



GE Healthcare

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0257 8 DEC 19 P1:25^{HSA}

December 17, 2008

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

Re: Docket FDA-2008-D-0525; Draft Guidance for Industry on New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products

Dear Sir or Madam:

GE Healthcare, a global manufacturer of imaging devices, contrast agents and radiopharmaceuticals, appreciates and fully supports FDA activities to develop guidance on new contrast imaging indications for diagnostic imaging devices used with approved contrast agents and radiopharmaceuticals. We believe that clear guidance will help ensure timely and effective development and review of new indications and help further public health through more rapid availability of safe and effective new imaging applications.

As a manufacturer of both imaging devices and drugs, GE Healthcare offers a unique perspective within the medical imaging industry. Attached are our comments on the draft guidance, as well as a line-numbered version of the guidance we created to facilitate the commenting process.

We encourage FDA to hold a public workshop to discuss the guidance and obtain wider stakeholder comment before issuing the final guidance document. Since the guidance affects both drug and device development, and the drug and device industries bring sometimes differing experience and perspectives, a public workshop would help ensure clarity of views and provide better confidence that the final guidance will provide the kind of roadmap envisioned by the MDUFMA performance goal.

We would be happy to provide any additional information or clarification regarding our perspective on these issues. Please do not hesitate to contact me at (262) 544-3435 or by email at gerald.buss@ge.com if you would like to further discuss.

Sincerely yours,

Gerald L. Buss, RAC
Executive, Regulatory Affairs
GE Healthcare

FDA-2008-D-0525

C

GE Healthcare Comments
Draft Guidance for Industry: New Contrast Imaging Indication Considerations
for Devices and Approved Drug and Biological Products
Docket Number FDA-2008-D-0525; 73 FR 58604
December 17, 2008

Lines 41-43: The guidance recommends that the data necessary to establish new contrast indications for devices should be developed in accordance with FDA's "Developing Imaging Drug and Biological Products" guidance. Since the "Developing Imaging Drug and Biological Products" guidance was focused on new imaging agents, and the current guidance, by definition, addresses already approved agents, we believe that a blanket statement to apply the 2004 drug/biological product guidance is too general and may be inappropriate or unnecessary in some circumstances. Since the imaging agent will, in many circumstances described in the current guidance, be used in a manner that is "otherwise consistent" with the imaging agent's approved use, the extent of data necessary might be only a subset of that anticipated in the drug/biological products guidance.

Furthermore, we note that the 2004 "Developing Imaging Drug and Biological Products" guidance has not been as effective as initially intended in supporting the development of new imaging drug and biological products and bringing approved new agents and new indications to the medical community. We recommend that FDA consider whether revision to the 2004 guidance or its implementation may be warranted to facilitate the development of new imaging agents/indications by both drug and device sponsors.

Lines 47-50: We suggest that this section be clarified. The current statement could be interpreted two ways: (1) that drug or biological product application holders *should* (i.e., are routinely encouraged/expected to) submit an efficacy or labeling supplement to add labeling for a new indication approved/cleared under a device application OR (2) if a drug or biological product application holder *wishes* to add labeling for a new indication approved/cleared under a device application, they would do this by submitting an efficacy or labeling supplement. It is currently unclear whether the current statement is meant to describe the regulatory pathway to be used as an option to drug application holders (as implied in the parallel section governing device applications in lines 51-53), or whether FDA intends that drug application holders are routinely encouraged/expected to update their labeling following approval/clearance of a related device application. Please clarify whether such supplements are expected and if so, in what time frame.

Lines 67-69: FDA should consider whether the definition of a "contrast indication" is too narrow for the purposes of this guidance. While most new uses of an imaging device with an imaging drug would likely appear in the indication or intended use section of the device labeling, some readers may interpret this definition to mean that analogous statements made in other sections of the device labeling do not constitute a "contrast indication" for the purposes of this guidance and therefore may be added without adhering to the principles outlined in this guidance.

Lines 199-200: One of the stated intentions of the guidance is to promote “comparability in labeling format and content (to the extent permissible under the different regulatory authorities),” but the guidance does not otherwise address how the labeling of the drug and device should be made comparable in format or content. If this remains one of the intentions of the guidance, additional information on labeling format and content for imaging devices and drugs should be included.

Lines 206-216: We agree that, in appropriate circumstances and with appropriate supporting data, the labeling of the imaging device could be expanded without requiring conforming changes to the drug labeling. This will help promote public health by facilitating the approval/clearance of innovative new uses of imaging devices that depend on approved imaging agents, even in cases where the imaging drug application holder may not be interested in pursuing that new use.

