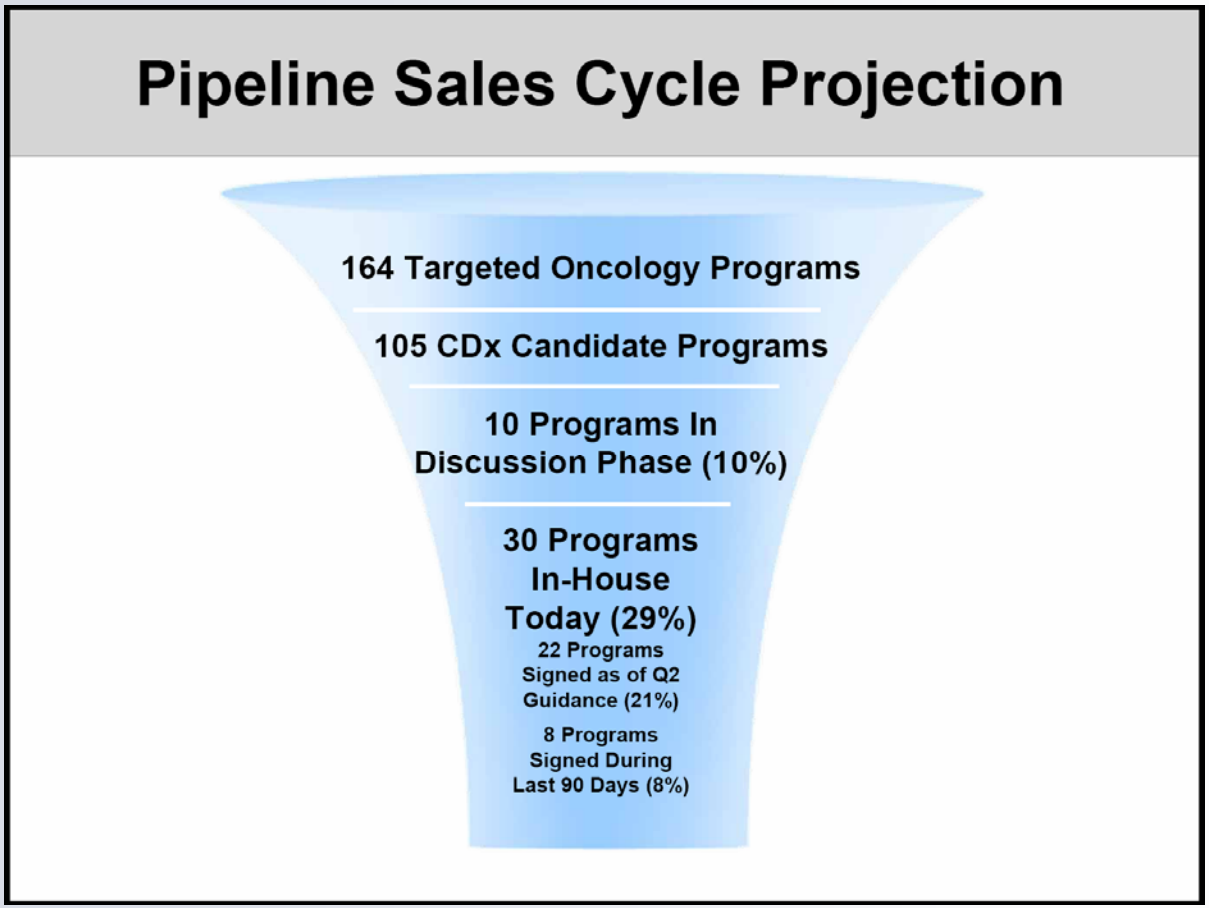
Challenges for Co-Development of New Medical Products: A Regulatory Perspective

