What is needed to link device approval to clinical application approval?

David Litwack, PhD
Biomarker Qualification Program
CDER/FDA

Ernest.Litwack@fda.hhs.gov
Disclaimer

• I have no financial relationships to disclose.
• I will not discuss off label use and/or investigational use of any specific product in my presentation.
Qualified biomarker

In vitro diagnostic

Using diagnostic tests to direct treatment
The test is important

• Problems with the test could:
  – Compromise the ability of the trial to demonstrate an effect of treatment.
  – Compromise the ability to determine whether the test can appropriately identify the subjects for whom the therapeutic product is intended to provide benefit.
Companion Diagnostics

• The FDA issued final guidance *In Vitro Companion Diagnostic Devices* Aug. 2014

• Defined companion diagnostic (CoDx) as IVD that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

• Described CoDx uses:
  – Identify population most likely to benefit or most at risk of adverse reaction.
  – Monitor response to adjust treatment.
  – Identify population for whom product is known to be safe and effective.

• Clarified that, in general, the FDA expects contemporaneous regulatory approvals of the CoDx and therapeutic product.

• Principles may apply more broadly.
CDx are a subset of IVDs; drugs and their companion tests refer to each other in their labels
*(as of 09/11/2017*
Codevelopment

- Codevelopment does not require simultaneous development of CoDx and therapeutic product from beginning to end.
- Biomarker discovery (↓) and test development can occur at any point during the therapeutic product development process.
Draft Guidance
Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

• Intended to provide the “how to” — the practical aspects of codevelopment to support the design and implementation of successful codevelopment programs.

• The guidance describes:
  – General principles to guide codevelopment to support obtaining contemporaneous marketing authorization
  – Certain regulatory requirements
  – Considerations for therapeutic product clinical trial that includes investigation of an IVD CoDx
  – Submission process for the therapeutic product and CoDx

Elements of FDA Premarket Review for IVDs

- Analytical validity. Does the IVD detect the intended analyte accurately and reproducibly?

- Clinical validity. In detecting the analyte, does the IVD correctly identify a disease, condition, or state of health?

- Labeling. What claims are made about the test? Are those claims supported by evidence?

- Assessment based on intended use
Problems

• Test not adequately analytically validated prior to use in trial
• Multiple tests with different performance used in trials
• Tests changed during trials
• Bias from prescreening
Coordinating Review Timelines

• Submissions
  – Drugs – New Drug Application (NDA)
  – Biologics – Biologics License Application (BLA)
  – CoDx will likely be Class III and require a Premarket Application (PMA)

• Statutory timelines differ for therapeutic products and IVDs

• In practice, IVD review keeps to therapeutic product timelines
  – Therapeutic product expedited review/accelerated approval shorten timelines
Requirements for Investigational Products

• Both the therapeutic product and the IVD may be investigational

• Both have own regulatory requirements
  – Therapeutic Product: Investigational New Drug, 21 CFR 312
  – IVD: Investigational Device Exemption (IDE) Regulation, 21 CFR 812

• Compliance with one set of requirements doesn’t fulfill compliance with the other
Labeling

- Product labels should be consistent with each other
- IVD claims based on the trial design
  - **Prediction**: supported by evidence that clinical benefit accrues only to, or primarily to, a population defined by the IVD result or that serious adverse reactions are confined to a population defined by the IVD result
  - **Selection**: trial designs in which only test-positive (or test-negative) subjects are selected for enrollment in a trial typically support IVD companion diagnostic claims for patient selection
  - **Monitoring**: beyond guidance scope
Beyond One Test-One Drug

One indication - more than one drug

BRAFV600 mutation:
- Roche cobas BRAF V600 Mutations Test for Zelboraf® (vemurafenib)
- BioMérieux THxID BRAF Kit for Tafinlar® (dabrafenib)/Mekinist® (trametinib)

Two tests – same gene but different allele representation

EGFR activating mutations:
- Roche cobas EGFR Mutation Test for Tarceva® (erlotinib)
- Qiagen therascreen EGFR RGQ PCR Kit for Gilotrif® (afatinib)
Companion or Complementary?

• A **companion diagnostic** is an IVD that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

• A **complementary diagnostic** is an IVD that identifies a biomarker-defined subset of patients with a different therapeutic product effect, but that is not a prerequisite for receiving the therapeutic product.  

***THIS IS NOT AN OFFICIAL DEFINITION***
PD-1/PD-L1 Tests

• Three drugs, one companion diagnostic, two complementary diagnostics, multiple indications
• Each drug developed with its own IHC test
  – Different antibody clones
  – Different staining protocols and platforms
  – Different clinical decision points
  – Different assessment methods (Tumor cells, TILs, both)
  – Different scoring methods (% staining, H-score)
• The tests are not interchangeable.
Complementary Diagnostics

• Questions:
  – How are they identified?
  – What goes into the drug label?
  – What goes into the IVD label?
  – What evidence is required?
  – Will contemporaneous approval be required?

• Developing guidance to answer some of these questions
Thank you!