
Guidance for Industry:

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit written or electronic comments on the draft guidance by 90-days after publication in the *Federal Register*.

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

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

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

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

September 2008

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

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

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

September 2008

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION.....	4
II.	PURPOSE.....	5
III.	TERMINOLOGY	5
IV.	SCOPE	6
V.	BACKGROUND	6
VI.	REVIEW PRINCIPLES.....	9
VII.	PREMARKET DEVELOPMENT CONSIDERATIONS.....	10
	A. Determinations of Lead Center Responsible for Premarket Review	10
	B. Considerations for Data Necessary to Support Approval of the New Contrast Indication for Use.....	11
	C. Considerations on the Type of Marketing Submission to Provide When Using a Device Application Alone	13
VIII.	POSTMARKET CONSIDERATIONS.....	14
IX.	INTERACTION WITH FDA AND THE REVIEW PROCESS	15
X.	HOW MAY I OBTAIN MORE INFORMATION?	16
XI.	GLOSSARY.....	17

Contains Nonbinding Recommendations

Draft — Not for Implementation

1 **Guidance for Industry¹**
2 **New Contrast Imaging Indication Considerations for**
3 **Devices and Approved Drug and Biological Products**
4
5

6
7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's)
8 current thinking on this topic. It does not create or confer any rights for or on any person and
9 does not operate to bind FDA or the public. You can use an alternative approach if the approach
10 satisfies the requirements of the applicable statutes and regulations. If you want to discuss an
11 alternative approach, contact the FDA staff responsible for implementing this guidance. If you
12 cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of
13 this guidance.
14

15
16
17 **I. INTRODUCTION**
18

19 FDA intends this guidance to assist developers² of medical imaging devices and imaging
20 drug/biological products that provide image contrast enhancement. Particularly this
21 guidance focuses on approaches in developing new contrast indications for imaging
22 devices for use with already approved imaging drug or biological products. FDA intends
23 for the recommendations in this guidance to promote timely and effective review of, and
24 consistent and appropriate regulation and labeling for imaging drugs and devices.
25

26 This document supplements existing guidance developed by the Center for Devices and
27 Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and
28 the Center for Biological Evaluation and Research (CBER), and the Office of
29 Combination Products (OCP).
30

31 This guidance does not address the specific scientific or technical content to provide in a
32 regulatory submission to demonstrate safety and effectiveness of an imaging product(s)
33 for specific indications.
34

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

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

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

40 **II. PURPOSE**

41

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

45

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

66

67

68 **III. TERMINOLOGY**

69

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

71

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

78

79

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>

Contains Nonbinding Recommendations

Draft — Not for Implementation

80 IV. SCOPE

81

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

92 fulfills FDA’s commitment to issue draft guidance by the end of FY 2008.

93

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

106

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

111

112

113 V. BACKGROUND

114

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

120

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

139
140 Most imaging drugs are modality specific and chemically distinct from one another.⁵ For
141 example,

- 142
- 143 • X-ray and CT imaging drugs are iodine-containing compounds that in part are
144 specifically designed to absorb x-rays;
 - 145 • MRI imaging drugs contain paramagnetic metallic ions, most commonly
146 gadolinium, iron or manganese. These imaging drugs are designed in part to alter
147 the magnetic properties of body tissue;
 - 148 • US imaging drugs typically consist of a gas contained within a lipid or protein
149 shell (i.e., microbubbles or related microparticles). These products are designed
150 in part to reflect sound waves; and,
 - 151 • Radiopharmaceutical imaging drugs contain in part a radionuclide that exhibits
152 spontaneous disintegration of unstable nuclei with the emission of nuclear
153 particles or photons.
- 154

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

159
160 FDA existing guidance identifies imaging drug contrast indications in four broad
161 indication areas:⁶

- 162 1) Structural delineation,
163 2) Disease or pathology detection or assessment,
164 3) Functional, physiological or biochemical assessment, and
165 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.

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

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

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

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

207
208

Contains Nonbinding Recommendations

Draft — Not for Implementation

209 **VI. REVIEW PRINCIPLES**

210

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

223

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

228

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

239

240

241 2. *When might only an imaging drug application suffice?* When an imaging
242 drug modification (i.e., formulation, dosage, rate, or route of administration)
243 enables the drug to be used with an approved or cleared imaging device for a
244 new indication, the NDA/BLA holder should submit a supplement to FDA to
245 request approval for such change. For example, an NDA is most appropriate
246 for a drug reformulation to allow enhanced biodistribution to a new area, but
247 using the same imaging software. In most instances, FDA expects to review

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

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

248 an NDA submission to add such an indication to the drug labeling without the
249 need for a device submission or conforming labeling to the imaging device.

250

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

253

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

257

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

266

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

273

274 Regardless of which label (imaging device, drug or biological product) adds the new
275 contrast indication, the safety and effectiveness of the new contrast indication should be
276 established by data collected from appropriately designed clinical trials using both the
277 drug and the device. The regulatory pathway does not affect the scientific and technical
278 information that is most appropriate for establishing the safety and effectiveness of the
279 new contrast indication. (For additional information please see section VII.B,
280 *Considerations for Data Necessary to Support a New Contrast Indication for Use*).