2007 Cardiovascular Biomarkers and Surrogate Endpoints Symposium

Bethesda, MD
October 19, 2007

Felix W. Frueh, PhD
Office of Clinical Pharmacology
CDER/FDA

Drug-Test Co-Development is happening as we speak



Ventana – Companion Diagnostics Outlook, September 2007

Drug-Test Co-Development is happening as we speak, cont'd

The New York Times
nytimes.com

June 26, 2007

Roche Is Pursuing Ventana

By REUTERS

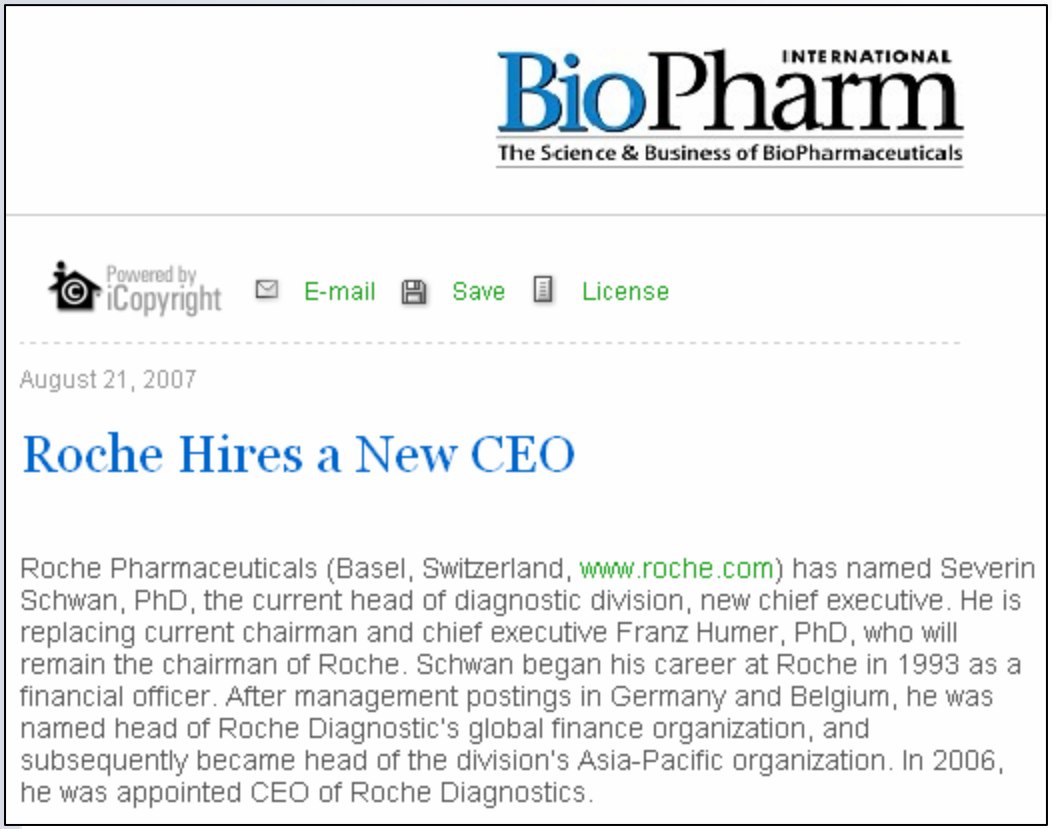
The Swiss drug maker Roche said yesterday that it would start a tender offer to acquire Ventana Medical Systems for about $3 billion, or $75 a share, after its efforts to negotiate a merger were rebuffed.

The offer represents a 45 percent premium to Ventana's closing stock price of $51.74 yesterday. Roche said that it made several attempts to talk to Ventana about a deal, and that it remained open to negotiations.

An acquisition of Ventana, which is based in Tucson and specializes in histopathology, or tissue-based diagnostics, would allow Roche to diversify its products and broaden its diagnostic offerings, Roche said.

Ventana's technology can help researchers and doctors better determine which drugs are most appropriate for individual patients, an emerging concept known as personalized medicine.

Drug-Test Co-Development is happening as we speak, cont'd



BioPharm INTERNATIONAL
The Science & Business of BioPharmaceuticals

Powered by iCopyright E-mail Save License

August 21, 2007

Roche Hires a New CEO

Roche Pharmaceuticals (Basel, Switzerland, www.roche.com) has named Severin Schwan, PhD, the current head of diagnostic division, new chief executive. He is replacing current chairman and chief executive Franz Humer, PhD, who will remain the chairman of Roche. Schwan began his career at Roche in 1993 as a financial officer. After management postings in Germany and Belgium, he was named head of Roche Diagnostic's global finance organization, and subsequently became head of the division's Asia-Pacific organization. In 2006, he was appointed CEO of Roche Diagnostics.