- However, we believe some key terms should be clarified so that this guidance will be more useful, particularly for device sponsors considering the development of new contrast indications:
 - FDA explains that device approval/clearance without requiring drug relabeling “may occur when the device technology does not alter the drug and when the drug use is *otherwise consistent* [emphasis added] with its approved labeling.” Much of the applicability of this guidance is predicated on a clear understanding of what it means for the drug use to be “otherwise consistent” with its approved labeling. The single example provided in this section of the guidance (quantitative angiography) concerns a situation that appears to be completely consistent with the current use of the drug. In order for this guidance to address the innovation and public health issues that led to the MDUFMA requirement for its development, we believe FDA should exercise appropriate discretion in determining what is meant to be “otherwise consistent.” We respectfully request that FDA provide additional examples to further elucidate these principles. We also request that FDA clarify what is meant in line 214 by a “new yet consistent contrast indication.”
 - Similarly, later in that same paragraph, in explaining when a device submission alone should suffice, FDA notes that the “drug labeling does not need revision.” The guidance should better define, and illustrate by way of examples, what it means for use of the drug to be “otherwise consistent” with its approved labeling, and when the “drug labeling does not need revision.” It should also be clarified whether the drug labeling can be revised by cross-reference to the device approval/clearance if the drug sponsor should decide to do so. (See also our comments to lines 47-50 above and footnote 8 below.)
 - It would be helpful to have additional clarification on what it means for the device technology to “alter the drug.” For example, in the past, manufacturers have discussed with FDA new applications of ultrasound imaging that require bursting of ultrasound microbubbles, which some might interpret as “alter(ing) the drug.”

Would this kind of ultrasound imaging not be amenable to the “device only” application strategy FDA outlines in this guidance, if all other conditions are met?

- It would be helpful if the guidance explained with whom in FDA device sponsors should work (e.g., Office of Combination Products, Radiology Devices Branch in CDRH, etc.), and using what mechanisms (e.g., pre-IDE submissions), to determine whether a proposed new contrast indication is considered “otherwise consistent” or instead drug relabeling will be required and when. We believe it is important that such determinations be made relatively early in product development, before sponsors invest considerable resources only later to learn that drug relabeling will be necessary and the drug application holder is not interested in pursuing the labeling change.
- We recommend that the guidance clarify the impact of approval/clearance of devices for new contrast claims when conforming changes to the drug label are not necessary. In particular, sponsors such as GE Healthcare, which manufacture both imaging devices and drugs, would need clarity as to whether it could market approved/cleared new contrast indications for its devices without risk that the Agency would find that such device promotion constitutes inappropriate (or indirect) promotion of its imaging agents for these new uses, if for business reasons we were to pursue approval of new contrast indications for our devices but not for our drugs. This is a concern not faced by companies that market only imaging devices.

Lines 223-231: Similar to our comment for lines 206-216 above, the guidance should clarify what is meant for a contrast indication to be “consistent with the drug’s approved indication.”

We recommend that FDA consider the following factors in determining whether a device’s new contrast indication is “otherwise consistent” and therefore would not require conforming changes to drug labeling as a condition for device approval or clearance: (1) no change in the drug formulation is necessary for the new indication, i.e., the drug can be used in its currently marketed form; (2) the imaging drug is already approved for same broad body structure or function imaging use; (3) the new indication would use the drug at the same (or lower) dose, rate of administration and route of administration as currently approved; and (4) the studies of the new indication do not raise significant new safety issues, e.g., new types of adverse events.

We propose that in select circumstances, such as when the device’s new contrast indication significantly affects or alters the safety profile of the drug, both the drug and device labels should be changed in order to ensure safety and effectiveness of the concomitant use. Factors that might make it more likely for the drug label to also need to be changed are when the new indication: (1) addresses a significantly different patient population, body structure or function imaging use, or requires a significantly different dosing regimen necessitating significant new safety and efficacy studies; (2) raises new safety issues not currently reflected in the drug product labeling; or (3) affects the approved drug product’s benefit-risk ratio.

Examples might be a patient population at significantly greater risk or likely to experience significantly greater exposure (e.g., due to slower excretion), a change in administration likely to

result in greater exposure (e.g., slower infusion), or an application with significantly lower diagnostic benefit, thereby reducing the benefit/risk ratio or therapeutic index. Another factor necessitating drug relabeling might be when the new indication is tied to a particular drug-device combination, i.e., the new device indication applies only to an individually specified drug and meets the definition of a combination product. In these above cases, relabeling both the drug and device may help prevent user confusion that may arise if only the device is relabeled.

