

701 Pennsylvania Avenue, NW
Suite 800
Washington, DC 20004-2654
Tel: 202 783 8700
Fax: 202 783 8750
www.AdvaMed.org



January 5, 2008

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

Re: Docket No. FDA-2008-D-0525; Draft Guidance for Industry on New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products

Dear Sir or Madam:

The Advanced Medical Technology Association (AdvaMed) provides these comments in response to the Food and Drug Administration (FDA) “Draft Guidance for Industry on New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products.”

AdvaMed is the world’s largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed’s more than 1,300 members and subsidiaries manufacture nearly 90 percent of the health care technology products purchased annually in the United States and more than 50 percent purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies. More than 70 percent of our members have less than \$30 million in domestic sales annually. Among our members companies are manufacturers of innovative imaging technologies used in the care of patients.

GENERAL COMMENTS

AdvaMed appreciates FDA’s efforts to provide clarity through guidance for industry regarding medical imaging device, drug, or biological products and new contrast imaging indications. We believe the guidance provides a starting framework in helping to address the issues of how to bring to market an imaging device for a new indication for use with previously approved imaging drugs or biological products. Flexible policy approaches are essential to support technological advancements and assure significant new challenges will not be added to pathway development for such products. The guidance notes that imaging



devices in many cases are approved for use with a class of drugs, not with an individually specified drug, and do not constitute “combination products.” Importantly, the guidance allows for device submission alone to address the previously approved drug used in a number of cases without requiring change in imaging drug labeling.

While this is an important first effort in providing clarification for industry, we are concerned that the guidance imposes a rigid regulatory review process, rather than risk-based individual review, for these devices and uses ambiguous, inconsistent language in setting out review and labeling requirements. We have outlined our specific comments below for further clarification and guidance from FDA.

SPECIFIC COMMENTS

With those general comments in mind, we provide the following comments on particular elements of the draft guidance. Proposed recommendations are also noted.

1. Type of Marketing Submission: Appropriate Premarket Review Process

The draft guidance states that when a device sponsor seeks to develop a contrast indication for an already approved drug(s) using a device application, the submission should in most cases be a Premarket Application (PMA). According to the guidance, “need for a PMA reflects the new type of safety and effectiveness questions arising when the new imaging drug-device indication is added to the device submission . . .” While we understand FDA’s rationale that some changes to 510(k)-cleared imaging devices to include new contrast indications may require PMA applications, we believe FDA must take a case-by-case approach in making this determination.

Further, the approach should be based on the longstanding principles embodied in the Office of Device Evaluation’s “Substantial Equivalence Decision-Making Process” described in Blue Book Memorandum #K86-3 *Guidance on the CDRH Premarket Notification Program Review Program* and subsequently codified into statute and regulations. According to FDA’s longstanding substantial equivalence decision-making process, one must consider whether “new types of safety and effectiveness questions” are raised if the device has different technological characteristics that could affect safety and effectiveness. In some cases, the device may not require technological changes in order to permit the new contrast indication, and therefore “new types of safety and effectiveness questions” may not play a role in the decision-making process.

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

The guidance also singles out “the absence of a concurrent NDA” as a particular scenario necessitating a PMA submission for a proposed new contrast indication using an approved drug. This further reiterates the need for better understanding when a PMA would still be necessary or whether a 510(k) could be submitted when the same type of changes are being made but a concurrent NDA is being submitted. Furthermore, we note that new contrast indications related to structural assessment are not specifically included in the list of categories necessitating PMA and request that FDA clarify whether such indications may be more amendable to a 510(k) submission.

With regard to 510(k) submission, only one example is provided for when such submission would be appropriate. According to the guidance, a 510(k) submission “might be acceptable if the approved imaging drug and cleared imaging device are already indicated for the *same or consistent* contrast indication.” (emphasis added). We are unclear what constitutes a “consistent” contrast indication and why additional pre-market approval/clearance would be necessary if an imaging device is already indicated for the same contrast indication. We might assume that “consistent” is intended to mean “similar” and not “identical”, but clarification and more illustrative examples is essential for industry to meaningfully understand the guidance and appropriate regulatory pathway.

2. Review Principles: When Imaging Device Application is Sufficient, Use of Terminology

The draft guidance sets out that “under the appropriate circumstances” the labeling of an imaging device may be expanded without requiring conforming changes to the drug label. FDA explains that “this may occur when the device technology *does not alter the drug* and when the drug use is *otherwise consistent* with its approved labeling.” (emphasis added). While the guidance is a promising step forward in its effort to identify when an imaging device application alone will suffice for new contrast imaging indications, we believe that it is fundamentally important that the guidance provide a clear understanding and definition of key terms such as “otherwise consistent.”