Challenges for Co-Development: Drivers and Roadblocks

- *Business case* ~ opportunity to distinguish yourself from competition, but reduce market share
- *Biomarkers* ~ can identify responder but marker is not 100% specific and sensitive
- *Clinical dilemma* ~ can identify non-responder, but no alternative treatment exists
- *Reimbursement* ~ can reduce cost, but do we really know
- *Regulation* ~ how to encourage, but not stifle the field
- Etc.

All drivers are important, but …

- I believe that *science* will be the main driver because:
  - I can't think of anything that will stop scientific curiosity
    - (there is no one entity that decides over scientific progress; geographical and political borders will be crossed)
  - Therefore, we will continue to learn more about how to personalize medicine
  - Advancements in medical science usually have become part of medical practice over time
    - (other factors usually follow suit, but it may take time)
- The fact that we're here to talk about the science of CV biomarkers and how to use them in research and drug development it is a good example!

Drugs and Tests

- One way to foster the advancement is to encourage the development of drugs with tests that help to make better decisions about how to use the drug in question
- There are two types of such tests
  - Tests that have been developed after a drug has come to market (e.g. CYP2C9 and VKORC1 for better determining the starting dose for warfarin)
  - Tests that are being developed in conjunction with the drug and are “required” for drug use (e.g. Her2/neu measurement for Herceptin therapy)
- I will be talking about the latter, highlighting some general considerations for what we call “drug-test co-development”

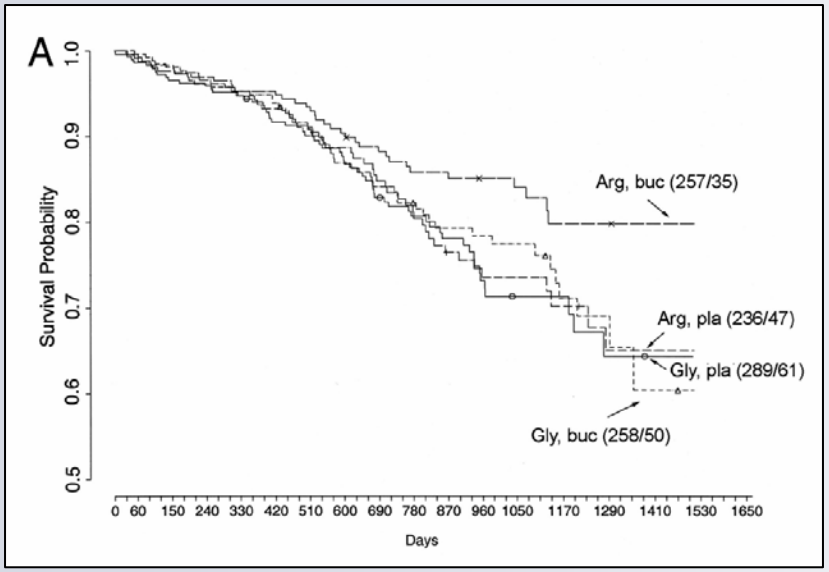
Drug-Test Co-Development: What is it ?

