

## The Retrospective Approach To Companion Diagnostics

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Companion diagnostic tests, developed for use in conjunction with therapeutic drugs and biologics, drive personalized medicine. These tests, which are regulated by the U.S. Food and Drug Administration as medical devices when they are marketed as kits,[1] are indispensable to personalized medicine because they provide “information that is essential for the safe and effective use of a corresponding therapeutic product.”[2] Not surprisingly, the FDA classifies many companion diagnostics as high-risk Class III devices which require prior approval of a premarket approval application (PMA) before the test can be commercialized. Regulatory approval requires the manufacturer to demonstrate (with reasonable scientific evidence — usually from well-controlled clinical trials), the test’s safety and effectiveness.



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The FDA’s expressed preference is for the co-development of a diagnostic with a corresponding therapeutic.[3] Co-development offers the opportunity to study a population that “represents the intended use population in an appropriately designed prospective manner.” [4] Perhaps more importantly, biomarker guided clinical trials have demonstrated significantly improved success in advancing therapeutics through phase III clinical trials and the approval process.[5]

For example, in a recent study of new agents targeting advanced nonsmall cell lung cancer, the average success rate — defined as the likelihood that a new drug would successfully pass all phases of clinical trial testing and be approved — was 11 percent.[6] In contrast, the cumulative success rate for biomarker targeted therapy was 62 percent, which was nearly six times higher than the average success rate.[7] The study also revealed that when the impact of therapeutic mechanism was analyzed, the cumulative success rate was 31 percent for receptor-targeted therapies, which exceed the 11 percent success rate for nontargeted therapies by almost three-fold.[8] Thus, companion diagnostics may increase clinical trial success rate for multiple reasons.

Accordingly, while there are significant advantages to following FDA’s preferred path, in many instances co-development of a diagnostic and a therapeutic may not be practical. In these situations, it is important to consider developing a companion diagnostic after a therapeutic has come to market (i.e., retrospectively).

## **Retrospective Development of a Companion Diagnostic is Common[9]**

In a Dec. 16, 2008, Oncologic Drugs Advisory Committee Meeting FDA Briefing Document, the FDA acknowledged that its preferred approach of co-developing a companion diagnostic and a therapeutic has been underutilized, even though co-development can significantly increase average success rate.[10] While there may be many underlying causes for lack of co-development, two reasons stand out. First, co-development can be a financial disincentive to a therapeutic manufacturer because the drug's target population will necessarily be limited by the diagnostic, thereby potentially and significantly limiting the therapeutic revenues.[11] Second, there may be inadequate scientific knowledge during the development of the therapeutic that may prevent co-development of a companion diagnostic — leaving retrospective development of the diagnostic as the only viable path to market.[12] An example of a companion diagnostic approved after its corresponding therapeutic is the DAKO EGFR PharmDx Kit.

## **Factors to Consider Before Embarking on Retrospective Companion Diagnostic Development**

Before embarking on retrospective development of a companion diagnostic, several factors merit careful consideration. Such factors include issues associated with access to patient data developed during therapeutic development, tissue sample integrity and overall return on investment when developing a therapeutic (where the patient population who will receive the therapeutic will be limited by the diagnostic).

### ***Patient Informed Consent Issues***

Diagnostic developers need access to patient tissue and blood samples and their corresponding patient data to determine the presence or absence of biomarker(s) in these patients with a confirmed disease of interest that could form the basis for developing a companion diagnostic and to aid in validating these biomarker(s). The gatekeeping mechanism to access patient samples and data is the patient informed consent form.

When a therapeutic is developed independently from a companion diagnostic, patient informed consent forms (prepared by the therapeutic manufacturer and approved by institutional review boards) will likely only authorize access of patient information (and patient tissue samples) by the therapeutic developer — not any other third party, including a downstream diagnostic developer. If the scope of patient informed consent is limited (which can only be determined by a detailed review of the informed consent form used by the therapeutic developer), the diagnostic developer is legally prohibited from gaining access to or using patient data that was developed during the therapeutic clinical studies — unless the patient re-consents and authorizes access to the diagnostic developer.

Attempting to obtain re-consent from patients after the fact can be impractical for several reasons. Some patients may move and be difficult to locate. Some patients may die rendering any re-consent impossible. Also, the privacy rule implemented under the Health Insurance Portability and Accountability Act may present further obstacles. For example, HIPAA may require that a doctor, who has little time and incentive, be the one to contact the patient and attempt to obtain the patient's re-consent. Therefore, a recommend practice is for therapeutic manufacturers to allow for the possibility of downstream companion diagnostic development after therapeutic approval and ensure an appropriately broad scope of patient informed consent.

The FDA has also offered a possible solution when re-consenting patients is not feasible. FDA believes "it is possible in certain circumstances for IVD device investigations to be conducted using leftover specimens

obtained without informed consent, while protecting the human subjects who are the source of such specimens.” [13] Informed consent may not be required in retrospective studies if, among additional requirements, the subject who provided the sample is not identifiable and where collection risk to the patient and privacy concerns are minimized. [14] Companion diagnostic developers contemplating relying on this option should engage early with the FDA to ensure the option will work for them. For example, this option may not be an appropriate solution to some companion diagnostic developers because of the need for much of the underlying data to be associated with individual patients with confirmed disease.

