Highlights of FDA Guidances:

Drug Development Tools, Enrichment Strategies, and Companion Diagnostic Devices

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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

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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

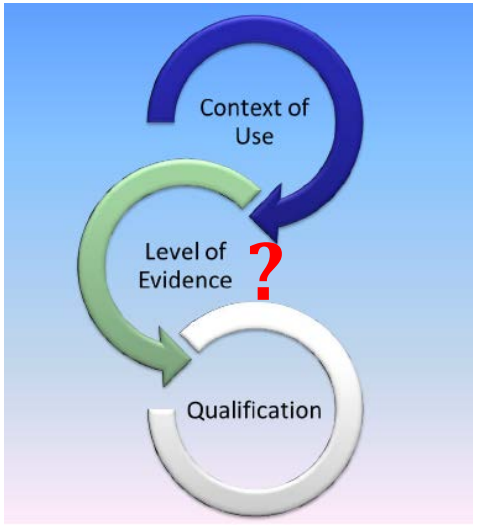
Response (Pharmacodynamic) Biomarker
⇒ Indicator of intended drug activity
⇒ Monitor adverse effects
⇒ **Surrogate for a clinical endpoint**
(e.g., HIV viral load, blood pressure)

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



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

Clin. Pharm. Ther. 2015; 98(1): 34-46.

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

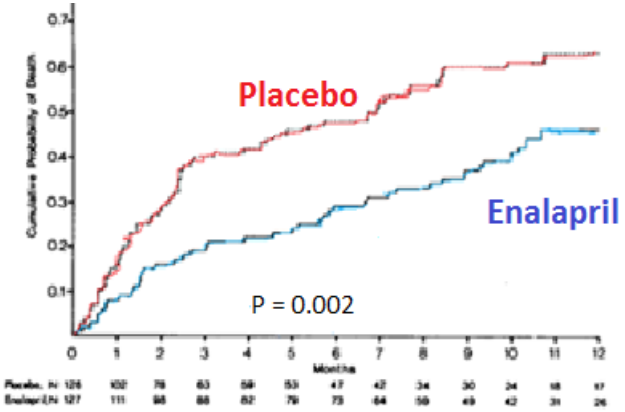
Example: **Enalapril** Trials in Patients with Congestive Heart Failure

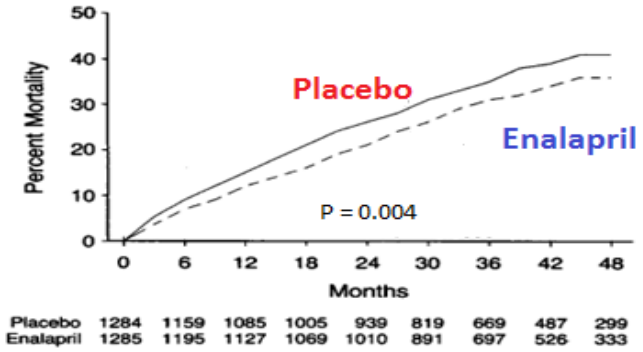
CONSENSUS (*NEJM 1987*)