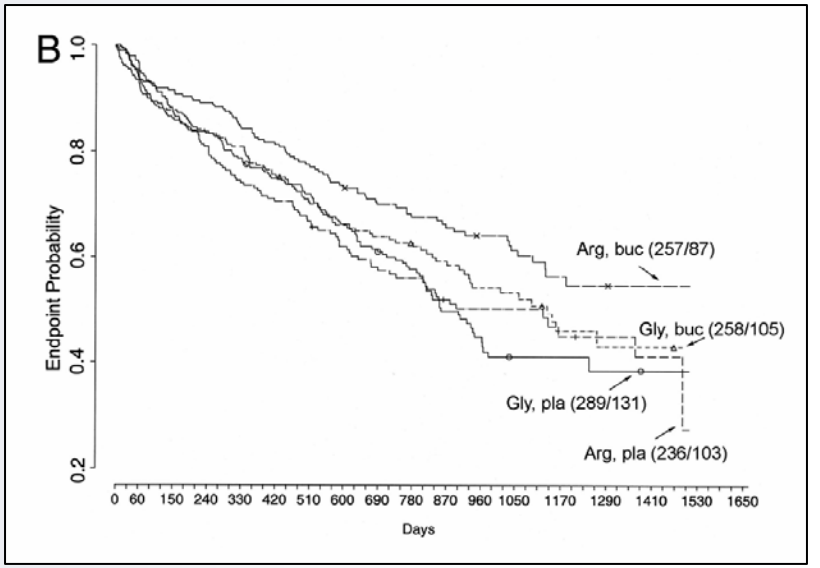
- Strategy to coordinate the development of a drug with the development of a test when a biomarker appears to be a useful tool to determine efficacy and/or safety in a sub-population
- Drug and test are investigational (biomarkers are considered “exploratory” or “probable valid”)
- Clinical phase of drug development program will provide evidence of clinical utility (i.e., value) of the diagnostic test
- Claim for test would be for use with drug, drug cross-labeled for use with diagnostic, diagnostic will be required
- Other parts of drug and diagnostic development programs (e.g., analytical validation) would proceed as usual

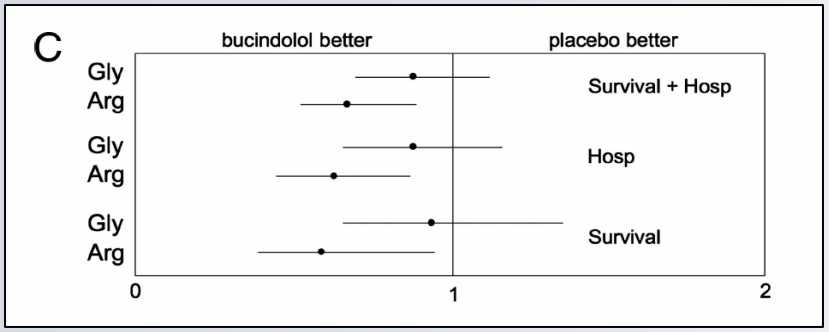
What Happens to the Biomarker During Drug-Test Co-Development ?

- The problem is that markers need to be developed (qualified) in the context of their intended use
- Therefore, **we don't know how good the marker / test is before going into clinical studies (context of use!)**
- Many other clinical and environmental factors influence outcome
- It is therefore reasonable to assume that the clinical validation of a biomarker is never 100%, even if the analytical validation is 100% (i.e. the test always reports a correct measurement)
- **Goal**: use marker to enhance benefit while reducing risks

Co-Development Example: Bucindolol study stratified by treatment and beta-1 AR genotype



