



Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
T 617-252-7500

9368 '05 JUL 18 A9:11

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:

We at Genzyme believe we are uniquely positioned to discuss the Drug Diagnostic Co-development as a biotechnology company who develops therapeutic products (Drugs, Biologics and *In Vitro* Diagnostics) for unmet medical needs *and* as a laboratory service provider of genetic testing and clinical pathology. We at Genzyme thank FDA for their consideration of our following comments on the "**Draft Drug-Diagnostic Co-Development Concept Paper**"

GENERAL COMMENTS

Genzyme supports FDA's recognition (page 3) that over-regulation of the drug -diagnostic co-development for pharmacogenetic tests could stifle innovation. At the DIA/FDA/PhRMA workshop, Janet Woodcock stated that pharmacogenetics was identified as a key portion of FDA's "Critical Path" document and that current frameworks of drug development may not be appropriate for the targeted populations and approaches of the twenty first century and new business models must be considered.

However, it is apparent to Genzyme that much of the document seems to be based on the model presented in Figure 1. This model is an idealized classic model of twentieth century drug development. Some of the drugs produced today use a modified approach to that depicted in Figure 1. 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. It is often not until phase two trials that we learn enough about the drugs behavior to investigate possible biomarkers or clinically relevant analytes. Usually, a great deal of information on the new drug/ biologic needs to be collected prior to deciding whether a diagnostic test will be needed.

It would be more useful to describe the more likely situation of co-development of a drug and diagnostic test in which the identification of the clinically relevant analyte does not take place prior to phase 2 clinical trials (and may be later). Furthermore, the clinical validation of the

2004N-0279

C4

biomarker and the development of the diagnostic kit may take place after the completion of phase 3 clinical trials (i.e., during the NDA filing period). We recommend that FDA consider this common timeframe to encourage regulatory accommodation of such situations without delaying approval & launch of the drug product. We also urge FDA to work with the laboratory community to develop guidelines for laboratory derived tests to be utilized in lieu of the fact that not all tests will be appropriately marketed as kits. This is especially true as esoteric tests or very small targeted populations create a situation where there may not be an economic incentive to manufacturers to produce "kits".

Clinical utility is mentioned in the Act however 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". Genzyme believes this paper once again gives examples but never sets a definition or criteria of what is required to show "clinical utility". The definition in the glossary is different from all previous definitions we are aware of and in some ways inconsistent with the text of the paper. 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 limited to restrictive thinking of the past where 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". Rarely is a diagnostic test absolute. It is not the purpose of a test to provide certainty but to reduce uncertainty by providing further information.

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 tests approval. While two or more well controlled clinical trials are the standard for drug development, the medical devices, by law, need only valid scientific evidence of safety and efficacy.

SPECIFIC COMMENTS

1.3 Scope

The statement "*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*", and the timeline in Figure 1, warrant clarification from the FDA whether the guidance intends to discuss diagnostic tests such as Analyte Specific Reagent (ASR) and homebrew assays, or IVDs. The latter seems to be supported by the statement in the penultimate paragraph of this section "*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 guidance.

2.2 Procedures

Figure 2. Drug Device Co-development Process:

The guidance should address other more-probable co-development pathways which begin during the end of phase 2 or even phase 3 of drug development. It may help to adapt Figure 2 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 timeline would be that the pre-IDE meeting takes place in mid-to-late phase 3 drug development.

It should be taken into consideration that a great deal of information has been collected during the drug/biologic 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/biologic requiring a diagnostic test is efficient and timely but realistic.

3.1. General Recommendations to Support Premarket Review

The paper 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 may be totally independent of the drug trial. It needs to stand on its own merits and prove safety and efficacy or substantial equivalence.

The following sentence should be changed to “*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*” so that we are not guided to pursue unobtainable perfection.

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

The paper 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

The paper 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/biologic and diagnostic test in which a need for a diagnostic test development may not be evident until late during the drug development.

5. GENERAL APPROACHES TO DEFINE CLINICAL TEST VALIDATION

It is stated in the paper “*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 cutoff 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.

6. CLINICAL UTILITY

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).

It is stated “*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.

The paper states, “*If changes are made to a test during the clinical validation process that results 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. 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.

Therefore, Figure 3 and its accompanying texts should be modified to allow for the possibility that the diagnostic statistical analysis may be conceived and conducted after the drug clinical trial is completed.

6.2. Issues to Consider in Selecting Study Populations

It is stated that *“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, the paper 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.”

It is stated, *“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).

6.4. **Verification of Clinical Test Utility – Statistical Consideration**

It is stated that “... *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.*” Clarification of what constitutes an independent dataset for analytical characterization will help. A more complete discussion of date sets and references to specific statistical papers on the topics of validation sets would be helpful.

The paragraph on “*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.

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.

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

The paper 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.*” Genzyme believes this to be an example of “informational utility” mentioned above. It should not be predicate on response or outcome.

This is further reinforced in Addendum C: “*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.*”

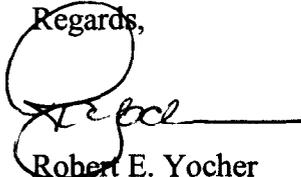
Performance measures other than sensitivity and specificity can also be used to determine if a test is informative. A test is informative only if one of the following equivalent statements is true: (1) sensitivity plus specificity is greater than 100%, (2) PPV plus NPV is greater than 100%, (3) +LR or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

Genzyme is pleased to discuss further with FDA any portions of these comments and to participate in future discussions on Pharmacogenetic test or drug-diagnostic "co-development".

Please direct all questions or communications concerning our comments directly to me at:

Robert Yocher
VP RA /Corporate Quality Compliance
Genzyme Corp.
500 Kendall St.
Cambridge, MA 02142
robert.yocher@genzyme.com
617-768-6275

Regards,



Robert E. Yocher
Vice President Regulatory Affairs and Corporate Quality Compliance
Genzyme Corp.