Lines 234-242: It seems entirely appropriate, as FDA recommends, that changes to an imaging drug's formulation should be the subject of an NDA/BLA supplement. Certainly in the case of a formulation change, a device company would not be in the position to unilaterally effect such a change. The guidance provides the example of a drug reformulation change made to allow enhanced biodistribution to a new "area" (assumed region of the body) using the same imaging software. In this case, FDA recommends that an NDA/BLA supplement would be needed, and that a device application would not be necessary. Would the converse be true? If changes to imaging device software are made to allow better visualization of contrast in a region of the body to which the drug was already distributed, would such use be considered "otherwise consistent," and therefore could be approved/cleared under a device application without the need for a drug application? (See also our comments to lines 47-50 above and footnote 8 below.)

Footnote 8: We recommend that this statement be clarified (see also our comments to lines 47-50 above). It is unclear if FDA intends for this statement to mean that approval of a new contrast indication in a device application does not in itself permit the drug application holder to change its labeling, i.e., because an efficacy or labeling supplement would be required to obtain approval for such change OR whether FDA intends this statement to mean that approval/clearance of a new contrast indication in a device application may not support approval of the analogous change to the drug labeling.

We believe FDA's intent is that this guidance should establish similar and consistent review methodologies that would lead to approval/clearance decisions supportive of related changes to both the drug and device labels, if both sponsors choose to pursue them. To that end, we recommend that the guidance clarify whether a drug/biological product application holder's efficacy or labeling supplement could cross reference the approval/clearance of the device application, or whether the drug application holder would need to provide its own (additional) safety and efficacy documentation in support of its supplement.

Finally, while we recognize that the new drug product exclusivity provisions of the Act apply to drug and biological product applications, and not device submissions, we request that FDA clarify whether drug and biological product application holders who submit efficacy supplements for new contrast indications supported by cross-reference to approval/clearance of a new contrast indication in a device application, will each receive exclusivity for that indication, starting from the date of approval of the new indication for the drug.

Lines 253-256: The guidance implies that FDA may require labeling changes to both the imaging device and drug for new contrast indications provided at lower than approved doses of the contrast agent. We recommend that FDA consider the significance of a dosing change on a case-by-case analysis rather than as a general principle. If the imaging agent is already approved

at higher doses, it is less likely that the new contrast indication would adversely affect the safety profile of the drug. Please refer to our comments regarding lines 223-231 above for more information about when drug relabeling may be appropriate.

Lines 258-263: Rather than introduce new terms or principles in this guidance, we recommend FDA clarify when a device submission is required to reflect an imaging drug modification by tying the trigger for a device submission to existing CDRH guidance, i.e., “Deciding When to Submit a 510(k) for a Change to an Existing Device” and the draft guidance “Modifications to Devices Subject to Premarket Approval – the PMA Supplement Decision Making Process.”

Line 267: We suggest that FDA broaden its discussion of the kind of data that will be required to establish a new contrast indication. While we understand that “clinical trials” will be necessary in most cases, in appropriate cases, it is possible that other data may be adequate. Language such as “clinical trials or other appropriate data” would clarify this.

Lines 304-305: The guidance explains that clinical studies conducted by device developers wishing to add a new contrast indication should “proceed under the investigational device exemption (IDE) regulations *with a submission to CDRH*” [emphasis added]. Some imaging device investigations are considered “non-significant risk” (NSR). While these NSR studies are conducted under the IDE regulations and require IRB approval, they do not require IDE submission to CDRH. It would be helpful if FDA clarified the investigational submission requirements for NSR imaging device sponsors wishing to add a new contrast indication.

Line 351: Similar to our comment above regarding line 267, we recommend this section be written more generically in that some changes may not require full scale clinical trials.

Lines 362-363: Similar to our comments above regarding lines 267 and 351, we recommend replacing “trials” by “studies” here and where applicable throughout the document. Furthermore, one or more examples might help illustrate what FDA intends by lines 362-363. One example might be the recommendation for cardiac monitoring for possible arrhythmias during and immediately following the administration of ultrasound microbubble contrast agents.