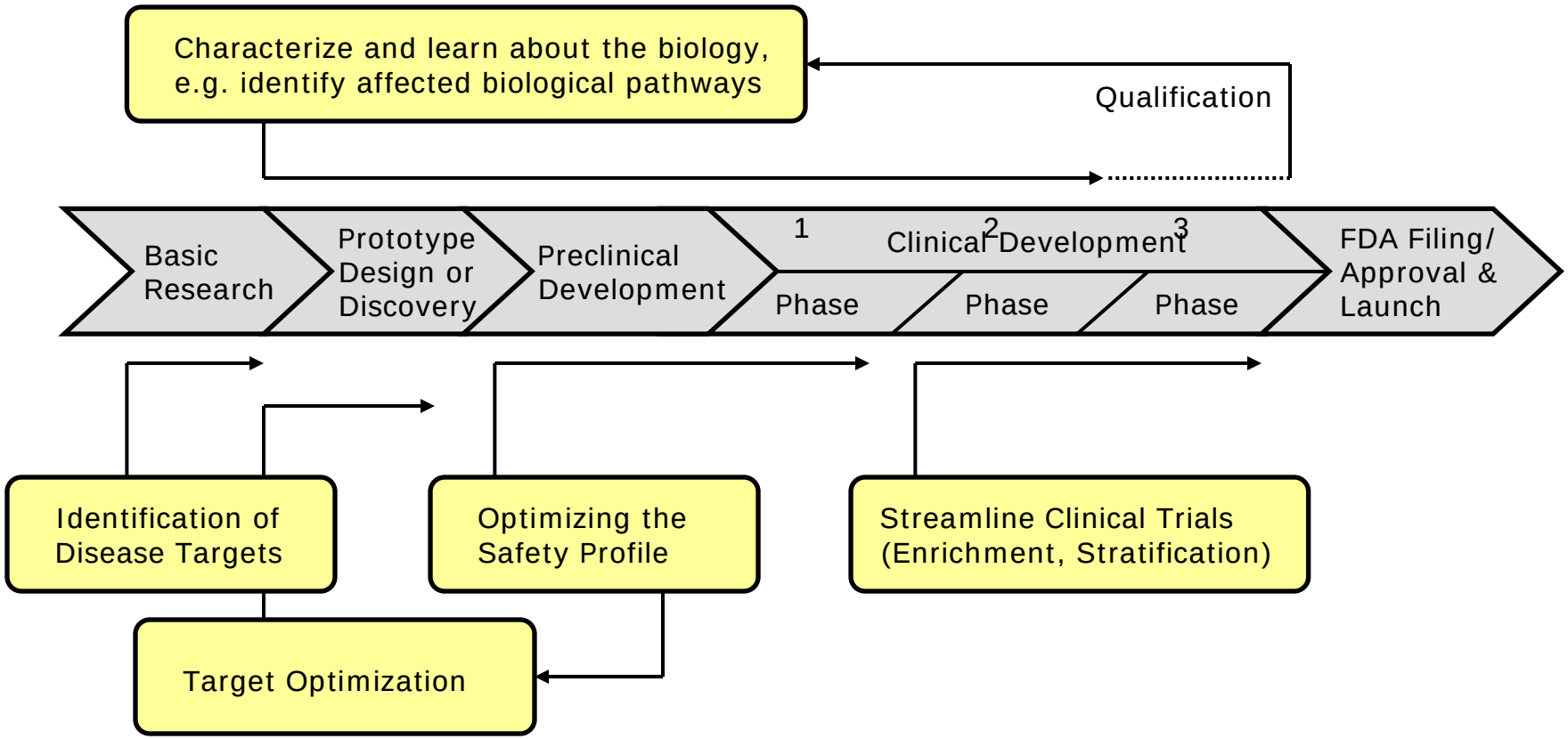




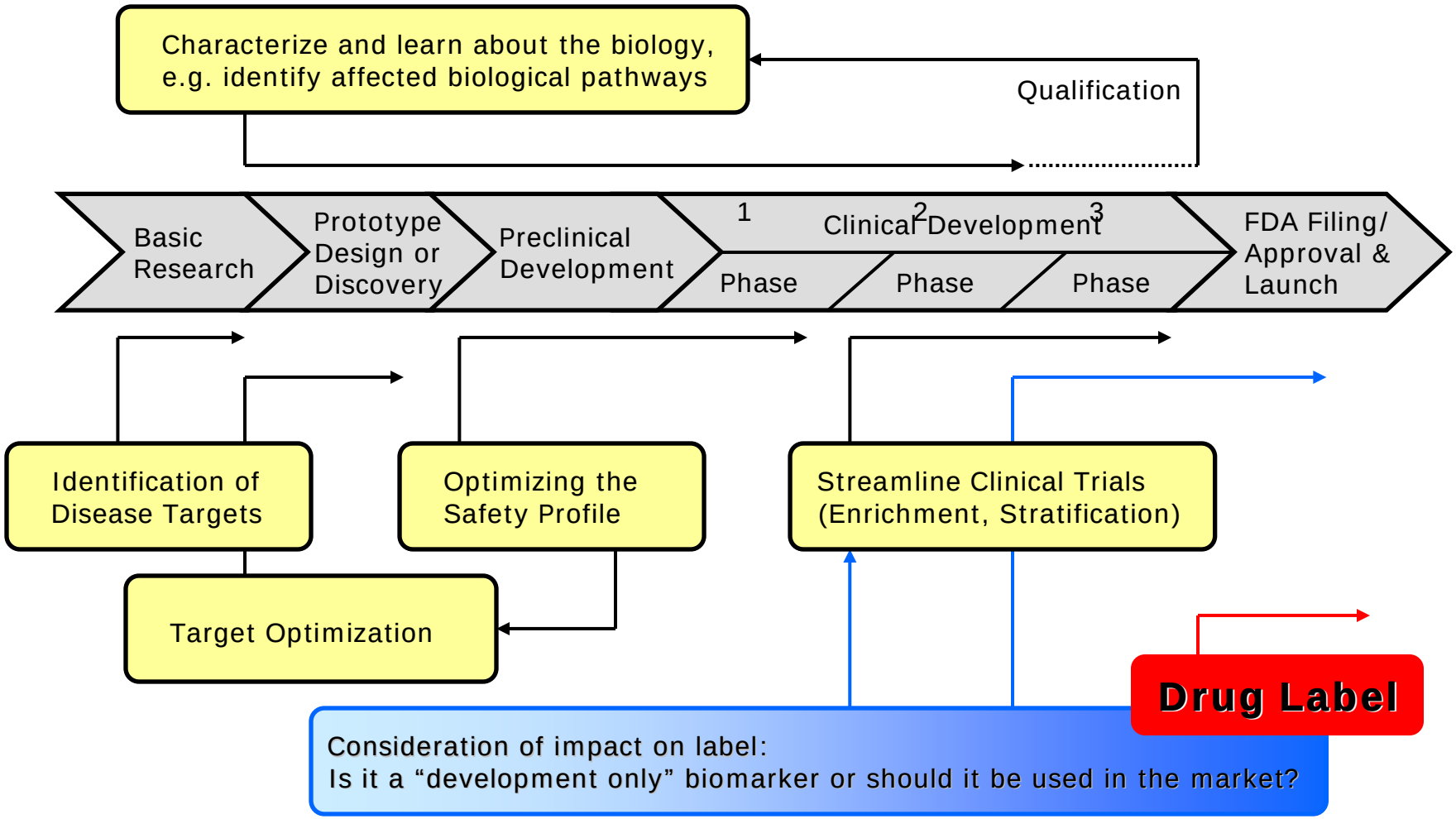
(A) survival
