUCT LABELING CONVENTIONS

1. Imaging drug indication statement: Imaging drug labels typically are more specific and may follow the illustration below:

Drug X is a [*drug class*] gadolinium based contrast agent indicated for [*administration*] intravenous administration in [*imaging procedure*] magnetic resonance imaging of the [*body region*] brain and spine to [*clinical use*] visualize lesions with abnormal vascularity in [*population, age*] adult or pediatric patients (age 2 or older) with known or suspected CNS lesions including tumors.

2. Imaging device imaging contrast indication statement: The degree of specificity in the labeling of imaging devices varies. 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

Contains Nonbinding Recommendations

software but does not explicitly appear in the labeling. The following example may be used for a device indication statement:

Device Y is indicated for [*imaging procedure*] magnetic resonance imaging of the breast with [*drugs X, Y, Z*] or [*FDA approved for*] as a second line (after mammography) diagnostic procedure [*clinical use*] to aid in the evaluation of breast lesions in patients [*population*] with an abnormal breast examination or an abnormal mammogram. *Limitations [if applicable]* Device Y is not indicated for breast cancer screening and is not an alternative to biopsy.

APPENDIX 2 – TYPE OF MEDICAL IMAGING PRODUCTS

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.³⁵ 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 water present in the body.
- 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.
- Nuclear imaging drugs, also known as radiopharmaceuticals, contain in part a radionuclide that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons.
- Light sensitive (emitting, absorption) imaging drugs contain molecules for activation by electromagnetic energy or light at specific wavelengths.

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

³⁵ For purposes of this document, the term imaging or contrast drug applies to both drug and biological product including radiopharmaceutical products.