Lines 402-416: While we understand FDA’s rationale that some changes to 510(k)-cleared imaging devices to include new contrast indications may require premarket approval (PMA) applications, here and in lines 44-46, we believe FDA should take a case-by-case approach in making this determination. Further, the approach should be based on the longstanding principles embodied in the Office of Device Evaluation’s “Substantial Equivalence Decision-Making Process” described in Blue Book Memorandum K86-3 and later codified into statute and regulations. While the draft guidance asserts that “the need for a PMA reflects the new type of safety and effectiveness questions that arise when the new imaging drug-device indication is added to the device submission, particularly in the absence of a concurrent NDA,” according to FDA’s longstanding substantial equivalence decision-making process, one must ask whether “new types of safety and effectiveness questions” are raised only if the device has different technological characteristics that could affect safety and effectiveness. In some cases, the device may not require technological changes in order to enable the new contrast indication, and therefore “new types of safety and effectiveness questions” do not play a role in the decision-

making process. We believe a more appropriate mechanism to address this concern in the guidance is to note that, for 510(k)-cleared devices, new contrast indications will be assessed using the established substantial equivalence decision-making process, as required by statute, regulation and long-standing policy. The established substantial equivalence decision-making process provides considerable flexibility to permit FDA to direct contrast indications into either the PMA or 510(k) process, as appropriate, given the specific situation.

This section of the guidance also recommends that a PMA is necessary in certain situations, “particularly in the absence of a concurrent NDA.” In the case where the same type of changes are being made but a concurrent NDA *is* being submitted, we request that the guidance clarify whether a PMA would still be necessary, or whether a 510(k) could then be submitted.

Lines 420-424: Please reference our comment relevant to lines 402-416 above, i.e., that “new types of safety and effectiveness questions” may not necessarily be part of the substantial equivalence decision making process for a 510(k)-cleared imaging device, depending on the changes necessary to effect the new contrast indication.

In addition, we believe the single example FDA cited as to when a 510(k) may be appropriate requires clarification. The draft guidance notes that a 510(k) “might be acceptable if the approved imaging drug and cleared imaging device are already indicated for the same or consistent contrast indication.” If the imaging device is already indicated for the “same” contrast indication, why would any additional premarket approval/clearance (whether PMA or 510(k)) be necessary? Furthermore, as noted in other comments described above, FDA should clarify what it means for a new contrast indication to be “consistent” with that in an approved product.

Finally, while lines 407-409 of the draft guidance note that a PMA may be needed particularly for new contrast indications within the categories of disease or pathology detection or assessment; functional, physiological or biochemical assessment; and diagnostic or therapeutic patient management, we note that the omission of structural delineation implies that structural claims may be more amenable to a 510(k) approach. It would be helpful if the guidance further clarified this point.

Lines 430-432: The draft guidance notes that “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.” This is reasonable, though we recommend that lines 47-50 and footnote 8 be clarified (see comments above) to make the document internally consistent. Further, based on the guiding principles described in the guidance, we recommend that the guidance clarify that the data necessary to support such a drug labeling supplement should be consistent with what was required to support the device approval/clearance.

Lines 436-437: The draft guidance recommends that 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*” [emphasis added]. It would be helpful for FDA to clarify what types of “other changes” should be monitored, and how.

Lines 439-442: The draft guidance states that “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*.” We recommend that the guidance clarify that such reports would be submitted under the manufacturer’s obligations under the Medical Device Reporting (MDR) regulation, 21 CFR 803. Further, we recommend that the wording be clarified so as not to imply that the adverse events should actually be submitted (or added to) the device labeling, as could be construed from the sentence as currently worded. Removal of the words “in its labeling” would provide clarity without any loss of meaning from the remainder of the sentence.

Line 468: FDA previously stated (lines 282-283), and we agree, that most concomitant use of imaging devices and contrast agents does not represent a combination product. Line 468, however, uses the term “combination product,” apparently inadvertently. We recommend that the final clause “for the combination product” be removed without any loss of meaning from the remainder of the sentence.

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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

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

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

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

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

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

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**U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP) in Office of the Commissioner
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1 **Guidance for Industry¹**
2 **New Contrast Imaging Indication Considerations for**
3 **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.

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7 **I. INTRODUCTION**
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9 FDA intends this guidance to assist developers² of medical imaging devices and imaging
10 drug/biological products that provide image contrast enhancement. Particularly this
11 guidance focuses on approaches in developing new contrast indications for imaging
12 devices for use with already approved imaging drug or biological products. FDA intends
13 for the recommendations in this guidance to promote timely and effective review of, and
14 consistent and appropriate regulation and labeling for imaging drugs and devices.
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16 This document supplements existing guidance developed by the Center for Devices and
17 Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and
18 the Center for Biological Evaluation and Research (CBER), and the Office of Combination
19 Products (OCP).
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21 This guidance does not address the specific scientific or technical content to provide in a
22 regulatory submission to demonstrate safety and effectiveness of an imaging product(s) for
23 specific indications.
24

25 FDA's guidance documents, including this guidance, do not establish legally enforceable
26 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and
27 should be viewed only as recommendations, unless specific regulatory or statutory
28 requirements are cited. The use of the word *should* in Agency guidances means that
29 something is suggested or recommended, but not required.
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¹ This guidance has been prepared by Office of Combination Products, in the Office of the Commissioner, in conjunction with the Center for Devices and Radiological Health and the Center for Drug Evaluation and Research.

