



The Ever-Evolving Role of “Companion Diagnostics”

by Randy Prebula

Since 2004, the Food and Drug Administration (FDA) has focused on the concept of the “critical path” initiative — the agency’s effort to stimulate and facilitate the modernization of the sciences through which FDA-regulated products are developed, evaluated and manufactured. As part of this initiative, FDA has highlighted the potential of genetic/genomic testing to create targeted drug and biologic therapies. To that end, the agency has issued guidance documents and concept papers addressing both the procedural and scientific issues that may be considered in the development of drug-diagnostic test combinations, or “companion diagnostic tests” using genomic data. Whether companion diagnostics are used to identify and select patients who may benefit from (or avoid) specific therapies, adjust drug dosage or frequency of administration or predict the likelihood of disease progression or recurrence, these tests reflect the true promise of personalized medicine — the provision of individually safe and effective treatment.

Pharmacogenomics is defined by FDA as the use of a pharmacogenomic or pharmacogenetic test in conjunction with drug therapy.¹ FDA has observed that such tests hold the potential to determine why some individuals may respond positively to a drug while others may not respond, or may experi-

ence side effects. The tests also may reduce drug development costs by allowing sponsors to better predict which drug candidates may warrant further development.

FDA encourages drug sponsors to conduct pharmacogenomic testing and submit their results to the agency.² The agency’s guidance clarifies current policies with regard to pharmacogenomic data, and describes the mechanism by which drug sponsors may integrate genomic data into their drug development programs.

As described within these guidances, FDA initially viewed the use of pharmacogenomic data in drug development to be rapidly evolving but in large part, not mature. FDA, for example, originally distinguished within its guidance documents between valid biomarkers (i.e., the results of pharmacogenomic tests with well established performance characteristics and known physiologic, pharmacologic, toxicologic or clinical



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significance), probable valid biomarkers (i.e., results which appear to have predictive value for clinical outcomes, but may not yet be widely accepted or independently verified), and exploratory or observational data. FDA observed that most biomarkers were not yet “valid,” but anticipated that more biomarkers would be considered valid as the science develops.

FDA Requirements

Although FDA encourages all sponsors conducting pharmacogenomic testing to submit the results to FDA, the agency only *requires* sponsors to submit such information to their investigational new drug applications (INDs), new drug applications (NDAs) and biologics license applications (BLAs) in certain scenarios. Specifically, FDA provides that pharmacogenomic data must be submitted in an IND where the test results relate to a valid biomarker³ or where the results are used to inform decision making for clinical trials,⁴ or to direct drug utilization (e.g., dose selection, dosing schedule). Pharmacogenomic data must be submitted in an NDA or BLA when related to a valid biomarker or probable valid biomarker, or when the test results will be included in the drug labeling or as part of the database being used to support product approval.

Despite the initial view that few valid biomarkers had been well-characterized, FDA (immediately prior to and over the four years since the initiation of FDA’s Critical Path initiative) has identified 28 companion diagnostic tests for valid genomic biomarkers in the context of FDA-approved drug labels. These tests are categorized by FDA within four broad groups

- (1) “test required;”
- (2) “test recommended;”
- (2a) “test for at risk populations;” and

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(3) tests for “information only.”⁵

FDA has identified four tests as “required,” nine as “recommended,” one for “at risk populations,” and 14 as “for information only.” Within the four “required” drug/companion diagnostic tests, FDA includes two for the expression or overexpression of tumor-associated proteins (EGFR expression for identification of patients for treatment with Erbitux (cetuximab) and HER2 protein overexpression for identification of patients for treatment with Herceptin (trastuzumab), one for the identification of individuals with a specific chromosome (Philadelphia chromosome), and one for the identification of viral coreceptor tropism in individuals eligible for treatment with an anti-retroviral agent, Selzentry (maraviroc). The remaining “recommended,” “for at risk populations,” and for “information only” companion diagnostic tests similarly include assays for tumor antigen expression or overexpression, gene deletions and insertions, allelic variation, and enzymatic deficiency.