(B) death or hospitalization
(C) Hazard ratios

Liggett et al PNAS 103(30), 11288–93

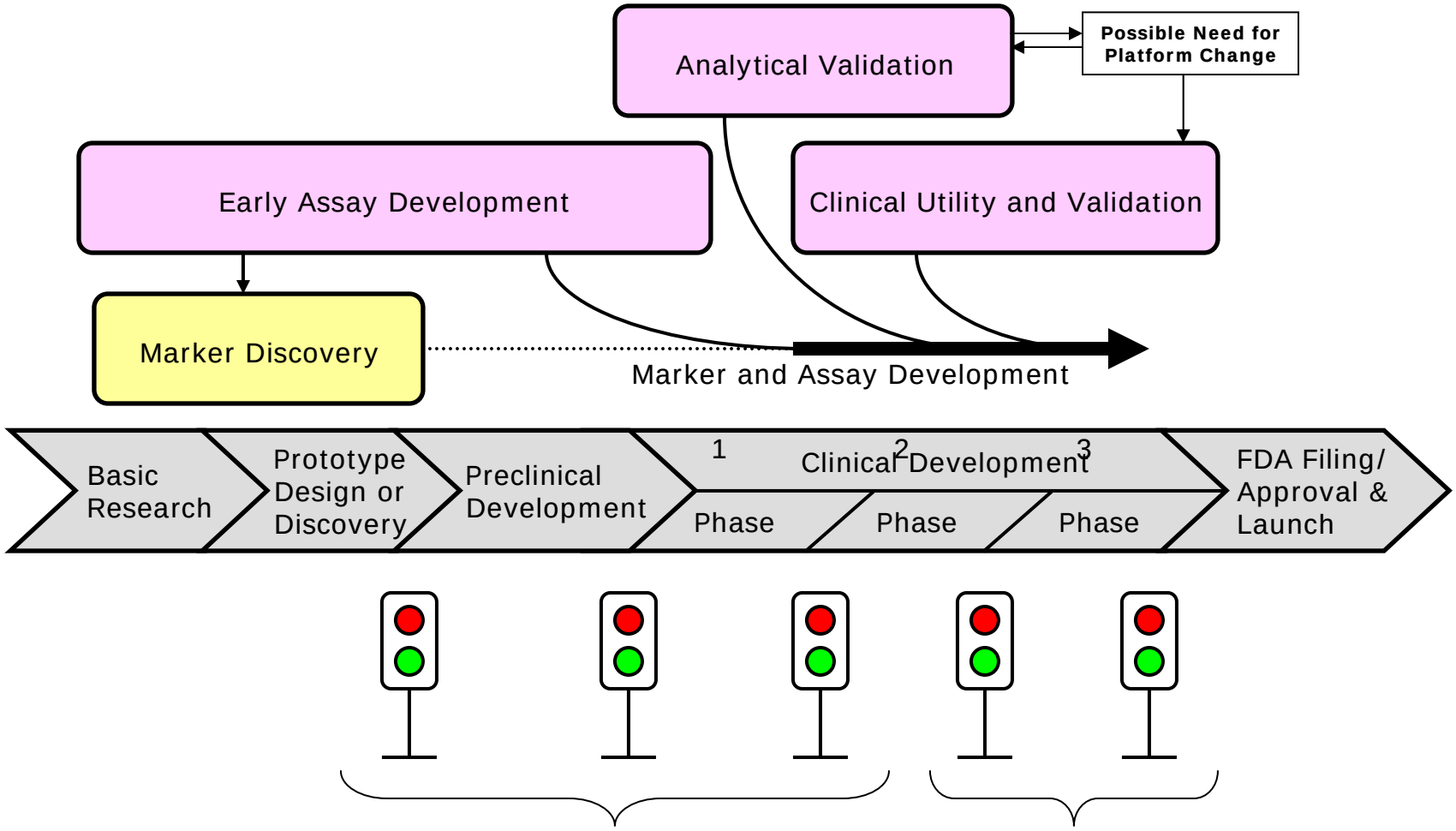
Use and qualification of (clinical) biomarkers during DD