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

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32 **II. PURPOSE**

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

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

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60 **III. TERMINOLOGY**

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62 For purposes of this document, the following conventions apply.

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

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

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IV. SCOPE

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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.

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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.

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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.

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V. BACKGROUND

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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).

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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

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

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

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

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

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153 FDA existing guidance identifies imaging drug contrast indications in four broad
154 indication areas:⁶

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- 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.

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

171
172 Imaging device software and hardware engineering technologies that utilize imaging drugs
173 evolve rapidly (i.e., once or twice a year) and typically out-pace development of new
174 imaging drugs or new indications for already approved imaging drugs. Device
175 advancements may create an opportunity for a new indication using an approved imaging
176 drug without any change to its dose, rate, or route of administration. For example, if a
177 drug that is approved for use in imaging the lung is systemically distributed in the body,
178 new device software may allow the drug to be used in imaging the liver. If the drug and
179 device manufacturer do not cooperate to seek approval for the new indication in the drug
180 labeling, the pathway to market for the new device technology may be unclear.

181
182 This guidance describes principles under which either a drug or device developer can seek
183 marketing approval of new contrast indications using an already marketed imaging drug.
184 In developing these principles, FDA considered the scientific and technical issues that may
185 occur when using a class of drugs and class of devices together, approaches to leverage
186 prior Agency decisions, approaches to ensure consistency of information regardless of the
187 submission being used to establish new contrast indications, and approaches to ensure the
188 consistency of the regulatory vehicle for submission under the drug, biological, or device
189 provisions being used to establish similar types of contrast indications. FDA intends for
190 these principles to promote:

- 191
192 • The ability of the imaging device applicants to add certain new imaging contrast
193 indications for use of the device with the already approved imaging drugs without
194 having modification of labeling for both the device and the drug;
- 195 • Consistency in the type of scientific or technical information submitted to establish
196 a new indication for use regardless of the type of marketing submission; i.e., NDA,
197 BLA, PMA, premarket notification (510(k) submission (to the extent permissible
198 under the different regulatory authorities); and
- 199 • Comparability in labeling format and content (to the extent permissible under the
200 different regulatory authorities).

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VI. REVIEW PRINCIPLES

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

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

1. *When might only an imaging device application suffice?* When an imaging device or device modification enables the device to be used with an approved imaging drug (i.e., at its approved formulation, dose, rate, and route of administration) for a contrast indication that is consistent with the drug's approved indication, in most cases FDA expects to be able to make a review determination based on an original or supplemental submission from the device application holder alone. A favorable decision on the application would allow the imaging device sponsor to add the contrast indication to the device labeling without the need for a conforming change to the imaging drug labeling.⁸
2. *When might only an imaging drug application suffice?* When an imaging drug modification (i.e., formulation, dosage, rate, or route of administration) enables the drug to be used with an approved or cleared imaging device for a new indication, the NDA/BLA holder should submit a supplement to FDA to request approval for such change. For example, an NDA is most appropriate for a drug reformulation to allow enhanced biodistribution to a new area, but using the same imaging software. In most instances, FDA expects to review an NDA submission to add such an indication to the drug labeling without the need for a device submission or conforming labeling to the imaging device.

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.

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243
244 3. *When might both an imaging drug and device application be most appropriate?*
245

246 Generally there are two circumstances when both an NDA/BLA and a device
247 application should be provided to request approval of a new indication for using the
248 imaging drug and the imaging device together.
249

- 250 a. When an imaging device modification also necessitates a change in the imaging
251 drug formulation, dosage, rate, or route of administration for the same imaging
252 indication or for a new indication, FDA will generally need to review both a
253 drug and device submission to ensure labeling conformity. For example, if a
254 change in device design provides for enhanced imaging at lower doses of the
255 drug, to ensure appropriate drug safety, FDA may determine that the drug
256 dosing information should be in both the imaging drug and device labels.
257
- 258 b. When an imaging drug modification (i.e., formulation, dosage, rate, or route of
259 administration) also necessitates a change in the approved imaging device
260 performance characteristics, specifications, or design for its labeled imaging
261 indication or for a new indication for use, FDA will generally need to review
262 both a drug and a device submission to request approval for the new indication
263 and labeling changes.
264