- **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



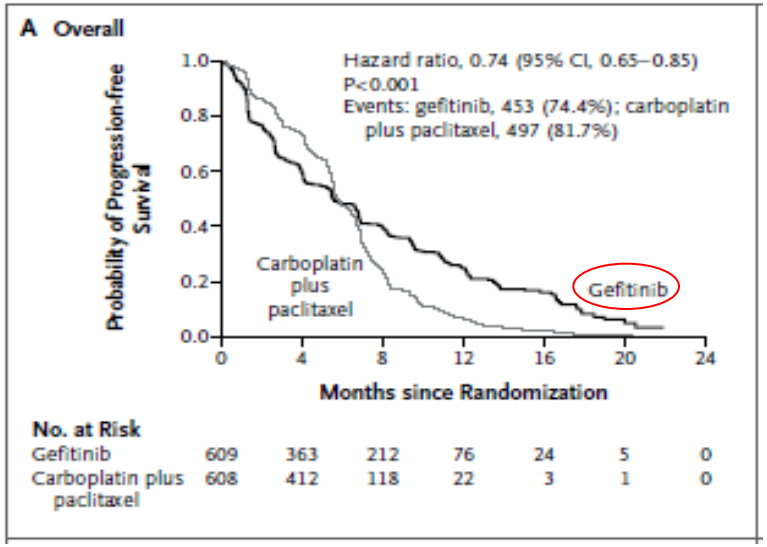


Predictive Enrichment – Selecting Likely Responders

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

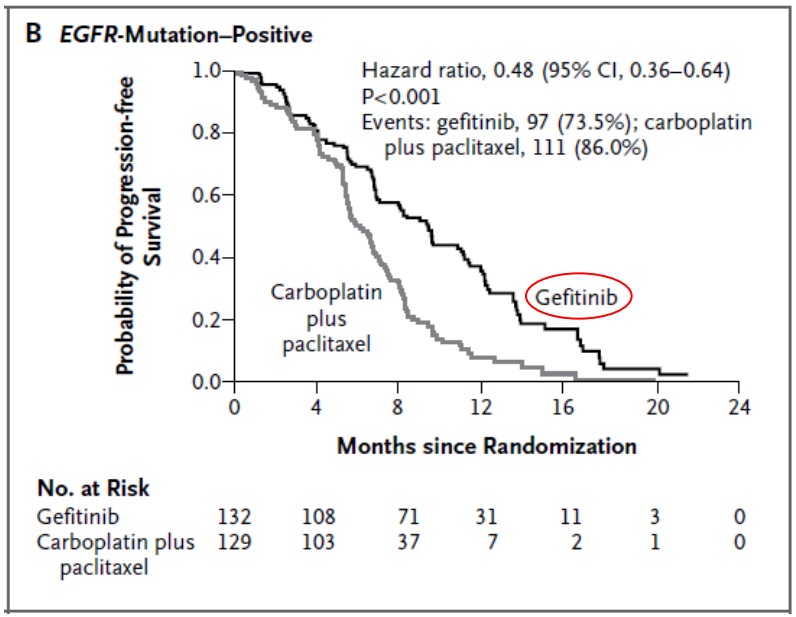
Example: IRESSA® (gefitinib)

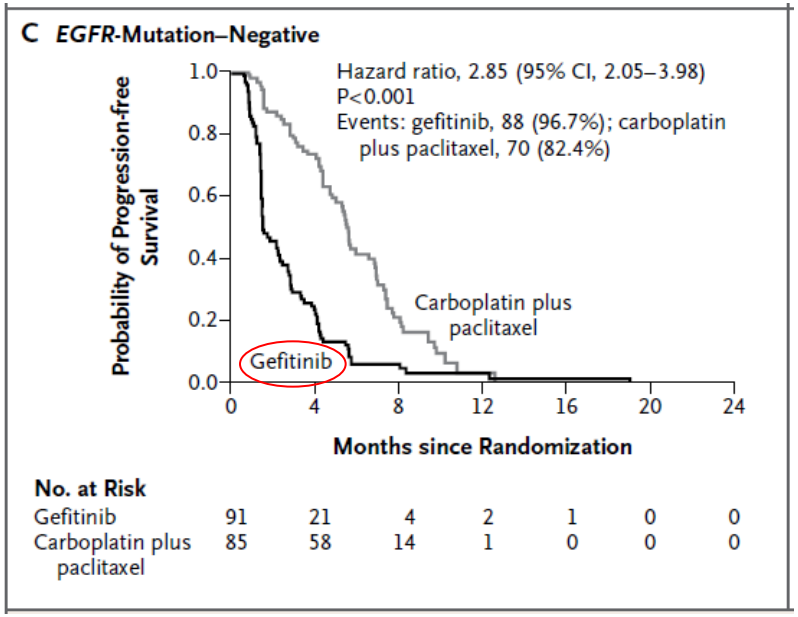
- **2003:** Accelerated approval based on results of surrogate endpoint (objective response rate) in patients with advanced NSCLC
- **2005:** FDA withdrew approval because post-marketing commitment studies failed to demonstrate clinical benefit in overall survival
- **2009:** IPASS Trial (*Mok T et al. 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 in 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

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2) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf

3) http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262327.pdf

4) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

5) S Amur, L LaVange, I Zineh, S Buckman-Garner and J Woodcock: "Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regualtory Acceptance, and Utilization". *Clin. Pharm. Ther. 2015; 98(1): 34-46.*

6) The CONSENSUS Study Group: "Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)". *NEJM 1987; 316: 1429-35.*

7) The SOLVD Investigators: "Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure". *NEJM 1991; 325: 293-302.*

8) Mok T. et al.: "Gefitinib or Carboplatin – Paclitaxel in Pulmonary Adenocarcinoma". *NEJM 2009; 361: 947-957.*