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Companion Diagnostics versus Combination Products				
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.	Additional guidance on the demarcation between "combination products" and "companion diagnostics" is needed.		
De Novo Reclassification				
2	Under what circumstances (e.g., intended use/indication) might a de novo 510(k) be an appropriate pathway for a companion diagnostic?	Therefore the CPC recommends that FDA provide additional guidance on the use of the de novo process with companion diagnostics, including examples of scenarios that FDA believes would be amenable to the de novo review process.		While the FDA has expressed its intent to classify most companion diagnostic devices as Class III devices requiring PMAs, the situations in which a device would be classified as de novo 510(k) are unclear.
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			

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	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 –	**Specific sub-questions are addressed in detail below.**		
3(a)	Adding a companion diagnostic to a currently marketed therapeutic for which no companion diagnostic currently exists;	The addition of a companion diagnostic to a currently marketed therapeutic could provide benefits of improved safe and effective use of the therapeutic. However, development in this case could be made more difficult due to the lack of availability of specimens and patient data (medical records, outcome – as established with the therapeutic upon approval) from the therapeutics approval. Providing guidance on what to do in these situations short of an outcome study ("OS") trial is needed, to facilitate innovation vis-à-vis marketed therapeutics.		
3(b)	Adding a companion diagnostic to a currently marketed therapeutic for which one or more companion diagnostics currently exist.	Where a companion diagnostic is already available, FDA should make clear in guidance that a follow-on IVD for the same use could be evaluated through concordance trials comparing IVD performance with appropriate samples (e.g., banked samples from a prior trial, samples from a relevant patient population). The guidance should also explicitly state that studies involving the therapeutic (e.g., outcome studies) would not be required. We believe this is important to providing a uniform treatment across the Agency.		
3(c)	Adding a new specimen type to a currently approved companion	When adding a new specimen type, an IVD device manufacturer should demonstrate equivalency of the two		

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	diagnostic.	specimens. FDA should provide guidance which explicitly states that studies involving the therapeutic (e.g., outcome studies) would not be required. We believe this is important to providing a uniform application of policy across the Agency.		
3(d)	Evidence required for a widely available already marketed test (e.g. clinical chemistry blood test) that is being used as a companion diagnostic test. For example autoantibody/antigen tests, etc. may be used to stratify patients during clinical development and this subpopulation will be reflected in the label for an approved therapy, but these tests have not been developed as an official companion diagnostic with CDRH. How will these tests be classified?	If a test is in wide use and has a well-established track record this should reduce the evidentiary burden manufacturers must meet to support a companion diagnostic approval. Also, wide spread use should be considered to support re-classification of the product through the de novo process. FDA guidance should be clear on these points.	When there is a standard test used to diagnose a disease/disorder, and (a) it is noted that a certain subset of (-) or (+) patients is more likely to respond during pivotal testing (b) the test is used as part of the inclusion/exclusion criteria or pre-specified criteria for analysis, and (c) and the test is not currently approved as a companion diagnostic ("CDx") but has been widely marketed for years, how does the FDA plan to address this test?	
3(e)	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? - What approach does FDA envision when the therapeutic's NDA/BLA holder won't share the underlying dataset that supported the therapeutic's approval?	A statistically valid sampling of banked samples from the therapeutic clinical trial could support approval of a companion diagnostic. In addition, FDA should not continue its current practice of requiring greater than 90% of the original data set in testing. Manufacturers should be allowed to do a prospective collection of specimens and/or supplement a data set from the patient population indicated in the therapeutic's labeling.		
3(f)	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	When no gold standard exists, evaluations should consider therapeutic outcome to be truth.		

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	companion diagnostic?			
3(g)	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? 1. When is it necessary to evaluate both biomarker-positive and biomarker-negative subjects to support a companion diagnostic approval? 2. 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? 3. What are the circumstances where performing safety only versus benefit/risk assessment of diagnostically negative (unselected) patients would be acceptable?	There needs to be a clear framework to determine when it is appropriate to exclude biomarker negative/positive patients during clinical development. If, for example, the sponsor has reason to believe that a product will only be of benefit in biomarker negative patients (based on, e.g., be literature sources, known biology, preclinical information or early clinical data) that sponsor should be able to limit its study in patients receiving the therapeutic to the group it wants to study, both because of its control over the indication and to address potential ethical or safety concerns. With respect to the specific sub-points – 1. It should not be necessary to evaluate biomarker negative and positive patients in a clinical trial where the therapeutic is used unless the proposed indication(s) address both populations. A sponsor may need to evaluate positive and negative patient samples to show it can distinguish between these groups, but this can be done separately from therapeutic trials. 2. The sponsor should not be required to evaluate safety and effectiveness in populations that are not part of its indication.	A compound is entering Phase II. It is known that a competitor has completed Phase II with a similar class of drug where a predictive biomarker has been demonstrated to correlate to improved outcomes. It is also known from the preclinical literature and through preclinical studies that the biomarker is overexpressed in particular tumor types. If the sponsor wishes to pursue a program focused on only biomarker positive patients, is it acceptable to utilize the marker to select biomarker positive patients in Phase II and III studies? A limitation in the label for use of the drug would be anticipated. Would any biomarker negative data be required to support the filing of the drug and or diagnostic application?	There is no clear guidance on what is the appropriate level of evidence (preclinical and/or clinical) required for the evaluation of only biomarker positive subjects during clinical development as well as what is required for approval of a companion diagnostic.
3(h)	What is required to receive approval to label a companion diagnostic for use with a therapeutic *class* as opposed to a single therapeutic product?	Evidence should be provided for an IVD device to support each indication and population, independent of the drug class.		

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3(i)	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).	A statistically valid sampling of banked samples from the therapeutic clinical trial could support approval of a companion diagnostic.		
3(j)	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?	Where a companion diagnostic currently exists for the therapeutic and the new diagnostic product is measuring the same parameters as the currently approved/cleared companion diagnostic, it is unnecessary to reestablish clinical utility or validity. Comparative/concordance studies with appropriate samples comparing the new and previously approved tests should be sufficient.		
3(k)	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?	Clarification on this topic would be useful.		
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	It should be acceptable for the sponsor of Drug B to discuss with the FDA whether it is necessary to conduct preclinical studies to compare the CDx for Drug A to the CDx for Drug B prior to the approval of Drug B. If required, these preclinical studies would enable comparison of the performance of both assays. These studies should only be done as a post-market commitment if required and not be a	It is understood in this scenario that the companion diagnostic and drug B would need to be evaluated and a gap assessment completed. But assuming the gaps/differences between the two situations are relatively small (same sample type, etc.) would the Agency require independent demonstration of clinical validity or utility?	There is no current FDA guidance provided on this particular scenario. This scenario is going to become more common, especially in particular tumor types such as lung, colorectal and breast cancer.

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	A's companion diagnostic with Drug B? a) What kind of information would be required? Could the information be provided post-approval (i.e., after the approval of Drug B)?	pre-market requirement.		
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?	There needs to be a framework that allows for a pre-specified analysis of blinded samples to so that potential therapy-enabling companion products (therapeutics and diagnostics) to be brought to the public more quickly. If a marker is identified during Phase III retrospectively that makes a strong case for approval of a therapy, it may require additional years for the combination of drug and diagnostic to be brought to the public if a prospective pivotal trial is required.	For a program that was intending to transition from Phase I to Phase III, the FDA agreed at an EOP2 meeting to allow two versions of the companion diagnostic to be used. An early non-PMA ready version would be used for the initial screening and the IVD PMA-ready version would be used prospectively for a portion of the samples in the envisioned real world context. Concordance would be established between the precursor assay to the IVD assay based on real-time and banked samples. Alternative scenario: Similar facts to the above but samples remain blinded for a complete retrospective analysis.	Would the FDA allow EOP2 decisions to be revisited during the conduct of Phase III? Would the FDA be open to a retrospective validation of a companion diagnostic with appropriate blinding (e.g., using banked blinded samples from a therapeutic's clinical trial)?
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	The FDA's Draft Guidance document Pharmacogenetic Tests and Genetic Tests for Heritable Markers (June 19, 2007) includes detailed requirements related to "the preparation of a submission for a medical device that measures pharmacogenetic or genetic information" (Section III). However, it is unclear whether or how these recommendations apply to the design of a bridging study for a pharmacogenomic marker or a non-pharmacogenomic marker. Specifically, what are the requirements for the following		No threshold for concordance is suggested in current guidance. The CPC would like confirmation what data might be required beyond analytical concordance. Guidance should also address whether samples need to be run on commercial kits and whether all outcomes analyses need to be generated for both old and new versions of a test.

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	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?	aspects of a bridging study?: • Comparison to a reference method, or acceptance of medical outcome data • Sample type and number • Statistical analyses • Analytical validation • Clinical validity • Clinical utility We recommend that new FDA Guidance include a section on the requirements and potential review issues such as sample stability, <90% sample ascertainment, lack of an available gold reference standard, and statistical analysis approaches (i.e., acceptable thresholds, cut-off comparisons, etc.) for establishing concordance between analytically-validated assays used in a clinical trial of a therapeutic product and investigational devices that will be submitted for FDA review as a companion diagnostic device.		
7	In programs with complex disease biology where 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?	If there is appropriate preclinical evidence and scientific rationale, clinical validation of each biomarker separately should not be required.	A Phase 2 study design is contemplated for NSCLC where a subgroup of patients is identified with a particular marker (Marker A) via LDT (Test 1). This particular subpopulation with Marker A is known to be resistant to an existing drug in the market (Drug A). Of this subpopulation with Marker A, another marker (Marker B) is believed to identify a smaller subpopulation of patients that would respond to a novel drug (Drug B). Would both tests need to be submitted as PMAs as part of the approval package for Drug B? If Test 1 is on the market as an approved IVD kit, but not as a cdx for Drug A, would a PMA(s) need to be filed for Test 1 at the time of Drug	Addressing this issue is important for next generation sequencing in which the assay will be designed to evaluate disease based on an evaluation of several biomarkers. If multiple biomarkers yield a status, e.g. mutation negative, that the patient would benefit from a therapy, then a multiple biomarker combination would be required to predict effectiveness of the therapeutic.

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			B filing?	
8	***New Question (added after our June meeting with FDA)*** To date, FDA has been consistent in stating that the CDx used in the pivotal trials must be the same version intended to be marketed. However, when the cutoff is set for an assay pre-Phase 3, there is a chance that the results may differ from the hypothesis. Would the agency consider allowing the cutoff being changed post-pivotal trials in the scenarios below? a) The primary endpoint is met in all-comers however, there is a subset that may derive greater efficacy, but the cutoff point is slightly off from the pre-specified value? b) The same as part a, but replacing efficacy with safety.	CPC proposes re-adjusting the threshold upon data evaluation to assure that the Dx-selected population has a clinically meaningful benefit based on currently available knowledge. This approach would be feasible if the primary endpoint is met in the pre-specified Dx subset (using original threshold) and would include biomarker negative patients or all-comers in the case where a subpopulation of patients is not captured by the pre-specified cutoff.	New treatment options emerge while a trial is on-going that result in a change in how the disease is molecularly classified and treated – as a result, higher efficacy may be needed for approval. There also could be a statistically significant benefit in the population selected with the pre-specified cut-off, but the estimate of the benefit is less than expected. In other cases, benefit could be observed in the population selected with a pre-specified cut-off in addition to the subpopulation of patients not included as a result of the pre-specified cut-off.	Industry requests flexibility to improve labeling of benefit/risk for appropriate subpopulations of patients (especially under circumstances where the cut-off is a continuous range). In particular, refining the cut-off enables a better understanding of clinical benefit for patients who are considered borderline positive by evaluating the patients who are borderline negative, thereby allowing better assessment of the cut-off point.
9	***New Question (added after our June meeting with FDA*** What is the FDA's perspective on allowing an exploratory cohort followed by a confirmatory cohort in a pivotal trials? Would an interim analysis be necessary or would a predefined threshold for the confirmatory cohort be sufficient?	Sponsors must have flexibility to address late breaking markers and avoiding lengthy delays to making a drug and cdx available in marketplace. Another confirmatory study should not be necessary provided the confirmatory cohort in the pivotal study demonstrates substantial evidence for the safe and effective use of the test to identify a subpopulation of patients to treat with drug therapy.	A drug enters Phase 3 with a strong biomarker hypothesis. The drug company meets with FDA at EOP2 to discuss Phase 3 trial design where exploratory and confirmatory cohorts are outlined. Both cohorts would be randomized and powered appropriately. Upon completing study (prior to un-blinding), exploratory cohort is analyzed to assess association to outcomes and to then identify an appropriate pre-specified cutoff for the confirmatory cohort. The company then utilizes the pre-specified cut-off to assess the confirmatory cohort. The data replicates and is provided as substantial evidence to support submission of a drug and CDx.	