265 Regardless of which label (imaging device, drug or biological product) adds the new
266 contrast indication, the safety and effectiveness of the new contrast indication should be
267 established by data collected from appropriately designed clinical trials using both the drug
268 and the device. The regulatory pathway does not affect the scientific and technical
269 information that is most appropriate for establishing the safety and effectiveness of the new
270 contrast indication. (For additional information please see section VII.B, *Considerations*
271 *for Data Necessary to Support a New Contrast Indication for Use*). Further, the labeling
272 of product(s) adding the new indications should reflect the essential information that
273 establishes the contrast indication (e.g., the clinical study description, imaging device
274 characteristics and settings, imaging drug dosing regimen, target organ).
275
276
277

VII. PREMARKET DEVELOPMENT CONSIDERATIONS

278

A. Determinations of Lead Center Responsible for Premarket Review

279

280 Most imaging devices and drugs approved for use with a class of drugs or class of devices
281 do not meet the definition of a combination product under 21 CFR 3.2(e). For example,
282 the imaging device or drug contrast indications refer respectively to a class of imaging
283 drugs (gadolinium contrast) or a class of imaging devices (magnetic resonance imaging).⁹
284
285

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.

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

291
292 In some instances, the use of a diagnostic imaging device and imaging drug may constitute
293 a combination product under 21 C.F.R. 3.2(e)(3).¹¹ For example, certain dedicated
294 imaging drug-device products may constitute a combination product; e.g., a specific
295 imaging drug to bind receptors for imaging with a dedicated software algorithm. Although
296 a detailed discussion of how FDA applies combination product authorities is beyond the
297 scope of this guidance, if a manufacturer has a combination product, the lead center
298 determination, as with other products, will be in accordance with the primary mode of
299 action regulations in 21 CFR 3.4.¹² Developers of a specific drug-device imaging product
300 may wish to contact FDA to discuss whether a request for designation would be useful.¹³

301
302 As described further in this document Section IX, *Interaction with FDA and the Review*
303 *Process*, for developers of an imaging device wishing to add a new contrast indication for
304 a class of imaging drugs, the supportive clinical study should proceed under the
305 investigational device exemption (IDE) regulations with a submission to CDRH. For
306 imaging drug developers wishing to add a new contrast indication, the supportive clinical
307 trials should proceed under the IND regulations with a submission to CDER. For a
308 combination product, the submission should be sent to the lead center as determined by the
309 product specific primary mode of action. Typically, the type of investigational application
310 for a combination product is that of the lead center (e.g., an IND for CDER and IDE for
311 CDRH).

B. Considerations for Data Necessary to Support Approval of the New 314 Contrast Indication for Use

315
316
317 As noted in this document Section IV, *Scope*, there are four large categories of imaging
318 contrast indications. In existing FDA guidance documents, the Agency provides

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320
321

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/combo/Guidance-How%20to%20Write%20an%20RFD.pdf>

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

- 327 • Conducting Safety Assessments;
- 328 • Clinical Indications; and
- 329 • Design, Analysis, and Interpretation of Clinical Studies

330

331 Further, for the subset of imaging products that are combination products, the FDA
332 guidance entitled *Early Development Considerations for Innovative Combination Products*
333 provides information on how known information might be useful in product development.
334¹⁴

335

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

347

348 1. Imaging Drug Class Considerations

349

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

361

362 In designing a trial for a class of FDA-approved imaging drugs, FDA recommends that
363 the design(s) include features to address unique aspects of the class of imaging drugs.
364 A sponsor should also consider what is different about the new indication or
365

¹⁴ See <http://www.fda.gov/oc/combinatiion/innovative.pdf>

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

373 374 2. Imaging Device Class Considerations

375
376 Imaging devices typically have similar indications or intended uses. When developing
377 a new contrast indication under a drug application, the devices evolve and often evolve
378 quickly. There may be differences in the settings that can be adjusted or those that are
379 locked for safety. For imaging drug manufacturers considering a new contrast
380 indication for a class of devices, FDA recommends considerations of clinical trial
381 designs that study the similarities and differences in the class of marketed imaging
382 devices that are most appropriate for the new indication. Also, consider what imaging
383 device changes have occurred since your imaging drug was first approved. For the
384 new contrast indication, FDA also recommends considering trial designs that
385 encompass both the most recently marketed imaging devices as well as those that are
386 most widely available. If the new indication depends on a unique imaging device, then
387 the indication should be device-specific.