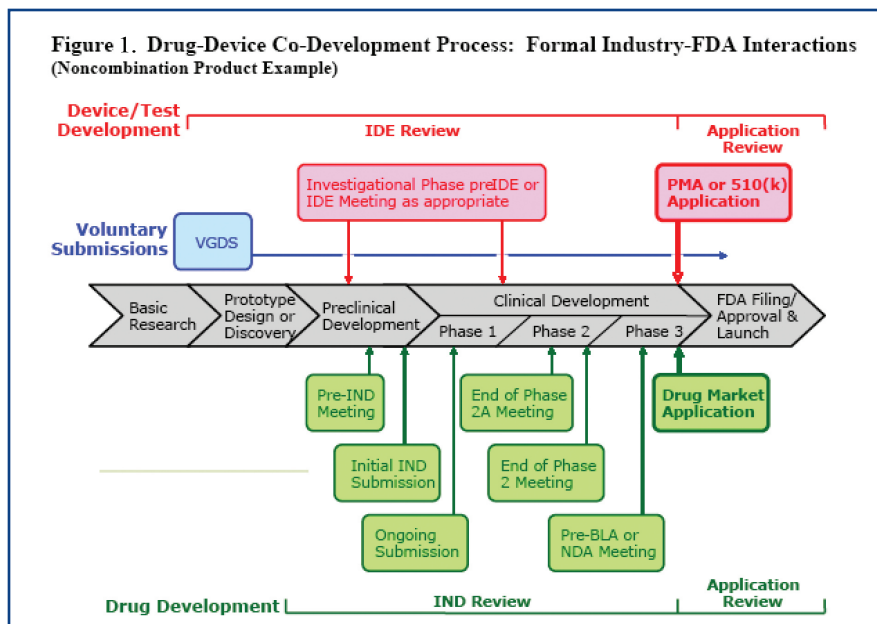
Drug-Diagnostic Co-Development

Irrespective of a companion diagnostics’ possible categorization as “required,” “recommended” or otherwise, sponsors wishing to use genomic data in guiding drug clinical development process

may concurrently seek to develop a diagnostic assay that identifies the relevant biomarker. Drug-diagnostic co-development refers to the simultaneous development of an investigational diagnostic test and an investigational drug, where biomarkers identified by the test and utilized in the drug study are exploratory or probably valid. In 2005, FDA published a draft concept paper on Drug-Diagnostic Co-Development.⁶ The concept paper reviews FDA’s position on both the process for initiating a co-development program and the scientific data that should be developed in support of the drug and device applications. FDA recommends that sponsors of co-development programs work closely with FDA’s Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER), as applicable, and the Center for Devices and Radiological Health (CDRH) beginning at the pre-IND/pre-IDE stage to coordinate an appropriate development plan.

FDA Recommendations

FDA’s concept paper provides specific recommendations related to analytical test validation, clinical test validation, and assessment of clinical test utility. In general, FDA encourages sponsors to study and validate a new diagnostic in parallel with early drug development (phase 1 or 2 trials), allowing for



pre-specification of key analytical and clinical validation aspects for late phase 2 or phase 3 studies. The clinical phase of the drug development program should be designed to provide both evidence supporting the safety and efficacy of the drug and evidence of the utility of the diagnostic test. The clinical phase should also verify the utility of the biomarker in patient selection. More recently an interagency guidance document, *Pharmacogenetic Tests and Genetic Tests for Heritable Markers* (June 2007), jointly issued by CDER, CBER and CDRH, provides a basic framework for the types of analytical and clinical validation issues that FDA views should be addressed in premarket regulatory submissions for genetic tests.⁷ Interestingly, however, some companion diagnostic tests have previously, and likely in the future will continue to be, marketed as laboratory developed tests (regulated by the Center for Medicare and Medicaid Services (CMS) under Clinical Laboratory Improvement Amendment requirements), rather than as in vitro diagnostic tests (regulated by FDA pursuant to the Federal Food, Drug and Cosmetic Act (FDCA)).

FDA's 2005 Drug-Diagnostic Co-Development concept paper, furthermore, envisioned a process in which a companion diagnostic would be developed and validated analytically during phase 1 and phase 2 drug studies, and validated clinically during phase 3 drug trials. However, this type of approach may be unrealistic, given that companion diagnostic assays likely will undergo several design iterations during the various phases of drug trials. A final test configuration may not be available until after phase 3 drug studies are completed. Although parallel development is optimal, the agency has stated that FDA's eventual draft guidance is planned to address drug-diagnostic co-development in which diagnostic test development may not be realized until late during drug development. FDA has acknowledged the agency will accept as supportive data for assay approval, use of retrospective samples that are collected during the drug trial and then later used for the validation of a biomarker. As previously mentioned, for such an approach, FDA expects that these types of retrospective samples are shown to be stable and stor-

