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# 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## ***DRAFT GUIDANCE***

**This guidance document is being distributed for comment purposes only.**

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

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

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

**September 2008**

*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

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

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1 **Guidance for Industry<sup>1</sup>**  
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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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6  
7 **I. INTRODUCTION**  
8

9 FDA intends this guidance to assist developers<sup>2</sup> 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.  
15

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).  
20

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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<sup>1</sup> 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.

<sup>2</sup> 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.

37

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.<sup>3</sup>

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.

58

59

### 60 **III. TERMINOLOGY**

61

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

63

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

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### **74 IV. SCOPE**

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

86

87

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

100

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

105

### **106 V. BACKGROUND**

107

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

113

114 Most medical imaging relies solely on device technology such as ultrasound (US),  
115 computerized tomography (CT), magnetic resonance imaging (MRI) and traditional  
116 radiology (x-ray) techniques. For example, many diagnostic US examinations are  
117 performed without administration of an imaging drug to the patient, using only the US  
118 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),<sup>4</sup> in order to produce  
127 an image it is necessary to simultaneously use the imaging device and the  
128 radiopharmaceutical imaging drug (i.e., a useable image can not be produced by the device  
129 alone). Medical imaging devices are marketed under the device provisions of the Act.  
130 Medical imaging drugs and biological products are marketed under the drug and biological  
131 provisions of the Act.

132  
133 Most imaging drugs are modality specific and chemically distinct from one another.<sup>5</sup> For  
134 example,

- 135
- 136 • X-ray and CT imaging drugs are iodine-containing compounds that in part are  
137 specifically designed to absorb x-rays;
  - 138 • MRI imaging drugs contain paramagnetic metallic ions, most commonly  
139 gadolinium, iron or manganese. These imaging drugs are designed in part to alter  
140 the magnetic properties of body tissue;
  - 141 • US imaging drugs typically consist of a gas contained within a lipid or protein shell  
142 (i.e., microbubbles or related microparticles). These products are designed in part  
143 to reflect sound waves; and,
  - 144 • Radiopharmaceutical imaging drugs contain in part a radionuclide that exhibits  
145 spontaneous disintegration of unstable nuclei with the emission of nuclear particles  
146 or photons.

147  
148 In addition to these general properties, these imaging drugs are formulated to interact with  
149 the body to facilitate imaging. For example, some imaging drugs bind to receptors,  
150 interact with a metabolic pathway, cross abnormal blood brain barriers, or are engulfed by  
151 macrophages.

152  
153 FDA existing guidance identifies imaging drug contrast indications in four broad  
154 indication areas:<sup>6</sup>

- 155 1) Structural delineation,
  - 156 2) Disease or pathology detection or assessment,
  - 157 3) Functional, physiological or biochemical assessment, and
  - 158 4) Diagnostic or patient management.
- 159

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<sup>4</sup> SPECT = single photon emission computerized tomography; PET = positron emission computerized tomography

<sup>5</sup> For purposes of this document, the term imaging drug applies to both drug and biological products including radiopharmaceuticals

<sup>6</sup> 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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### 204 **VI. REVIEW PRINCIPLES**

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

217

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

222

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

232

233

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

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<sup>7</sup> During the comment period, industry is welcome to provide other suggestions of what they believe might be a consistent indication

<sup>8</sup> 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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### 3. *When might both an imaging drug and device application be most appropriate?*

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

247

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

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

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

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## **VII. PREMARKET DEVELOPMENT CONSIDERATIONS**

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### **A. Determinations of Lead Center Responsible for Premarket Review**

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

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<sup>9</sup> 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.<sup>10</sup>

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).<sup>11</sup> 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.<sup>12</sup> Developers of a specific drug-device imaging product  
300 may wish to contact FDA to discuss whether a request for designation would be useful.<sup>13</sup>

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 Contrast Indication for Use**

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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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<sup>10</sup> Imaging drug and biological products including radiopharmaceuticals are regulated in CDER.

<sup>11</sup> 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.”

<sup>12</sup> 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> H

<sup>13</sup> See FDA guidance for industry entitled *How to write a request for designation*; <http://www.fda.gov/oc/combinations/Guidance-How%20to%20Write%20an%20RFD.pdf> H

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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.  
334 <sup>14</sup>

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

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<sup>14</sup> See [Hhttp://www.fda.gov/oc/combinatiion/innovative.pdf](http://www.fda.gov/oc/combinatiion/innovative.pdf)

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365 patient population.<sup>15</sup> 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

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<sup>15</sup> 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

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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.<sup>16</sup> 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.<sup>17</sup> 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.<sup>18</sup>

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<sup>16</sup> 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 H <http://www.fda.gov/cdrh/devadvice/pma/H> )

<sup>17</sup> In considering such a new indication, FDA will also determine whether the imaging drug label revision is also appropriate.

<sup>18</sup> 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,<sup>19</sup> CBER<sup>20</sup> and CDRH<sup>21</sup> 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.<sup>22</sup>

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480

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<sup>19</sup> See <http://www.fda.gov/cder/guidance/3683fnl.pdf>.

<sup>20</sup> See <http://www.fda.gov/cber/gdlns/ind052501.htm>.

<sup>21</sup> 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>

<sup>22</sup> 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*<sup>23</sup>  
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](mailto: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>

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

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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/7086fnl.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> ;  
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542

## **XI. GLOSSARY**

- 543 • Combination product; 21 C.F.R. 3.2(e)  
544  
545  
546 “(1) A product comprised of two or more regulated components, i.e.,  
547 drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are  
548 physically, chemically, or otherwise combined or mixed and produced as a  
549 single entity;
- 550 (2) Two or more separate products packaged together in a single package or as  
551 a unit and comprised of drug and device products, device and biological  
552 products, or biological and drug products;
- 553 (3) A drug, device, or biological product packaged separately that according to  
554 its investigational plan or proposed labeling is intended for use only with an  
555 approved individually specified drug, device, or biological product where both  
556 are required to achieve the intended use, contrast indication, or effect and where  
557 upon approval of the proposed product the labeling of the approved  
558 product would need to be changed, e.g., to reflect a change in intended use,  
559 dosage form, strength, route of administration, or significant change in dose; or
- 560 (4) Any investigational drug, device, or biological product packaged separately  
561 that according to its proposed labeling is for use only with another individually  
562 specified investigational drug, device, or biological product where both are  
563 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.