CPC COMBINATION PRODUCT COALITION

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Questions for FDA's Consideration in Finalizing Companion Diagnostic Guidance
Provided By:
Combination Products Coalition Personalized Medicine Working Group
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The following questions highlight areas for clarification that the Combination Products Coalition Personalized Medicine Working Group has identified in reviewing FDA's Draft Companion Diagnostics Guidance. The Coalition feels that by addressing these questions in the final guidance FDA will resolve key uncertainties that remain in this area and spur further investment in the diagnostic technologies that are essential for personalized medicine.

The general areas that the questions cover are –

- FDA's thinking on the distinctions between companion diagnostics and combination products;
- The use of de novo petitions with companion diagnostics;
- The evidence required to support approval of companion diagnostics, with a focus on cases where companion diagnostics are not developed contemporaneously with therapeutics;
- Labeling associated with companion diagnostics;
- The timing of therapeutic and companion diagnostic approvals; and
- General issues regarding the regulatory process.

In asking these questions we understand that FDA may have had plans to address some questions in its anticipated biomarkers guidance. The Coalition does not express a preference as to the particular guidance the questions are addressed in, but does suggest they be addressed sooner rather than later (i.e., in the guidance that will be available first) given their importance to furthering personalized medicine.

<u>Companion Diagnostics versus Combination Products</u>

1) Under what circumstances is a companion diagnostic a combination product, and when *isn't* it a combination product?
   a) If a companion diagnostic is not a combination product will FDA treat it as a concomitant use product in the same way that it treats certain imaging agents when used with diagnostic imaging devices?
   b) Can you provide specific examples? Please describe the relevant labeling statements for the therapeutic(s) and/or companion diagnostic(s)/combination product(s) as part of the examples.

<u>De Novo Reclassification</u>

2) Under what circumstances (e.g., intended use/indication) might a de novo 510(k) be an appropriate pathway for a companion diagnostic?

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Evidence Required for Approval

3) Please provide detailed information on the evidence required for approval of companion diagnostics, such as the kinds of clinical and non-clinical studies that would be required and what would be necessary to demonstrate clinical utility and clinical validity. In answering this question and the questions that follow, please consider how the answers change with each of the scenarios listed below and any others you believe are pertinent –
   - Adding a companion diagnostic to a currently marketed therapeutic for which no companion diagnostic currently exists;
   - Adding a companion diagnostic to a currently marketed therapeutic for which one or more companion diagnostics currently exist;
   - Adding a new specimen type to a currently approved companion diagnostic.

   a) When adding a companion diagnostic to a currently marketed therapeutic product, when can a sponsor evaluate specimens from a *subset* of the population evaluated in the therapeutic's pivotal trial as opposed to the entire population?
      i) What approach does FDA envision when the therapeutic's NDA/BLA holder won't share the underlying dataset that supported the therapeutic's approval?
   b) If no gold standard exists for a novel test, how does this impact the review of clinical validity and clinical utility as well as final labeling for the drug and companion diagnostic?
   c) If a companion diagnostic is developed for a subpopulation that is shown to be more likely to benefit from use of a therapeutic, must evidence be provided to show that other subgroups do *not* benefit or benefit to a lesser degree?
      i) When is it necessary to evaluate both biomarker-positive and biomarker-negative subjects to support a companion diagnostic approval?
      ii) In addition to providing evidence of safety and effectiveness as to the target subpopulation, will the sponsor also be required to show that it would be safe/unsafe and/or ineffective in the other population?
      iii) What are the circumstances where performing safety only versus benefit/risk assessment of diagnostically negative (unselected) patients would be acceptable?
   d) What is required to receive approval to label a companion diagnostic for use with a therapeutic *class* as opposed to a single therapeutic product?
   e) What is required to receive approval of a companion diagnostic intended to identify subgroups that show greater benefit from a therapeutic, as opposed to selecting patients eligible for treatment (in other words, the therapeutic is approved for all comers but *improved* efficacy is shown in a subgroup defined by the companion diagnostic).
   f) Will clinical validation of a companion diagnostic be required for situations in which new tests are developed for the same therapeutic? Are there situations in which method comparison studies would suffice?
   g) What are the requirements for expansion of the intended use of a marketed companion diagnostic to a new indication in the same therapeutic class or a new indication in a different therapeutic class?

