

Companion Diagnostics

FDA Co-development

Simultaneous drug and diagnostic test development

Test Validation

Analytical and clinical validation requirements

Labeling Requirements

Regulatory guidelines for test-drug pairing

Market Examples

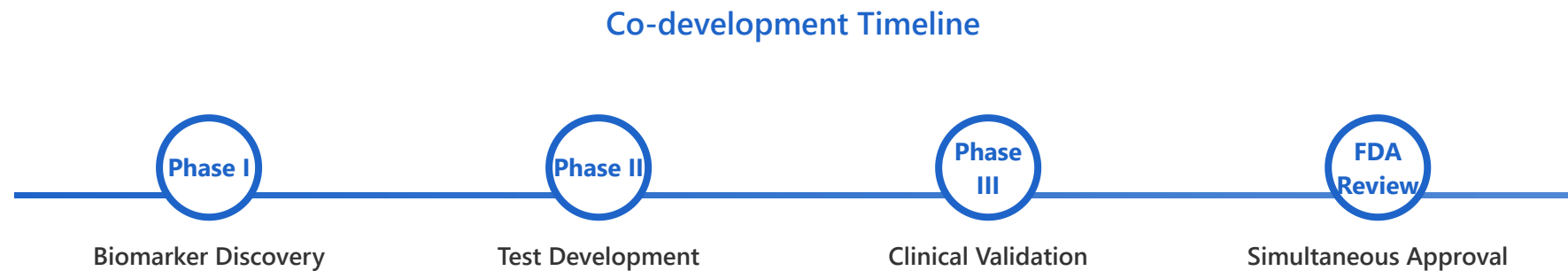
HER2 testing, EGFR mutations, ALK rearrangements

Future Trends: Multi-gene panels and liquid biopsy-based companion diagnostics

1 FDA Co-development Process

The FDA co-development approach requires pharmaceutical companies and diagnostic manufacturers to work together from the earliest stages of drug development. This parallel development ensures that the diagnostic test is ready for approval

simultaneously with the therapeutic drug, enabling immediate patient stratification and personalized treatment decisions.



Key Requirements:

- Early engagement with FDA through Pre-Submission meetings
- Coordinated review of drug and diagnostic submissions
- Shared clinical trial data demonstrating test utility
- Alignment of drug and test labeling requirements
- Post-market surveillance and quality control plans

2 Test Validation Requirements

Companion diagnostic tests must undergo rigorous analytical and clinical validation to ensure they accurately identify patients who will benefit from the targeted therapy. This two-tier validation process ensures both technical performance and

clinical utility of the diagnostic test.

Validation Framework

Analytical Validation

- ✓ Accuracy: Correct detection of biomarker
- ✓ Precision: Reproducible results
- ✓ Sensitivity: Detecting true positives
- ✓ Specificity: Avoiding false positives
- ✓ Limit of Detection (LOD)
- ✓ Robustness across samples

Clinical Validation

- ✓ Clinical Sensitivity: Patient response prediction
- ✓ Clinical Specificity: Non-responder identification
- ✓ Positive Predictive Value (PPV)
- ✓ Negative Predictive Value (NPV)
- ✓ Safety and efficacy correlation
- ✓ Real-world clinical utility

Validation Standards:

- Performance evaluated in prospective clinical trials
- Sample size must be statistically adequate for conclusions
- Inter-laboratory reproducibility studies required
- Quality control procedures established and documented

Labeling Requirements

FDA requires that both the drug and the companion diagnostic have coordinated labeling that clearly describes their relationship. The drug label must specify the companion diagnostic test required for patient selection, while the test label must identify the specific therapeutic drug it is intended to be used with.

Labeling Integration Flow



Essential Labeling Elements:

- **Indication Statement:** Clear description of test purpose and patient population
- **Intended Use:** Specific biomarker detection and clinical application
- **Limitations:** Known test limitations and contraindications
- **Performance Characteristics:** Sensitivity, specificity, and predictive values
- **Interpretation Guidelines:** How to use test results for treatment decisions

- **Quality Control:** Required procedures and acceptance criteria

4 Clinical Market Examples

Companion diagnostics have revolutionized cancer treatment by enabling precision medicine approaches. These FDA-approved test-drug pairs demonstrate the clinical value of molecular diagnostics in improving patient outcomes and reducing unnecessary treatments.

Major Companion Diagnostic Examples

HER2

HER2 Testing

Herceptin (Trastuzumab)

IHC and FISH tests detect HER2 protein overexpression or gene amplification in breast cancer patients to guide anti-HER2 therapy

EGFR

EGFR Mutations

Iressa (Gefitinib), Tarceva (Erlotinib)

PCR-based tests identify activating EGFR mutations in non-small cell lung cancer for EGFR TKI therapy selection

ALK

ALK Rearrangements

Xalkori (Crizotinib)

FISH or IHC tests detect ALK gene rearrangements in NSCLC patients eligible for ALK inhibitor treatment

Additional Notable Examples:

- **KRAS Mutations:** Predict resistance to EGFR-targeted therapies in colorectal cancer
- **BRAF V600E:** Identifies melanoma patients for BRAF inhibitor therapy (Zelboraf, Tafenlar)
- **PD-L1 Expression:** Guides immunotherapy selection with checkpoint inhibitors
- **BRCA1/2 Mutations:** Determines eligibility for PARP inhibitors in ovarian cancer
- **BCR-ABL:** Monitors chronic myeloid leukemia treatment with tyrosine kinase inhibitors

Clinical Impact: These companion diagnostics have demonstrated significant improvements in response rates (often 50-70% in biomarker-positive patients vs. 10-20% in unselected populations), reduced adverse events in non-responders, and more cost-effective healthcare delivery through targeted patient selection.