



Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

Tricia DeSantis
Senior Director
Regulatory Affairs

August 1, 2005

1700 Rockville Pike, Suite 445,
Rockville, MD 20852
Phone 301.881.6974, ext. 225,
Fax 301.881.7526

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

Re: Docket# 2004N-0279: Johnson & Johnson Consolidated Comments to the Drug
Diagnostic Co-development Concept Paper

Dear Sir or Madam,

On behalf of the Johnson & Johnson family of companies ("J&J"), we are providing the following comments and recommendations in response to the FDA preliminary concept paper, "Drug-Diagnostic Co-Development", released for comment in April, 2005. Our comments were gathered from several J&J operating companies engaged in pharmaceutical R&D, molecular diagnostics and pharmacogenomic research, namely: J&J Pharmaceutical Research and Development, LLC; Veridex, LLC; ALZA Corporation; Centocor, Inc.; Ortho Clinical Diagnostics, Inc.; Tibotec, Inc.; SCIOS, Inc; and Virco.

This document is an important step in FDA's attempt to help define the processes by which pharmaceuticals and companion diagnostics will be co-developed.

Johnson & Johnson supports FDA's premise that drug/test combinations have the potential to provide many clinical benefits for patients and welcomes the opportunity to comment on this and related draft guidances. From our perspective, it is crucial for industry and regulators to work together so that the science of pharmacogenomics can rapidly be translated into real advances in public health.

The preliminary concept paper is impressive for its level of detail but overall it still falls short in defining a new process to coordinate two different but related industries. We present first our general impressions of the draft, followed by section-by-section comments.

J&J General Comments

We have identified two main areas of concern:

1. The document describes an overly idealized situation where development of the diagnostic proceeds smoothly in parallel with the clinical development. This is unlikely to be the case when there is not a sufficiently robust hypothesis at the discovery/preclinical stage. In fact, it does not often become apparent until well into clinical development that a biomarker strategy is desirable or even feasible. Thus, guidance for these additional scenarios would be appreciated:

- When a hypothesis emerges later in development, (i.e. during clinical trials), there may still be merit in developing a diagnostic to better inform use of the drug post-approval. Under this scenario, the diagnostic would not be required for approval but would still be co-developed for launch at a later date
 - Similarly, having a validated diagnostic available later in clinical development may still have considerable value in designing follow-up studies for selected populations, either to “rescue” failed drugs or improve the safety profile of those which have the potential for variable pharmacokinetics.
 - There may be good reasons for retrospective development of the diagnostic also (e.g. post-marketing). Under this scenario, the diagnostic program would be initiated to improve clinical use of the drug (e.g. line extensions), or for legitimate business reasons such as patent extension.
 - By focusing only on the ideal prospective development scenario, the guidance fails to address the question of “When is it too late to initiate a biomarker program?” This is unfortunate as specific recommendations for analytical and clinical validation would generally be applicable to the additional scenarios described above.
 - The guideline should be more specific as to how patient benefit will be determined, particularly if use of the diagnostic will be “mandatory”.
2. Statistical requirements are both too stringent and unnecessarily rigid. In particular, the performance requirements for the diagnostic are unnecessarily proscriptive. The definition of what makes a test “informative” should not be expressed in absolute terms, but rather should reflect a judgment based on the totality of the data and the potential public health impact of the new therapy. It should also be recognized that technological advances will occur rapidly for diagnostics, potentially rendering early work obsolete before late stage clinical trials can proceed. With these caveats in mind, the draft should provide additional flexibility in development of the diagnostic:
- The document focuses on categorical end points; however, more specific guidance would be desirable regarding other methods of assessing response, recognizing that it is desirable to maximize the responder population for most analyses. Since response criteria can be very subjective, it would be helpful to have guidance on what the FDA considers acceptable.
 - We do not agree that it is desirable to finalize assay cutoffs prior to performing the pivotal clinical trials (Section 4.2). FDA should allow for follow-up discussion to revisit and revise the assay cutoffs post-hoc if appropriate justification exists.

- Accurate positive and negative predictive values for the diagnostic will not always be available at the start of clinical trials. In order to avoid delays, an acceptable range of values would be more appropriate than a fixed target.
- Thresholds for sensitivity and specificity should be considered in the context of the population under study (e.g., it may be appropriate to have different thresholds for safety diagnostics vs. those related strictly to efficacy).
- The document does not provide specific guidance on the use of panels of markers, focusing only on a single test for a single drug. Moreover, it is not clear whether data would be invalidated if more than one diagnostic were studied and the results were discordant.

J&J Section-by-Section Comments

I. INTRODUCTION, BACKGROUND, AND SCOPE

None

II. REVIEW PROCEDURE ISSUES

Section 2.2

- (point 2) We are not in favor of adding a VGDS as a required submission. However, if a VGDS has been previously submitted, an avenue should be provided to make additional information available as it is developed.
- Clarification would be appreciated as to whether the drug with accompanying diagnostic will be considered a “combination product”.
- (point 3) We question the inclusion of feasibility test data. Feasibility is not defined in the Glossary of Terms. Feasibility testing is typically conducted prior to the initiation of design controls. Therefore, it should not be required for a regulatory submission.

III. ANALYTICAL TEST VALIDATION

Section 3.1

- Additional guidance on the management and QC of banked samples would be helpful.
- No guidance is provided for Sponsors who wish to develop an assay in conjunction with a CLIA certified lab. This has advantages in that the assay can be made commercially available without the need for further 510(k) clearance or PMA approval while still making the Master File available to FDA. We recommend that the first sentence be changed to reflect this scenario (from “commercially distributed test kits” to “distributed by manufacturer or available through a CLIA certified reference laboratory”).
- The guidance should recognize that retrospective analyses will not always be possible (e.g., it is currently not feasible for the Veridex CellSearch

Circulating Tumor Cell Kit). We suggest modifying the last sentence to include the phrase "When Possible" (this suggestion also applies to the second sentence in **Section 3.5**).

Section 3.4.1

- There is no definition of the stage in the development of the diagnostic product at which the corresponding software should be verified.

Section 3.5

- See last bullet point under **Section 3.1**.

Section 3.6

- For multi-analyte diagnostic tests it is suggested that the degree of analytical validation will depend on the number of features or readouts represented on the test with validation of individual features necessary when the number is less than 10. We suggest that typical measures of validation (accuracy, precision, analytical specificity and sensitivity) for the assay system as a whole should be acceptable to prove the validity of the assay system, irrespective of the number of features represented on the test.

IV. PRECLINICAL PILOT FEASIBILITY STUDIES

Section 4.4

- We disagree that "better tests have larger areas (AUC)." This is a global generalization that many statisticians advocate, but does not necessarily reflect the complete clinical value. It is typically more complicated than that simple statement (i.e. given the risk profile of an assay, two assay conditions that give nearly equal AUCs made be widely divergent in terms of suitability of the assay for driving patient management, especially if the AUC is 0.8, as opposed to 0.99. Often the best assay is the one that offers optimal AUC under a small portion of the curve that includes the region of most importance.

V. GENERAL APPROACHES TO DEFINE CLINICAL TEST VALIDATION

None

VI. CLINICAL UTILITY

None

ADDENDA

Addendum A

- This should also include a description of sample preparation methods if it can be considered to be part of the device.

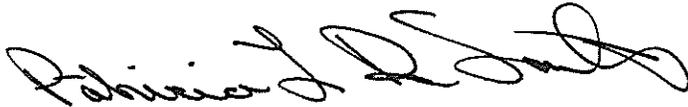
- Relevant FDA Special Control documents and/or CDRH/OIVD guidances should be cross-referenced.

Addendum C

- The following statement is a generalization that is highly dependent on the use of the assay and, consequently, is often not true: "Obviously, the closer the sum comes to 200% (sensitivity and specificity each 100%), the better the test performs." For example, if an assay will be used to identify patients who do not respond to a treatment that is currently given to all patients (that has an overall response rate of say, 20%), then an assay with 100% sensitivity and 50% specificity is much better than one with 50% sensitivity and 100% specificity. Conversely, if you are ruling in for treatment of the 20% of patients that should, but do not, receive a relatively toxic treatment because they are at low risk, then it is likely much better to have an assay that has 60% sensitivity and 90% specificity versus 100% sensitivity and 50% specificity.

In closing, we would like to thank the Agency in advance for its thoughtful consideration of our comments and recommendations. If we can provide further assistance, please to not hesitate to contact me at 301-881-6974.

Respectfully submitted,



Patricia L. DeSantis
Senior Director, Global Regulatory Policy and Intelligence
Johnson & Johnson Pharmaceutical Research & Development