4) If a therapeutic (Drug A) and associated companion diagnostic are approved before the start of a Phase 3 study for a second therapeutic (Drug B) which is (1) in the same drug class as Drug

A, and (2) is being studied with an unapproved companion diagnostic that measures the same marker as Drug A's companion diagnostic, when (if ever) would information be required evaluating the use of Drug A's companion diagnostic with Drug B?

a) What kind of information would be required?
b) Could the information be provided post-approval (i.e., after the approval of Drug B)?

5) Can FDA provide additional guidance on the following scenario? A therapeutic manufacturer plans to evaluate the use of a companion diagnostic with its product, but cannot do so during its Phase III trials. The manufacturer banks samples, and develops a pre-specified protocol to, e.g., retrospectively validate a clinical biomarker or conduct other analyses to support approval of a companion diagnostic after the Phase III trials are completed.
   a) What options are available regarding the timing of threshold pre-specification for primary analysis?

6) Can FDA provide additional guidance regarding "bridging" or concordance studies to link existing clinical data with older/different versions of an assay used in the clinical studies to a modified companion diagnostic that the manufacturer plans to market?
   a) What are the general requirements FDA envisions? If there are various scenarios regarding, e.g., the need for re-establishing clinical validity, can you please provide guidance and examples for those scenarios the Agency envisions?
   b) Are there circumstances where due to unavailability of sufficient numbers of clinical samples or the like, that *analytical* concordance could be considered sufficient approval? Can you please describe those circumstances?

7) In programs with complex disease biology and several markers may be necessary to identify patients likely to benefit from a therapy, what are the circumstances where it would be sufficient to validate the combination of markers and not each biomarker individually?

<u>Labeling Issues</u>

8) The FDA Guidance on companion diagnostics states that "[w]hen appropriate, the therapeutic product labeling should identify a type of FDA approved or cleared companion diagnostic device (i.e., the intended use of the device), rather than a specific manufacturer's companion diagnostic device."
   a) Are there situations in which the brand name of the diagnostic should be named? If so, what are those situations?
   b) What does a "type" of companion diagnostic mean? Does "type" refer to the specific biomarker being detected by the diagnostic or something else?

9) Must both therapeutic and companion diagnostic sponsors agree to cross-label with specific references to their products in indication/intended use statements?
   a) When and how is this requirement imposed?
   b) When is it necessary to revise labeling but not cross-label products?

10) What are the circumstances where inclusion of the benefit versus biomarker information in the clinical or mechanism of action ("MOA") section of a label is appropriate assuming the

therapeutic has an "all-comers" label (i.e., use of the companion diagnostic is not necessarily required, but could provide a benefit)?

Timing of Approval

11) Section IV.B of the Draft Guidance contemplates situations in which a therapeutic product might be approved before an approved companion diagnostic was available. Please provide additional guidance on potential access to investigational companion diagnostics in these situations.
    a) Would FDA consider the use of treatment INDs or other expanded access programs to allow for access to a companion diagnostic under review? What information would be required to support such access?

12) How does FDA envision disruptions in companion diagnostic supplies might be handled? For example, if a companion diagnostic goes through a class I recall or backorder, how will the therapy be marketed without the diagnostic?

Regulatory Process

13) Can the use of a companion diagnostic with two or more therapeutics be cleared or approved in a single 510(k) or PMA?

14) What are the implications of *priority review* for a therapeutic on the related companion diagnostic approval?
    a) What is the path forward for next generation sequencing, in particular regulatory guidance on analytical validation and references?
    b) Can you please clarify the rationale and associated scientific requirements for completion of a biomarker qualification program prior to approval of a therapeutic/diagnostic combination?

15) Is FDA amenable to creating more incentives, such as shortened review time goals, to therapeutic and IVD companies which develop companion diagnostics and associated therapeutics?

16) Does FDA have plans to address the issue of laboratory developed tests associated with companion diagnostics? If so, what are those plans?