388 389 **C. Considerations on the Type of Marketing Submission to Provide When** 390 **Using a Device Application Alone**

391
392
393 Under the principles set forth in this document Section VI, *Review Principles*, FDA
394 believes certain new imaging contrast indications can be reviewed in a device submission
395 alone when they entail only device modifications and when a change in the approved drug
396 labeling would not be necessary. As described below, when a device sponsor seeks to
397 develop a contrast indication using an approved drug, the submission may be a PMA or
398 510(k).

399 400 1. When is a PMA most appropriate?

401
402 FDA believes that approval of most proposed new contrast indications meeting the criteria
403 described in this document Section VI.1 (i.e., those arising from a change in the imaging

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.

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404 device alone that do not affect the imaging drug or require changes to drug
405
406 labeling) should be sought in a PMA. This particularly includes new contrast indications
407 within the categories of a) disease or pathology detection or assessment, b) functional,
408 physiological or biochemical assessment, or c) diagnostic or therapeutic patient
409 management. The need for a PMA reflects the new type of safety and effectiveness
410 questions arising when the new imaging drug-device indication is added to the device
411 submission, particularly in the absence of a concurrent NDA.¹⁶ For example, a new
412 contrast indication for breast cancer screening or diagnosis using an imaging drug that is
413 not approved for imaging that area of the body may present new types of questions of
414 safety and effectiveness.¹⁷ FDA believes the approach of reviewing a PMA for such a
415 labeling change will promote greater consistency pre- and post-market between the
416 regulation of the imaging device and the contrast drug.

417 418 2. When might a 510(k) be appropriate?

419
420 Although new indications for devices using imaging drugs are likely to raise new types of
421 safety and effectiveness questions that require review of a PMA, submission of a 510(k)
422 for the new indication might be appropriate. For example this might be acceptable if the
423 approved imaging drug and cleared imaging device are already indicated for the same or
424 consistent contrast indication.

425 426 3. What if my product is under an NDA or BLA?

427
428 Holders of an NDA or BLA for an imaging drug or biological product who seek to develop
429 new contrast indications that refer to devices should submit supplements to their
430 NDA/BLA in accordance with existing drug or biological product provisions. In addition,
431 if FDA approves or clears a new contrast indication in a device submission, the NDA/BLA
432 holder may submit a labeling supplement to add the indication to the imaging drug.
433

434 **VIII. POSTMARKET CONSIDERATIONS**

435
436 The holder of an approved device submission that includes a new contrast indication
437 should monitor changes to the marketed drug labeling as well as other changes to the drug.
438 In certain instances, FDA may require such monitoring or other postmarket surveillance
439 related to the drug upon approval or clearance of the device submission. Further to
440 enhance adverse event reporting, FDA expects that the application holder adding the new
441 contrast indication should submit to FDA any reports of adverse events related to the
442 indication in its labeling.¹⁸
443

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.

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443 **IX. INTERACTION WITH FDA AND THE REVIEW PROCESS**

444
445 Early communication and discussion between manufacturers and FDA concerning
446 potential new contrast indications should include concurrent discussion with the centers
447 and, as appropriate, OCP. Early dialogue allows manufacturers to obtain initial feedback
448 on the kinds of preclinical and clinical data that may be necessary to obtain approval of the
449 proposed new contrast indication. Such communication may identify critical issues for
450 product development and help to ensure an efficient development and approval process.
451 Further, early and frequent communication provides the opportunity for FDA to establish
452 its intercenter review team and to develop the appropriate scientific expertise to facilitate
453 timely and efficient reviews of any future submissions.

454
455 FDA strongly encourages any manufacturer who is considering medical imaging
456 development for use with a class of imaging products to contact the center that typically
457 regulates its product to request preliminary intercenter guidance.

458
459 CBER, CDER and CDRH provide guidance on milestone/collaboration meetings
460 throughout the development process and submission of investigational and marketing
461 applications. Pre-investigational (pre-IND and pre IDE) meetings are particularly useful
462 for discussing innovative products. Ideally the meeting background package should
463 provide a comprehensive discussion of the proposed contrast indication, the device
464 technology, a copy of the existing drug labeling, and outline of the type of clinical studies
465 being proposed. During ongoing development, pre-marketing submission meetings are
466 also helpful to discuss marketing application content, as well as the sequence and timing of
467 modular submissions or when more than one marketing submission will be provided for
468 the combination product. Guidance on how to arrange developmental meetings can be
469 obtained on the CDER,¹⁹ CBER²⁰ and CDRH²¹ websites.