281 Further, the labeling of product(s) adding the new indications should reflect the essential
282 information that establishes the contrast indication (e.g., the clinical study description,
283 imaging device characteristics and settings, imaging drug dosing regimen, target organ).

284

285

VII. PREMARKET DEVELOPMENT CONSIDERATIONS

286

A. Determinations of Lead Center Responsible for Premarket Review

287

288 Most imaging devices and drugs approved for use with a class of drugs or class of
289 devices do not meet the definition of a combination product under 21 CFR 3.2(e). For
290 example, the imaging device or drug contrast indications refer respectively to a class of
291 imaging drugs (gadolinium contrast) or a class of imaging devices (magnetic resonance
292
293

Contains Nonbinding Recommendations

Draft — Not for Implementation

294 imaging).⁹ A manufacturer of an imaging device who intends to develop a new contrast
295 indication for use with a class of imaging drugs would submit a device application to
296 CDRH. During the review process, CDRH will consult with CDER on issues including,
297 but not limited to, the scientific/technical, risk/benefit, labeling, potential interaction
298 issues for the drug or drug class, possible number of marketing applications.¹⁰
299

300 In some instances, the use of a diagnostic imaging device and imaging drug may
301 constitute a combination product under 21 C.F.R. 3.2(e)(3).¹¹ For example, certain
302 dedicated imaging drug-device products may constitute a combination product; e.g., a
303 specific imaging drug to bind receptors for imaging with a dedicated software algorithm.
304 Although a detailed discussion of how FDA applies combination product authorities is
305 beyond the scope of this guidance, if a manufacturer has a combination product, the lead
306 center determination, as with other products, will be in accordance with the primary
307 mode of action regulations in 21 CFR 3.4.¹² Developers of a specific drug-device
308 imaging product may wish to contact FDA to discuss whether a request for designation
309 would be useful.¹³
310

311 As described further in this document Section IX, *Interaction with FDA and the Review*
312 *Process*, for developers of an imaging device wishing to add a new contrast indication for
313 a class of imaging drugs, the supportive clinical study should proceed under the
314 investigational device exemption (IDE) regulations with a submission to CDRH. For
315 imaging drug developers wishing to add a new contrast indication, the supportive clinical
316 trials should proceed under the IND regulations with a submission to CDER. For a
317 combination product, the submission should be sent to the lead center as determined by
318 the product specific primary mode of action. Typically, the type of investigational
319 application for a combination product is that of the lead center (e.g., an IND for CDER
320 and IDE for CDRH).
321

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

322
323
324
325 As noted in this document Section IV, *Scope*, there are four large categories of imaging
326 contrast indications. In existing FDA guidance documents, the Agency provides

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

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

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

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

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

- 333 • Conducting Safety Assessments;
- 334 • Clinical Indications; and
- 335 • Design, Analysis, and Interpretation of Clinical Studies

336

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

341

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

354

355 1. Imaging Drug Class Considerations

356

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

368

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

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

380 381 2. Imaging Device Class Considerations

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

395 396 C. Considerations on the Type of Marketing Submission to Provide 397 When Using a Device Application Alone

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

405 406 1. When is a PMA most appropriate?

407
408 FDA believes that approval of most proposed new contrast indications meeting the
409 criteria described in this document Section VI.1 (i.e., those arising from a change in the
410 imaging device alone that do not affect the imaging drug or require changes to drug

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

422

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

424

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

430

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

432

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

439

440

VIII. POSTMARKET CONSIDERATIONS

441

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

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.

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

451

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

461

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

465

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

477

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

486

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

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

²¹ See <http://www.fda.gov/cdrh/devadvice/ide/approval.html>, and, *Early Collaboration Meetings Under the FDA Modernization Act, Final Guidance for Industry and CDRH Staff*, <http://www.fda.gov/cdrh/ode/guidance/310.html>

²² When the imaging drug and device meet the definition of a combination product, the labeling principles in this document would not affect the lead center assignment based on the primary mode of action. The principles affect only which label should contain the new information.

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

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

506

507

X. HOW MAY I OBTAIN MORE INFORMATION?

508

509

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

517

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

524

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

527

528

529

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

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

Contains Nonbinding Recommendations

Draft — Not for Implementation

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

547

548

XI. GLOSSARY

549

550

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

552

553

554

555

“(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;

556

557

558

(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;

559

560

561

562

563

(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

564

565

566

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

567

568

569

570

(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.”

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 571 • Contrast indication: A contrast indication is a statement in the indication or
572 intended use section of the labeling of either an imaging drug or imaging
573 device using an imaging drug or biological product
574
- 575 • Imaging drug: The term imaging drug applies to drug and biological products
576 including radiopharmaceuticals for use in medical imaging. This is consistent
577 with or includes the term contrast agent.