age of the samples to maintain stability is clearly documented.⁸

Where the drug and companion diagnostic will be marketed separately as finished products, CDER and CDRH would be involved in review and approval of the drug and diagnostic device, respectively. FDA recommends that sponsors work with both divisions beginning at the pre-IND/IDE stage to review and discuss the development plan. Moreover, CDER and CDRH are very interactive in the area of genomic assays that are of import to drug safety and efficacy. Below is a timeline excerpted from FDA's Draft Concept Paper on Drug-Diagnostic Co-Development that outlines the recommended interactions between the sponsor and the agency.

However, as noted above, this process may be complicated by the ability of CLIA high complexity laboratories to develop, validate and offer as a clinical laboratory service their own companion diagnostic methods. In these cases, each laboratory developed method would require development, analytical validation, control, and performance qualification by the developing clinical laboratory, along with submission of clinical data demonstrating the utility of the companion diagnostic for its intended purpose within the drug submission process. As a laboratory-developed companion diagnostic test, however, the developing laboratory would not, in most cases, seek CDRH review of the assay.

FDA also more recently has acknowledged that the co-development timeline may be unrealistic as companies may not have validated and finalized their diagnostic product at the time of drug studies. In fact, very few sponsors have yet pursued development of a companion diagnostic and drug product in perfect coordination. Consequently, the IDE

interactions indicated on the timeline above may be shifted to the right (i.e., later in the drug development process). In such instance, samples taken during the drug trial could later be tested for biomarkers if saved in a stable and clearly documented manner. Additional information on the timing of the development process and appropriate agency interactions is expected in the forthcoming Draft Guidance on Drug-Diagnostic Co-Development.

Conclusion

FDA's guidances, actions and adherence to the Critical Path Initiative in moving drug and diagnostic science forward in tandem appear to be maturing. As the science of companion diagnostics continues to advance, FDA likely will be presented with additional, novel and po-

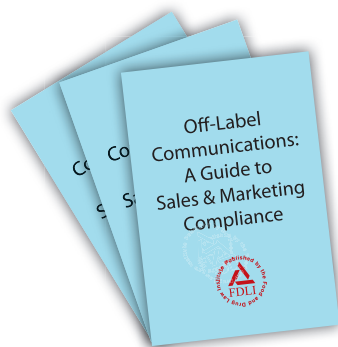
tentially complex methods for choosing the correct drug in the correct dose or frequency for the appropriately identified individual patient. In reviewing the development and utility of these companion diagnostic tests to help select and/or guide drug therapy, FDA will need to continue to be flexible in defining valid scientific evidence of safety and effectiveness, and in determining how specific companion diagnostic tests may best be used to benefit individual patients. ▲

- 1 A pharmacogenomic test is "an assay intended to study interindividual variations in whole-genome or candidate gene, single-nucleotide polymorphism (SNP) maps, haplotype markers, or alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response. In some cases, the *pattern or profile of change* is the relevant biomarker, rather than changes in individual markers."
A pharmacogenetic test is "An assay intended to study interindividual variations in DNA sequence

related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics), including polymorphic variation in the genes that encode the functions of transporters, metabolizing enzymes, receptors, and other proteins."

- 2 See Guidance for Industry, *Pharmacogenomic Data Submissions* (Mar. 2005); Draft Guidance for Industry: *Pharmacogenomic Data Submissions- Companion Guidance* (Aug. 2007).
- 3 Information on probable valid biomarkers does not need to be submitted to INDs except if used in human safety studies.
- 4 Mandatory submissions are also required for animal and in vitro studies used to support safety (e.g., the results will affect dose and dose schedule selection, entry criteria into a clinical trial safety monitoring, or subject stratification).
- 5 See http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm, accessed on Aug. 1, 2008, created (Sept. 15, 2006), last updated July 31, 2008.
- 6 An updated concept paper was expected to be available in Dec. 2007. However, no update has been published as of Aug. 1, 2008.
- 7 <http://www.fda.gov/cdrh/oivd/guidance/154.html>.
- 8 Steve Gutman, MD, Director, FDA's CDRH's Office of In Vitro Diagnostic Evaluation and Safety, 2007 American Association of Clinical Chemistry Annual Meeting.

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