CPC COMBINATION PRODUCT COALITION

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VIA ELECTRONIC SUBMISSION

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

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

Dear Dr. Love:

The Combination Products Coalition ("CPC") would like to offer its comments on the *Draft Guidance for Industry: New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products* (the "Guidance"). We commend the Agency on developing and publishing the Guidance in a timely manner in accordance with the Medical Device User Fee Amendments of 2007 ("MDUFA) Commitment for the Performance Goals and Procedures. FDA's commitments under MDUFA represent several important areas of policy development, and we support the Agency's efforts in this regard. Below, we offer some specific comments on the Guidance. For ease of reference, our comments refer to the line-numbered version of the Guidance.

By way of background, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination products area. One of the principal goals of our organization is to work collaboratively with the Agency on issues affecting combination products, in order to advance our common missions of providing the best possible health care for patients. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

As an initial matter, we want to commend the Agency on the stakeholder outreach and discussion it conducted throughout the Guidance development process. We believe such dialogue is a critical factor in developing policy that is beneficial for patients, the Agency, and the industry. We strongly urge the Agency to continue this type of outreach

and discourse as it finalizes the Guidance and develops other regulations, policy, and guidance documents.

In terms of the Guidance's substance, we agree with the principles the Guidance articulates concerning how only an imaging device application may be sufficient for FDA to evaluate that imaging device's use with an approved imaging drug. At a high level, such an approach should enable applicants to pursue indications in an appropriately efficient manner, thus encouraging patient access to these important technologies. That said, we also recommend that the Agency clarify some important terms and concepts in the Guidance's discussion of this new principle.

In particular, under VI, Review Principles, the Guidance provides that a device submission alone may suffice "when the device technology does not alter the drug and when the drug use is otherwise consistent with its approved labeling." The Guidance also gives an example, noting that a device application alone may suffice "when the drug is administered in accordance with the drug's approved labeling and when the drug labeling does not need revision." The Guidance goes on to say that "when the new yet consistent contrast indication may cause the drug and device to interact in a manner that affects the safety or effectiveness of the product(s), the drug and device labels should generally align closely." This discussion contains several important terms that require further explanation, such as: "otherwise consistent", "new yet consistent", "drug labeling does not need revision", and "generally align closely." Further, although the Guidance provides one example of when a drug is "otherwise consistent" (angiographic imaging; see lines 209-214), this example seems to focus on a situation in which the use would be completely consistent with the drug's existing use. Additional examples that tease apart and illustrate the key terms used in this discussion likely would be very helpful to industry and FDA in applying the Guidance.

We also believe the Guidance merits clarification in other areas, such as when drug or biological product labeling should be changed. The Guidance makes a number of seemingly inconsistent statements on this issue:

- "Drug or biological product application holders of the already marketed imaging drug or biological product should generally submit an efficacy or labeling supplement, as appropriate, to add labeling for the new indication initially developed under a device application." (Lines 47-50).

- "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." (Footnote 8).

- "[W]hen the drug is administered in accordance with the drug's approved labeling, and when the drug labeling does not need revision, the Agency believes that in most instances a device submission alone should suffice." (Lines 210-214).

Based on these statements, we are unclear on when a drug or biological product application holder may or should submit a supplement to add labeling for a new indication added under a device application. At one end of the spectrum, Footnote 8 seems to suggest that approval/clearance of a new contrast indication in a device application may not support approval of an analogous change to the drug labeling – i.e., that it is not appropriate to revise drug labeling by cross-reference to the device clearance or approval. On the other hand, Footnote 8 could also be read to say that while approval of a new contrast indication in a device application does not in itself permit the drug application holder to change its labeling, such a change may be acceptable if done through an efficacy or labeling supplement. At the other end of the spectrum, the language in lines 47-50 could be read to say that drug or biological product application holders are encouraged or expected to submit an efficacy or labeling supplement to add labeling for a new indication added under a device application.

Because a central purpose of this Guidance is to ensure consistency in the development and review process for contrast indications in devices, drugs, and biological products, we recommend that the Guidance clarify the above issues. Further, we believe the most appropriate position, and one that conforms to current statutes and regulations, is that when FDA approves or clears a new indication in a device application, the drug applicant may – but is not required to – make changes in the drug labeling based on statements in the device labeling.

We also suggest that FDA clarify the Guidance's definition of a "contrast indication." The current definition states that the indication must be a statement "in the indication or intended use section of the labeling." While we agree that most new uses of an imaging device with an imaging drug would likely appear in the indication or intended use section of the device labeling, this definition could be interpreted to mean that statements in other sections of labeling cannot constitute a "contrast indication" for the purposes of the Guidance and therefore may be added without adhering to the principles in the Guidance.

We also believe that the Guidance should refer to existing Agency guidance rather than unnecessarily introducing new terms and principles. For example, when discussing when a drug modification necessitates a device submission (see lines 258-263), it seems existing FDA guidance would be relevant, such as "Deciding When to Submit a 510(k) for a Change to an Existing Device" and the recently-finalized guidance on PMA supplements.

Similarly, in discussing when a PMA may be required for a new contrast indication, the Guidance asserts "[t]he need for a PMA reflects the new type of safety and effectiveness questions that arise when the new imaging drug-device indication is added to the device submission, particularly in the absence of a concurrent NDA." While in some circumstances this may be true, the Guidance should recognize that for 510(k)-cleared devices, new contrast indications should be assessed via the well-established substantial equivalence standard.

Also on the issue of determining whether a PMA or a 510(k) submission is required for a new contrast imaging indication, the Guidance states that a PMA is needed "particularly in the absence of a concurrent NDA." We suggest that the Guidance clarify and provide examples of instances in which a PMA is necessary when a concurrent NDA is submitted. Further, in discussing when a 510(k) might be appropriate, the Guidance says "this might be acceptable if the approved imaging drug and cleared imaging device are already indicated for the same or consistent contrast indication." However, if an imaging device is indicated for the "same" contrast indication, it seems no additional submissions – whether 510(k) or PMA – would be necessary. We suggest FDA clarify this point and provide additional examples to illustrate when a PMA or a 510(k) would be necessary to add a new contrast imaging indication.

As a couple other points of clarification, the Guidance provides that the holder of an approved device submission that includes a new contrast indication should monitor changes to the marketed drug labeling as well as other changes to the drug (lines 436-437). We suggest that the Agency clarify what "other changes" should be monitored. Also, line 468 of the Guidance seems to inadvertently use the term "combination product." To avoid confusion, we recommend that the word "combination" be deleted in that sentence.

Finally, in a number of areas, the Guidance discusses the types of data that are required for a new contrast imaging indication and often references "clinical trials" when describing what is required (see lines 267, 351, 362-363). Although clinical trials may be necessary in some or even most situations, sometimes other types of data may be appropriate. We therefore suggest that the Agency broaden its references to "clinical trials" to include other appropriate data.

Also with regard to clinical study requirements, the Guidance states that clinical studies conducted by device developers wishing to add a new contrast indication for a class of imaging drugs should "proceed under the investigational device exemption (IDE) regulations with a submission to CDRH." (Lines 304-305; Emphasis added). However, some imaging device investigations are considered "non-significant risk" and do not require IDE submission to CDRH. Therefore, we suggest that the Agency clarify the investigational submission requirements for non-significant risk imaging device sponsors.

We hope that our comments are helpful to the Agency as it finalizes the Guidance. If the CPC can help in any way, please do not hesitate to contact us.

Respectfully submitted,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition