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July 15, 2005

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

Re: Docket Number 2004N-0279: Drug Diagnostic Co-development Concept Paper

Dear Sir or Madam:

These comments are submitted on behalf of the Advanced Medical Technology Association (AdvaMed). 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 \$75 billion of health care technology products purchased annually in the United States, and more than 50 percent of the \$175 billion 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.

AdvaMed supports FDA's development of a concept paper to provide its preliminary thoughts on how to prospectively co-develop a diagnostic test with a drugs or biological therapy (drug). Such a diagnostic test could be used for several indications: patient qualification, patient monitoring, predicting/quantifying a patient's drug response, and/or independent diagnosis. We appreciate the opportunity to provide input to FDA prior to its development of guidance. We look forward to the opportunity of commenting on the draft guidance that will result from this effort.

GENERAL COMMENTS

AdvaMed appreciates FDA's recognition that certain tests, "*optional or exploratory tests that are not intended for further development or those that do not affect the results of clinical trials*" are not within the scope of this paper. We believe that inclusion of such tests would result in over-regulation of the drug-diagnostic co-development for pharmacogenetic tests and could stifle innovation.

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It appears that much of the document is based on the model presented in Figure 1, which represents an idealized classic model of twentieth century drug development. Not all drug development follows this model. In fact, many of the important breakthrough drugs utilized accelerated approval models or have less distinction between the classic phases depicted in that diagram (e.g. phase I/II trials rolled together or Phase II/III pivotal trials). This is especially true of biologic therapies that may not allow for traditional animal models or phase I testing. For some of the most current biotechnology-derived molecules, it is often not until phase II or even phase III trials that we learn enough about a drug's behavior to investigate possible biomarkers or clinically relevant analytes.

Usually, a great deal of information on the new drug needs to be collected prior to deciding whether a diagnostic test as described earlier will be needed. This is most common beginning in phase 2 when early data indicate potential variability of response among patients. Furthermore, the clinical validation of the biomarker and the development of the diagnostic algorithm may take place late in phase 3 clinical trials (i.e., during the NDA filing period). It would be more useful if the document described these situations providing flexibility of the diagnostic application as it may relate to clinical and research findings during the process leading up to an FDA submission for a therapy. In fact, additional work may need to be completed subsequent to a therapy submission before a related diagnostic submission would occur. We recommend that FDA consider this flexibility to encourage regulatory accommodation of such situations without delaying approval and launch of the drug product. We also recommend that FDA revise Figure 1 to be more consistent with actual drug and device development.

Clinical utility is not explicitly mentioned in the Act and never defined in the regulations. There have been internal FDA memoranda ("Blue Book") which give examples but never satisfactorily defined the term. It is imperative that FDA work with all stakeholders to define "clinical utility" in a clear and consistent manner. AdvaMed believes this paper gives examples but does not provide a clear definition or criteria of what is required to show "clinical utility". The definition in the glossary differs from previous descriptions. In other portions of the paper the explanation of clinical utility comes close to a description of what could be considered an indication for use. Further, it is our belief that the clinical utility of a "diagnostic test" must not be restricted to such that clinical utility is thought of in terms of how clinical practice will be changed by use of the test but must be broadened to include "informational utility". We recommend that as a starting point for defining informational utility it be defined as information obtained through a diagnostic test that is interpreted at the discretion of the clinician. There should also be a provision in the guidance, consistent with the *de novo* process and the *Pharmacogenomics Data Guidance*, to demonstrate clinical/informational utility or usefulness of a biomarker for which there is no predicate through scientific literature references, without the need to confirm clinical utility in a prospective clinical study.

Finally, the proposals for prospective analysis of diagnostic tests and increased requirements for banked specimens are not aligned with FDA's Least Burdensome Principles. We recommend that the guidance discuss the Least Burdensome Provisions of the FDAMA [§

205(a)] in the context of drug-diagnostic co-development programs. Some of the examples given indicate more than a single pivotal trial might be necessary for test approval. While two or more well-controlled clinical trials are the standard for drug development, medical devices by law, need only valid scientific evidence of safety and efficacy. We also suggest that the banked specimen recommendations in this document be further clarified and more firmly supported with the updated IRB and consent regulations that FDA has indicated have been under consideration for some time and for which industry has been anxiously awaiting.

SPECIFIC COMMENTS

1. INTRODUCTION, BACKGROUND, AND SCOPE

1.3 Scope

In the first paragraph on page 2, the document states *“This document addresses issues related to the development of in vitro diagnostics for mandatory use in decision making about drug selection for patients in clinical practice.”* This statement and the timeline in Figure 1, warrant clarification from the FDA whether the guidance intends to discuss only commercially-distributed IVD kits, or will it also consider laboratory-developed diagnostic assays developed using Analyte Specific Reagents (ASRs) and/or the ASRs themselves. Especially since the penultimate paragraph of this section states, *“FDA would expect many of these products – in particular those with high risk profiles – to be processed as class III products subject to premarket approval process.”* It is imperative that both be addressed in the guidance.

We also encourage FDA to work through the appropriate channels within HHS to ensure that laboratory-developed tests which generate results intended to be used by the medical community in the same/similar manner as their commercially-distributed counterparts, and pose similar public health risk(s), are regulated to the same standard defined in the guidance that stems from this Concept Paper.

In the second paragraph the document states *“This document addresses development of a single test in conjunction with a single drug.”* It is likely that multiple tests could be developed in parallel with a drug product or that additional markers could be added later. The concept paper should address these possibilities.

2. REVIEW PROCEDURE ISSUES

2.2 Procedures

This document should address other more-probable co-development pathways, which begin during the end of phase 2 or phase 3 of drug development. It may be helpful to adapt Figure 2 (Drug Device Co-development Process) to show how to time events to allow the preparation, filing, review and approval of the PMA or 510(k) for the

diagnostic test during the same timeframe in which the NDA is reviewed and approved. One possible scenario would be that the pre-IDE meeting would take place in mid-to-late phase 3 of the clinical trial and concurrent with initial drug labeling discussions.

It should be taken into consideration that a great deal of information has been collected during the drug development that may be used for the approval of the diagnostic test. This paradigm should be embraced and appropriate guidelines put in place so that the co-development and approval of a drug requiring a diagnostic test is efficient and timely but realistic.

3. ANALYTICAL TEST VALIDATION

3.1. General Recommendations to Support Premarket Review

On page 7 the document states, "*Study design should take into account statistical considerations for both the drug and the diagnostic.*" There should be recognition that clinical validation of the diagnostic product may come from clinical trials that did not take into account statistical considerations for the drug. The diagnostics study design and even much of the diagnostic submission supporting data may be totally independent of the drug trial. The diagnostic needs to stand on its own merits and prove safety and efficacy or substantial equivalence.

We recommend that the following sentence on page 7 be changed as follows:
"*Clinical trial specimens should be banked in ~~optimal~~ storage conditions ~~adequate to enable subsequent test development and/or retrospective hypothesis generation or confirmation of test performance~~*" as optimal storage conditions are not defined.

3.5. Analytical Validation of Changes to a Device in Late Stages of Development

On page 9 the document states, "*The stability and validity of using banked samples should be documented by demonstrating that the original assay results can be repeated at the time when the new assay results are obtained from the specimens.*" This statement is unreasonably prescriptive. We recommend changing to "***The stability and validity of using banked samples should be documented and information supporting sample integrity should be provided.***" This recommendation is consistent with FDA's Guidance "Drug Metabolizing Enzyme Genotyping System."

4. PRECLINICAL PILOT FEASIBILITY STUDIES

4.1. Introduction

On page 10 of the paper, the document states, "*Ideally, a new diagnostic intended to inform the use of a new drug will be studied in parallel with early drug development*

(phase 1 or 2 trials) and diagnostic development will then have led to prespecification of all key analytical validation aspects for the subsequent (late phase 2 and phase 3) clinical studies.” As previously mentioned, the proposed ideal model is, in reality, rarely the case. We propose that FDA focus on actual situations where industry needs guidance the most. To have a more significant practical value, the eventual guidance should address co-development involving a new drug and diagnostic test in which diagnostic test development may not be realized until late during the drug development.

5. GENERAL APPROACHES TO DEFINE CLINICAL TEST VALIDATION

On page 13 the document states, “*Clinical test validation of a new diagnostic for use in selecting drug therapy or avoiding drug therapy should be characterized by studying the test in relation to the intended clinical outcome in patient subgroups with and without the analyte of interest.*” Clinical test validation of a pharmacogenetic test may not be done in patient subgroups without the analyte of interest when that analyte defines the disease (e.g., chronic myelogenous leukemia). This possibility also needs to be accounted for in this discussion.

The concept paper focuses on a test in which there are positive and negative results with a single cut-off value (e.g., responder/non-responder). While this simplification is useful to present some concepts, the guidance also needs to account for tests that have more than two categories, return continuous values that place an individual in a specific portion of a benefit/risk spectrum, or that provide a range of probable outcomes for individuals based on their genotype. To illustrate, the following scenarios are provided.

- A possible example of a relevant efficacy biomarker is one that identifies three groups of asthmatics who can be expected on average to have a 5, 12 or 20% increase of FEV1 after 2 weeks on drug (or to put it another way, have a 20, 50 or 85% probability of attaining a clinically meaningful response after 2 weeks on drug).
- A possible example of a relevant safety biomarker is one that identifies three groups of cancer patients who can be expected to have different ranges of metabolic changes on drug.
- PPV and NPV may not be the main metrics if the outcome is continuous (see examples above). Hence, specification of cut-off values may not be so important for many pharmacogenetic tests.
- Finally, the document should not exclude the use of the diagnostic to help *determine* the relevant clinical subgroups.

6. CLINICAL UTILITY¹

On page 15, paragraph 2 states, *“To confirm clinical performance, including clinical utility, additional clinical studies may be called for to avoid post-hoc specification of the diagnostic cut-off points.”* The paper should recognize that a prospectively defined analysis of drug clinical trial data could be used to clinically validate the performance characteristics of the diagnostic test, negating the need to conduct additional clinical studies.

Further, the paragraph states, *“If changes are made to a test during the clinical validation process that result in major analytical changes, the ability to use and pool data from differing time periods or different sites may be compromised and may therefore undermine the evaluation of the clinical utility process.”* It must be recognized that the stability of DNA as an analyte allows for analytical changes to be made during clinical validation without undermining the evaluation of the clinical utility process. Additionally, such shifts can often be accounted for mathematically to allow pooling. Rather than being prescriptive on assay improvement data use, AdvaMed recommends that guidance be provided to account for such changes when providing data, pooled or not. The last sentence expresses the conditions under which this is possible: *“Although prospective data are preferred, in cases where the analyte is stable and where collection bias (...) can be carefully characterized and addressed, prospectively designed retrospective clinical utility studies may be possible.”*

6.1. Coordinating Drug and Diagnostic Studies

The concept that there will be a prospective study simultaneously assessing both drug response and the quality of the diagnostic is ideal, but it must be acknowledged as often unobtainable. FDA guidance should include more realistic scenarios. It is also our expectation that banked samples may often provide valuable information that should be considered in determining the S&E of the test. We recommend Figure 3 and its accompanying texts be modified to allow for the possibility that the diagnostic statistical analysis may be conceived and conducted after the drug clinical trial is completed and include, under the appropriate circumstances, to include prospective testing of banked specimens.

6.2. Issues to Consider in Selecting Study Populations

Paragraph 1 on page 17 states, *“In some cases, sponsors may wish to use enriched study populations to evaluate the likelihood of response to a drug treatment, such as*

¹ Note: As previously stated, clinical utility is a major concept that needs further explanation. The glossary definition does not aid in understanding of this section. A detailed discussion of clinical utility from a test standpoint is needed. FDA should work with all of its stakeholders on this effort. The definition of clinical utility should also be such that other HHS departments' requirements would accept the concept as well (e.g. CMS or CLIA).

in a proof of concept trial in early phase 2 of drug development.... Consideration should be given to how enrichment will relate to the ultimate claims made for the drug being evaluated.” The use of a pharmacogenetic test for a proof-of-concept trial is not a registration issue. Justification of the enrichment technique should not be a requirement, as long as there is no intent to also enrich the pivotal phase 3 studies.

Bullet points 1 and 3 on page 18 are applicable only to enriched pivotal phase 3 studies. Bullet point 2 is a practical issue but should not affect the scientific evaluation of a co-developed drug and diagnostic test products.

On page 19, paragraph 1 states, *“In cases where the testing is done as an ancillary part of the trial (i.e., not incorporated into the trial design or primary outcomes), resulting associations between test results and clinical outcomes would usually be considered exploratory and therefore these results would be more appropriate for assessing clinical test performance or generating hypothesis about clinical utility rather than confirming clinical performance or utility.”* The paper, as written, appears to recommend that additional prospectively designed confirmatory studies are necessary for confirmation of observations obtained from an ancillary part of a clinical trial. FDA’s Least Burdensome Approach, as required by statute, may permit use of such data.

Further, paragraph 3 states, *“Optimally, further confirmatory testing would be performed in prospective trials.”* The guidance needs to recognize that this will be the exception rather than the rule in development programs for regulatory co-approval of drugs and tests. We recommend that the guidance, when issued, address the “usual” situation instead of describing only scenarios considered “optimal.” Once again, AdvaMed asks FDA to more fully consider our mutual interest in “least burdensome” in providing guidance.

Finally, paragraph 4 states *“The approach to these associations and analysis should be pre-specified in advance and not after the study is completed.”* It must be made clear that the intent to perform the genetic analysis should be specified in advance but that the definite analysis plan may only be decided upon after the clinical analysis has been completed (In fact, in many situations this will be preferred.). In other cases, valuable clinical results, such as population and/or patient selection may only become obvious after the data are reviewed. FDA needs to allow for this important clinical information to contribute to new diagnostic algorithms.

6.4. Verification of Clinical Test Utility – Statistical Consideration

Paragraph 1 on page 20 states, *“... the analytical characterization of a diagnostic test should be based on a dataset that is independent from and prior to the prospective or retrospective samples on which it is to be clinically verified.”* We recommend FDA clarify what constitutes an independent dataset for analytical characterization. A

more complete discussion of data sets and references to specific statistical papers on the topics of validation sets would also be helpful.

Paragraph 2 addressing "*post-hoc characterization of a test*" may be misleading because it does not highlight the prospective (genetic)-retrospective (clinical) approach. Again, more discussion on this particular area of statistical science is needed with references. Additionally, the timing of the analytical characterization (...prior to the prospective or retrospective...) should not be required. As stated above, it is very possible that post-hoc data may be the most revealing and provide unanticipated significant clinical value.

GLOSSARY OF TERMS

The paper states: "**Clinical Utility** – The elements that need to be considered when evaluating the risks and benefits in diagnosing or predicting risk for an event (drug response, presence or risk of a health condition.)" This is an inadequate definition and, as stated previously, should be modified.

ADDENDUM B: STUDY DESIGN – EXAMPLES OF ISSUES TO BE CONSIDERED

3. **Analyte concentration specifications** (page 28).
A corollary for these considerations should be that no extra (array) elements should be included in an IVD.
4. **Cut-off** (page 29)
Note that cut-off values are applicable only to tests with categorical outcomes.

ADDENDUM C: DETERMINING IF A DIAGNOSTIC TEST IS INFORMATIVE

Paragraph one on page 32 of the document states: "*The first step in interpreting diagnostic test results is determining if a test is informative. A test is clinically useful only if it provides information to discriminate between patients with and without the condition or interest (e.g., response or adverse event). Examples of standard diagnostic test performance metrics are clinical sensitivity and specificity*". AdvaMed believes this to be an example of "informational utility" mentioned above. It should not be predicated on response or outcome.

This is further reinforced in Addendum C by the following statement on page 36:

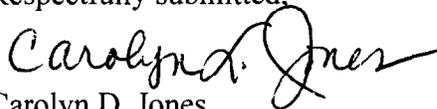
"A test is informative only if its sensitivity plus its specificity is greater than 100%. For tests with a combined sum of more than 100%, the strength of the test should be considered in terms of both numerical and clinical impact of the combined numbers. Obviously, the closer the sum comes to 200% (sensitivity and specificity each of 100%), the better the test performs. However, values between 100% and 200% that

are considered clinically meaningful would depend on clinical rather than mathematical considerations.

Performance measures other than sensitivity and specificity can also be used to determine if a test is informative. A test is informative only if one of the following equivalent statements is true: (1) sensitivity plus specificity is greater than 100%, (2) PPV plus NPV is greater than 100%, (3) +LR or -LRn is greater than 1, or (4) the odds ratio is greater than 1”.

Thank you for the opportunity to provide comments on the Co-Development Concept Paper. AdvaMed looks forward to additional opportunities for diagnostic member companies to provide input on diagnostic test co-development.

Respectfully submitted,



Carolyn D. Jones
Associate Vice President
Technology and Regulatory Affairs

Docket Management Comment Form

Docket: 2004N-0279 - Draft Drug-Diagnostic Co-Development Concept Paper

Temporary Comment Number: 18498

Submitter: Ms. Carolyn Jones	Date: 07/15/05
Organization: AdvaMed	
Category: Device Association	
Issue Areas/Comments	
General	
"See Attachment."	
Attachments	
No Attachments	

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