### ***Tissue Sample Integrity Issues***

Another factor that should be considered when contemplating developing a companion diagnostic after approval of a therapeutic drug is the storage and condition of patient samples. Samples that have not been properly barcoded, cataloged and stored may present obstacles to companion diagnostic development. For example, the samples may have decayed and become unusable. Also, it may not be possible to match a sample and its necessary accompanying patient data. For this reason one recommended practice is for the therapeutic developer to employ a contract research organization to ensure samples are properly stored, appropriately barcoded and inventoried. The storage ideally should include chain-of-custody documentation capable of surviving an audit. Additionally, in some instances, the FDA may require that 90-95 percent of samples be available for retesting to support a regulatory filing.

A further factor that should be considered before embarking on follow-on companion diagnostic development is the degree, if any, of sample collection bias. Collection bias occurs when samples are collected in such a way that some members of an intended population are less likely to be included than others. Collection bias can skew results leading to a test that disproportionately yields false positives or negatives. The retest (sample) population should therefore be representative of the intended use population for the companion diagnostic.

### ***Financial Considerations***

A final factor that should be considered when contemplating follow-on companion diagnostic development is expected rate of return on investment. Many therapeutics (e.g., blood pressure drugs, statins) are administered chronically. Chronic administration more easily allows a therapeutics' manufacturer to recoup its research and development costs and make a profit. Companion diagnostics, on the other hand, may only be employed infrequently, and not every time a companion drug is used. Thus, a recommend practice is to do a market analysis and, to the degree possible, ensure that if approved, the follow-on companion diagnostic will yield a satisfactory return on investment.

### **Successful Retrospective Companion Diagnostic Development — Oncology**

Oncology is the largest companion diagnostic market segment with greater than forty percent of companion diagnostic marketed products.[15] Other emerging market segments include, but are not limited to, cystic fibrosis, human immunodeficiency virus and severe growth failure.[16] In a recent analysis, only about eleven percent of companion diagnostics were co-developed (e.g., approved simultaneously with a therapeutic).[17] While co-development of therapeutics and diagnostics is expected to grow over time, retrospective companion diagnostic development will continue to be significant and important.

Some examples of successful retrospective companion diagnostic development, taken from the largest market segment, include the companion diagnostic for KRAS testing for Vectibix and Erbitux.[18],[19] In

the case of nonsmall cell lung cancer, the safety and effectiveness of the cobas EGFR Mutation Test was established through the retrospective analysis of a clinical validation study.[20], [21] The cobas EGFR Mutation Test was approved as a companion diagnostic for Erlotinib, a first-line treatment for patients who harbor the EGFR mutation.

## **Conclusion**

While the FDA prefers co-development of therapeutics and companion diagnostics, often such concurrent development cannot occur. Under certain circumstances, the FDA will accept reanalyzed data from previously performed clinical trials of therapeutics and study data from the retrospective analysis of banked patient samples as part of validating a companion diagnostic. Consequently, diagnostic developers and therapeutic product sponsors should appreciate the benefits, opportunities and risks associated with retrospective studies. Furthermore, as technology evolves and novel biomarkers are identified, the importance of leveraging the use of banked samples and new scientific knowledge to validate companion diagnostics is expected to grow. Diagnostic developers and therapeutic product sponsors should attempt to position themselves to take advantage of retrospective studies.

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[1] If the tests are marketed as laboratory developed tests (LDTs) and the LDTs are not directly marketed to patients, the FDA will likely exercise its enforcement discretion and not regulate the LDTs. The FDA's current position is subject to change, however, and this is a rapidly evolving area of law.

[2] "Guidance for Industry and Food and Drug Administration Staff — In Vitro Companion Diagnostic Devices", FDA, (2014), at 7.

[3] "Guidance for Industry and Food and Drug Administration Staff — In Vitro Companion Diagnostic Devices", FDA, (2014), at 8.

[4] "Drug-Diagnostic Co-Development Concept Paper (Draft — Not for Implementation)", FDA, (2005), at 16.

[5] “Paving the Way for Personalized Medicine: FDA’s Role in a New Era of Medical Product Development”, FDA, (2013), at 35.

[6] K. Boltz, “Clinical trial success enhanced by biomarker — and receptor — targeted therapies in NSCLC”, *Oncology Nurse Advisor*, March 3, 2014.

[7] *Id.*

[8] *Id.*

[9] For purposes of this article, we classify any companion diagnostic developed after approval of the therapeutic to be retrospectively developed.

[10] The Briefing Document, at 1.

[11] S. Padmanabhan, Ed., *Handbook of Pharmacogenomics and Stratified Medicine*, Elsevier, (2014), at 21.

[12] The Briefing Document, at 1.

[13] U.S. Food and Drug Administration, “Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff — Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That are Not Individually Identifiable,” (2006), at 7.

[14] *Id.* at 7-8.

[15] A. Agarwal et al., “The current and future state of companion diagnostics”, *Pharmacogenomics and Personalized Medicine* 8: 99-110 (2015), at 100.

[16] *Id.* at 101.

[17] *Id.*

[18] T. Ray, “FDA Official Offers Advice on Regulatory Path for Companion Diagnostics,” *Genomeweb*, 2010.

[19] Mandrekar et al., “Clinical Trial Designs for Predictive Biomarker Validation: Theoretical Considerations and Practical Challenges,” *Journal of Clinical Oncology*, 27:24, (2009), at 2.

[20] Karachaliou et al., “Targeted treatment of mutated EGFR-expressing non-small-cell lung cancer: focus on erlotinib with companion diagnostics,” 2014.

[21] “Summary of safety and effectiveness data (SSED), Premarket Approval Number: P120019.”