Only one example (quantitative angiographic imaging) is provided in which a device submission alone would suffice and it concerns a situation that appears to be completely consistent with current use of the drug. We are unclear when “drug labeling does not need revision” as referenced in the example. We would also appreciate clarification regarding what it means for a device technology to not “alter the drug”, although it appears to be the case when the approved imaging drug being used with the device is at its approved formulation, dose, rate, and route of administration. In addition to including other qualifying examples, we ask that FDA clarify what constitutes a “new yet consistent contrast indication.”

Ultimately, the guidance limits submission of a device application alone in cases when the contrast indication is “*otherwise consistent*” with the approved imaging drug’s approved indication. We believe that in many cases, particularly when a device application alone is sufficient, the 510(k) process will be appropriate.

As the guidance allows for a new contrast imaging indication in the labeling of an imaging device under specific circumstances without the need for a conforming change to the imaging drug label and footnote 8 explicitly states a drug sponsor is not required to change its labeling based on statements in the device labeling, we would recommend that Section II (Purpose) be amended to read “[d]rug or biological product application holders of the already marketed imaging drug or biological product ~~should generally~~ may *(added)* submit an efficacy or labeling supplement, ~~as appropriate,~~ to add labeling for the new indication initially developed under a device application.”

We believe that FDA intended this guidance to support similar and consistent review methodologies. Thus, we respectfully request that the guidance clarify whether the imaging drug application holder’s efficacy or labeling supplement could cross-reference the approval/clearance of the device application or whether the drug application holder would need to provide its own safety and efficacy documentation in support of its supplement.

3. Clinical Data to Support a New Contrast Indication for Use

As part of Section VI (Review Principles), the guidance generally sets out that 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, regardless of regulatory pathway. Data considerations are outlined in more detail under Section VII (Premarket Development Considerations).

While we understand that clinical trials will be necessary in most cases, we believe that some changes may require clinical studies but not necessarily full scale clinical trials. The need for clinical data for new imaging indications should be commensurate with the risk. Thus we recommend replacement of the term “clinical trials” with “clinical studies or other appropriate data” in the guidance.

We appreciate FDA’s efforts to clarify clinical data requirements for an imaging device manufacturer considering a new contrast indication for a class of imaging drugs. Industry would welcome a few examples related to addressing “unique aspects of the class of imaging drugs” in designing clinical studies. An example might be a recommendation for cardiac monitoring for possible arrhythmias during and immediately following the administration of ultrasound microbubble contrast agents.

4. Imaging Device Investigations under IDE Regulations

The guidance provides that an imaging device manufacturer “should proceed under the investigational device exemption (IDE) regulations *with a submission to CDRH*” (emphasis added) for its supportive clinical study. Some imaging device investigations, however, are “nonsignificant risk” (NSR). While NSR studies are conducted under the IDE regulations and require IRB approval, an IDE submission to the Center for Devices and Radiological Health (CDRH) is not required. We would appreciate clarification from FDA regarding submission requirements for NSR imaging device sponsors who seek to add a new contrast imaging indication.

5. Postmarket Considerations

FDA has existing authority to require device manufacturers to monitor drug changes in the postmarket setting. The guidance calls for monitoring of changes to the marketed drug labeling as well as “other changes to the drug.” To assist manufacturers in understanding FDA thinking, we would appreciate clarification regarding what specific changes should be monitored beyond changes to drug labeling and how companies should monitor such changes.

With respect to reporting postmarket adverse events, it would also be helpful to clarify that reports would be submitted under the device manufacturer’s obligations under the Medical Device Reporting regulations, 21 CFR 803. The guidance notes that most imaging devices approved for use with a class of drugs do not meet the definition of a combination product. Furthermore, appropriate postmarket safety reporting for most combination products may be achieved by following the regulatory provisions associated with the type of marketing application used for approval or clearance. We believe that such clarification would support consistency in adverse event reporting and avoid duplicate reporting.

AdvaMed thanks FDA for the opportunity to provide comments on this important draft guidance. We appreciate FDA’s efforts to help address the issue of how to bring to market an imaging device for a new contrast indication with previously approved imaging drugs or biological products. To further support these efforts, we believe it would be helpful to convene a public workshop to discuss the guidance. Such a forum would also allow for critical dialogue with stakeholders regarding terminology and overall impact of the guidance on technological innovation.

Sincerely,



Khatereh Calleja
Associate Vice President
Technology and Regulatory Affairs