470
471 The lead center should be contacted to schedule meetings in accordance with the
472 milestones applicable to the lead center. Lead center will consult or collaborate with other
473 centers or agency components in accordance with the scientific and technical issues in the
474 submission. As described further in this document Section VII.A, *Determination of Lead*
475 *Center Responsible for Premarket Review*, for device manufacturers who are considering
476 trials to add new contrast indications using a class of imaging drugs, the lead center is
477 CDRH. For a combination product, the lead center is determined by the primary mode of
478 action.²²

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¹⁹ See <http://www.fda.gov/cder/guidance/3683fml.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.

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

489
490 As appropriate, OCP will assist in developing additional focused procedures for the
491 imaging review divisions/branches. This will provide for an Intercenter Imaging Team to
492 review clinical protocols, labeling, considerations on the number or type of marketing
493 applications, and other practices to ensure consistency of developmental approaches and
494 relevance of results to submit under either the drug, biological, or device provisions. This
495 would include, but is not limited to, the scientific/technical, risk/benefit, labeling, or
496 potential interaction issues for the drug or drug class with the device(s). FDA expects that
497 such intercenter procedures will promote consistency in labeling and acceptability of new
498 indications requested based on prior agency determinations regardless of the regulatory
499 provisions used for approval or clearance.

500
501

X. HOW MAY I OBTAIN MORE INFORMATION?

502
503

504 OCP is available as a resource to developers and review staff throughout the lifecycle
505 (assignment, development, premarket review and postmarket regulation) of a combination
506 product. The Office can be reached at (301) 427-1934 or by email at
507 combination@fda.gov . In addition, the Office maintains an updated list of FDA guidance
508 documents that developers may find helpful in the development of their products. The
509 guidance is available at the Office's Internet Website at
510 <http://www.fda.gov/oc/combination> .
511

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

518

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

521

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

524

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

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- 524 • Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic
525 Devices; <http://www.fda.gov/cdrh/ode/guidance/793.pdf>
- 526 • Early Development Considerations for Innovative Combination Products;
527 <http://www.fda.gov/oc/combination/innovative.pdf>
- 528 • Exploratory IND studies; <http://www.fda.gov/cder/guidance/7086fml.pdf>
- 529 • FDA Radiological Health Program: Ultrasound Imaging;
530 <http://www.fda.gov/cdrh/radhealth/products/ultrasound-imaging.html>
- 531 • Guideline for Master Files; <http://www.fda.gov/cder/guidance/dmf.htm>
- 532 • FDA guidance *Developing Imaging Drug and Biological Products, Part 1:*
533 *Conducting Clinical Safety Assessments*,
534 <http://www.fda.gov/cder/guidance/5742prt1.pdf> ; *Part 2: Clinical Indications*;
535 <http://www.fda.gov/cder/guidance/5742prt2.pdf> ; *Part 3: Design, Analysis and*
536 *Interpretation of Clinical Studies*, <http://www.fda.gov/cder/guidance/5742prt3.pdf>
- 537 • Supplements to Approved Applications for Class III Medical Devices: Use of
538 Published Literature, Use of Previously Submitted Materials, and Priority Review
539 <http://www.fda.gov/cdrh/modact/evidence.html> ;
540

541

542

543 **XI. GLOSSARY**

544

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

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“(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;

550

551

552

(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;

553

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557

(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

558

559

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

560

561

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(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.”

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- 572
- **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.

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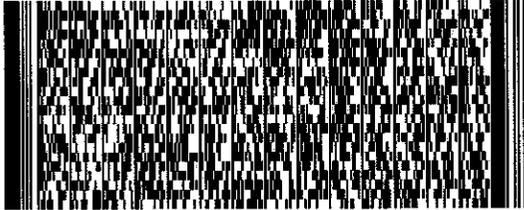
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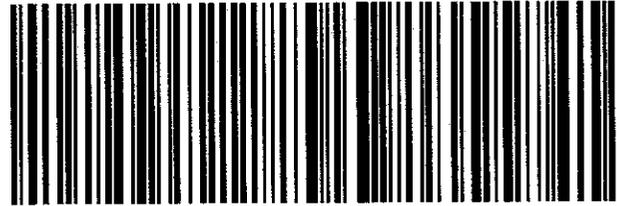
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