Highlights of FDA Guidances:
Drug Development Tools, Enrichment Strategies, and Companion Diagnostic Devices

Yan Wang, Ph.D.
Division of Biometrics IV
OB/OTS/CDER/FDA
Outline – FDA Guidance documents

1) Qualification process for drug development tools
   - Biomarker qualification

2) Enrichment strategies for clinical trials to support approval of human drugs and biological products
   - Prognostic and predictive enrichment strategies

3) In Vitro Companion Diagnostic Devices
   - For patient selection to increase efficacy/safety
Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

TABLE OF CONTENTS

I. INTRODUCTION ................................................................. 1
II. BACKGROUND AND GENERAL CONCEPT ............................. 2
III. DRUG DEVELOPMENT TOOLS ......................................... 3
   A. Biomarkers .................................................................. 3
   B. Clinical Outcome Assessments ....................................... 4
   C. Animal Models .......................................................... 5

January 2014
Definition of Biomarkers

A biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention”

**Diagnostic Biomarker**
Categorize patients by the presence or absence of a particular disease

**Prognostic Biomarker**
Provide information on the likely course of disease in an untreated individual

**Predictive Biomarker**
Categorize patients by their likelihood of response to a particular treatment relative to no treatment

**Response (Pharmacodynamic) Biomarker**
Show a biological response in patients after receiving a treatment intervention

**Note:** A biomarker can fit into more than one category (e.g., HIV viral load)
Biomarker Qualification

**Qualification** is "*a conclusion that within the stated context of use, a biomarker can be relied on to have a specific interpretation and application in drug development and regulatory review*"

Define the intended **context of use (COU)**
- The manner and purpose of use

Determine the **level of evidence** required for qualification
- *Driven by the intended COU*

Amur et al., Clin. Pharm. Ther. 2015
Examples of Potential “Context of Use” of Biomarkers

**Diagnostic Biomarker**
- Patient selection (*inclusion/exclusion criteria*)
  (e.g., galactomannan)

**Prognostic Biomarker**
- Enrich trials with patients likely to have disease or worsening condition

**Predictive Biomarker**
- Enrich trials with patients likely to respond to a new intervention

**Response (Pharmacodynamic) Biomarker**
- Indicator of intended drug activity
- Monitor adverse effects
- **Surrogate for a clinical endpoint**
  (e.g., HIV viral load, blood pressure)
Level of Evidence Required for Qualification

Guidance states:

“robust scientific evidence is needed to justify qualification of a biomarker for use as a surrogate endpoint”

• However, it does not define evidentiary standards for qualification

• **Evidentiary considerations** are described in a recent publication by FDA

  ![Diagram](Image)

  Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization

  S Amur, L LaVange, I Zineh, S Buckman-Garner and J Woodcock

Evidentiary Considerations for Qualification (Amur et al, 2015)

- **Assay considerations**
  - *Analytically validated* method to obtain reliable and accurate measurement

- **Type of data available** to assess the strength of association of the biomarker with its proposed clinical outcome
  - Retrospective or prospective, registry data and/or randomized clinical trial data

- **Reproducibility of data**
  - multiple studies, or a large study consisting of test dataset and confirmatory dataset

- **Use of appropriate, pre-specified statistical methods** to demonstrate the hypothesized relationships for the context of use
Three Biomarkers Qualified Recently

Submitted by study group/consortium

Collaborative Efforts

Galactomannan serum/BAL biomarker

COU: Patient selection/Enrichment of clinical trials in invasive aspergillosis

Submitter: Mycoses Study Group

Total Kidney Volume imaging biomarker

COU: Enrichment of clinical trials in autosomal dominant polycystic kidney disease (PKD)

Submitter: PKD Outcomes Consortium

Fibrinogen plasma biomarker

COU: Enrichment of clinical trials in chronic obstructive pulmonary disease (COPD)

Submitter: COPD Biomarker Qualification Consortium
Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

December 2012
Enrichment Strategies Are Used in Clinical Trials to Increase Study Power

• Definition - Enrichment
  – “the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population”

• Enrichment may also refer to the analysis population with the enrichment factor in a study of a broader population

• Prognostic enrichment strategies – selecting high risk patients
  – more likely to have outcome events, or worsening condition

• Predictive enrichment strategies – selecting likely responders to a new intervention
Prognostic Enrichment – Selecting High Risk Patients

*Smaller sample size and shorter study duration*

Example: **Enalapril** Trials in Patients with Congestive Heart Failure

**CONSENSUS (NEJM 1987)**
- 253 very ill CHF patients (NYHA Class IV)
- 7-month average follow-up
- 27% reduction in mortality rate

**SOLVD (NEJM 1991)**
- 2569 less ill CHF patients
- 41-month average follow-up
- 13% reduction in mortality rate
Predictive Enrichment – Selecting Likely Responders

*Enhanced risk-benefit relationship by avoiding potential toxicity in patients who cannot benefit from the drug*

Example: IRESSA® (gefitinib)

- **2003:** Accelerated approval based on results of surrogate endpoint (objective response rate) in patients with advanced NSCLC
- **2005:** FDA withdrew approval because post-marketing commitment studies failed to demonstrate clinical benefit in overall survival
- **2009:** IPASS Trial *(Mok T et al. NEJM 2009)*
  - A total of 1217 patients with NSCLC
  - Demonstrated superiority of gefitinib in PFS – hazard ratio: **0.74 (95% CI, 0.65-0.83)**
  - The treatment effect was not consistent
  - Interaction between treatment and epidermal growth factor receptor (EGFR) mutation
Example: IRESSA® (gefitinib) (cont.)

Gefitinib improved progression-free survival in patients with EGFR mutations, but not in patients without EGFR mutations.

**2013:** A small pivotal enrichment trial enrolling only patients with EGFR mutations (n=107) demonstrated treatment benefit.
Example: IRESSA® (gefitinib) (cont.)

- **2015:** Approved for patients whose tumors have **EGFR mutations.**

-------------- INDICATIONS AND USAGE --------------

IRESSA is a tyrosine kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
In Vitro Companion Diagnostic Devices

Guidance for Industry and Food and Drug Administration Staff

August 2014
Companion Diagnostic Devices

• Provide **information essential** for the safe and effective use of a corresponding therapeutic product

• Used to select the right patients for increased efficacy/safety (e.g., gefitinib)

• Developed contemporaneously

• Approved/cleared by FDA

• Included in the drug label

• Potential future examples in kidney transplantation
  - quantitative tests for HLA antibody
  - mean fluorescence intensity
Summary Remarks

- Lessons learned from other therapeutic areas
  - *Substantial* and *Collaborative* efforts are needed to develop biomarkers and surrogate endpoints

- Use of enrichment strategies in clinical trials can *increase efficiency* of drug development and *enhance risk-benefit relationship*
  - Challenge is determination of appropriate enrichment characteristics to “*predict*” response
References