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Labeling Issues				
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?	The therapeutic label should generally refer to an "FDA-Approved Test" except for the Clinical Studies section wherein the specific test used during the studies should be indicated. Referring to an "FDA-Approved test" allows new companion diagnostic tests to be used without a drug label change. Identifying the specific test used in the Clinical Studies section helps safeguard situations wherein performance of other devices may be significantly different. There needs to be clear guidance on when class effect labeling is allowed for a companion diagnostic. Additionally, clear guidance is needed on the impact of class effect labeling on other drugs, new or approved, within the class. With respect to the specific sub-issues – a) For clear guidance to the medical community the brand name should always be cross-labeled with the therapeutic. IVD device manufacturers are required to put into their labeling the therapeutic that the product was approved with, therefore the reverse would appear appropriate. b) FDA should clarify the meaning of "type."	Therapeutic (Drug A) and associated companion diagnostic (CDx A) 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 (CDx B) that measures the same marker as Drug A's companion diagnostic. What level of evidence would be required to obtain class labeling, covering both Drug A and Drug B, in the CDx B label? Assuming class effect labeling is obtained for CDx B, how does the class effect labeling impact the approval and labeling of a novel Drug C that is to be approved which falls into the same class as Drug A and Drug B? Can Drug C be approved based upon the class effect labeling of CDx B without submitting a PMA?	Current guidance is unclear. The CDx Draft Guidance provides that, "[w]hen appropriate, the therapeutic product labeling should identify a type of FDA approved or cleared IVD companion diagnostic device (i.e. the intended use of the device), rather than a specific manufacturer's IVD companion diagnostic. This will facilitate the development and use of more than one approved or cleared IVD companion diagnostic of the type described in the labeling for the therapeutic product." During a presentation on IVD Companion Diagnostics at the Next Generation Dx Summit on August 21-23, Dr. Alberto Gutierrez indicated that the therapeutic label will likely refer to "FDA approved test" to allow new tests to be used without drug label change. In contrast, the CDx Guidance provides that the labeling for an "IVD companion diagnostic device that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use." However, the Guidance recognizes an exception "if evidence is sufficient to conclude that the IVD companion diagnostic device is appropriate for use with a class of therapeutic products, the intended use/indications for use should name the therapeutic class, rather than each specific product within a class."

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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?	FDA can suggest, but not require, a CDx manufacturer to submit a PMA or PMA supplement when evidence becomes available that the use of the CDx is essential for the safe and effective use of a drug other than the one that was co-approved. FDA can impose a post-marketing requirement on the drug manufacturer to study Drug B with a CDx. Labeling for Drug B could then be revised to reflect data from the trial and to cross-label with the CDx. If both drugs are in the same class, FDA could require the CDx manufacturer to update the intended use for class labeling. Drug B would still require studies with a CDx to support addition of an "FDA approved test" in the label.	Company A owns approved therapeutic (Drug A) and associated companion diagnostic (CDx A). Drug A and CDx A were co-approved and cross-labeled. Evidence becomes available that the use of CDx A is essential for the safe and effective use of approved Drug B, owned by Company B. What if Company A does not want Company B to mention CDx A since Drug B competes with Drug A. Can FDA force Company A to submit a PMA or PMA supplement to include an indication for Drug B to the label for CDx A? If Drug A and Drug B are in the same class, can FDA require class effect labeling? If so, can Drug B obtain class effect labeling which includes the approved CDx from Drug A without conducting clinical studies of Drug B with the CDx from Drug A? Does it matter whether the marker is for efficacy versus safety?	The CDx Guidance indicates that when an IVD companion diagnostic device has been approved or cleared for use with one therapeutic product and evidence becomes available that use of the same device is essential for the safe and effective use of a different therapeutic product, a new PMA submission or supplement would be required and the labeling of the therapeutic product should also be amended through the submission of the supplement.
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)?	In the past FDA has allowed manufacturers to include label text where a class of tests may be recommended in this situation, but does not mention specifically how the test may better inform patients or physicians of increased efficacy. In the case where no IVD test is required, but the test demonstrates benefit, the therapeutic labeling should include information relative to benefit/risk to inform a decision about using the IVD test.	For example the Atorvostatsin label states, "Doasage should be individualized according to the recommended goal of therapy. Homozygous Familial Hypercholestremia (10-80 mg/day) and hetereozygous (10-20mg/day) Familial Hypercholestremia adjustment needed in pediatric patients"	It may be a good idea to describe in greater detail that the presence or absence of a test may be indicative of increased/decreased benefit and/or risk.