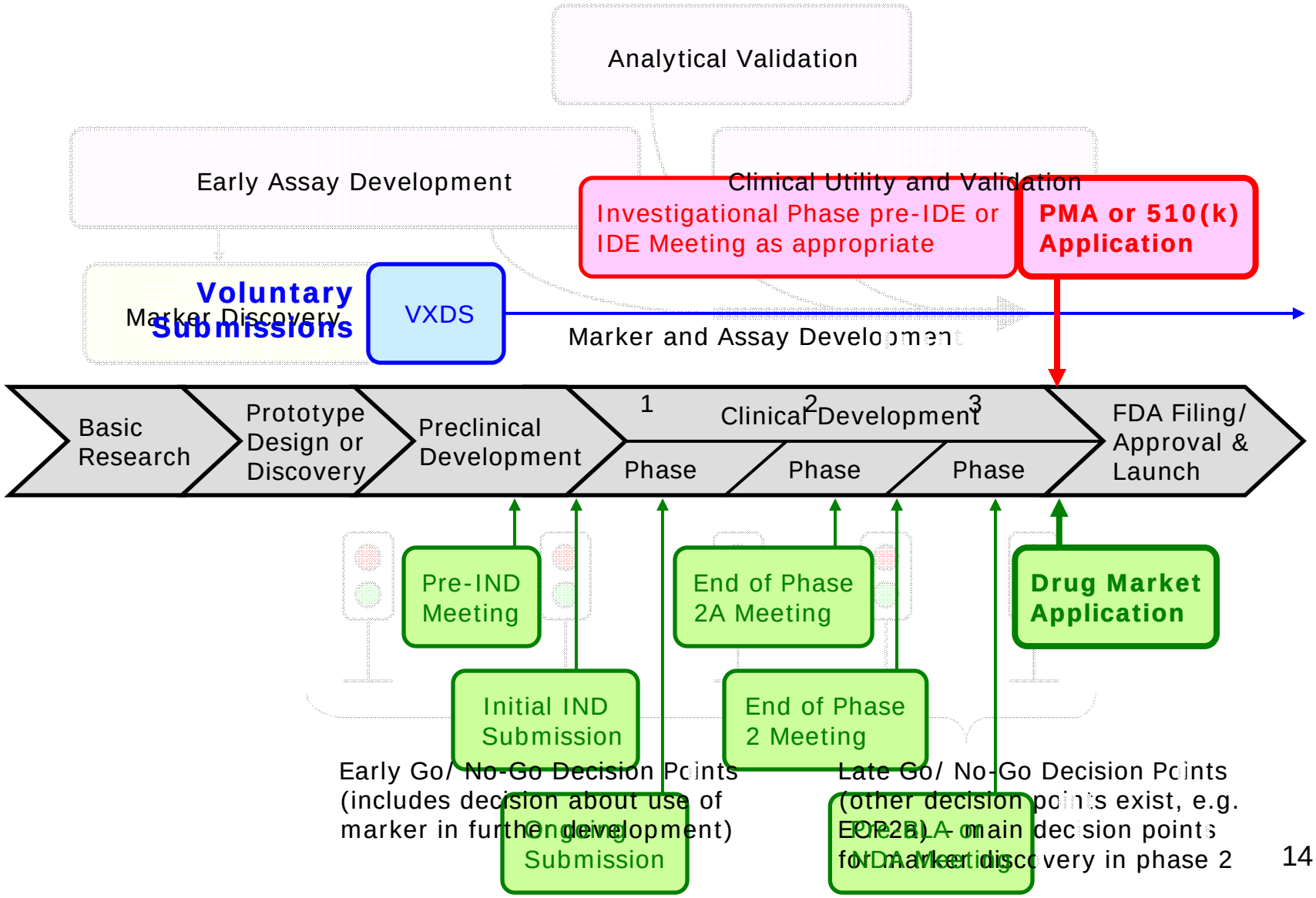
Impact of Biomarkers on Drug Label



Biomarker and assay development process



Sponsor – Regulator Interactions

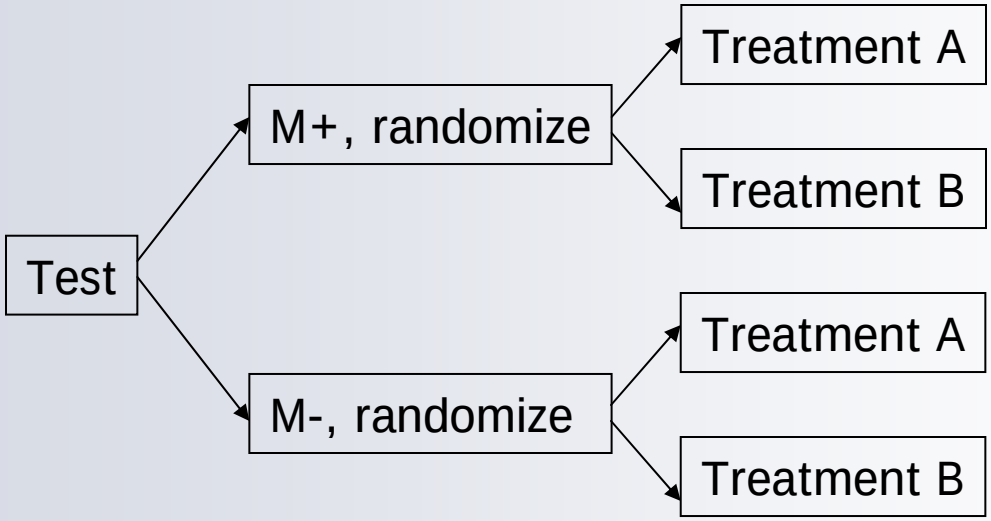


Key Questions and Decision Criteria About Biomarkers During Clinical Development

- What is the marker being used for?
  - Efficacy prediction or efficacy measurement
  - Safety
- Is it a prognostic (i.e. outcome related to disease, but not necessarily to drug therapy) or a predictive (i.e. outcome related to therapeutic intervention) marker and how does it, in either case, affect the development strategy
- How to use the marker in a clinical trial?
  - Can the marker not only be validated, but can it also be shown that using the marker actually helps in the clinic (i.e. clinical utility)?
- Should an enrichment or a stratification strategy be used?
  A. Upfront stratification
  B. Biomarker-based strategy

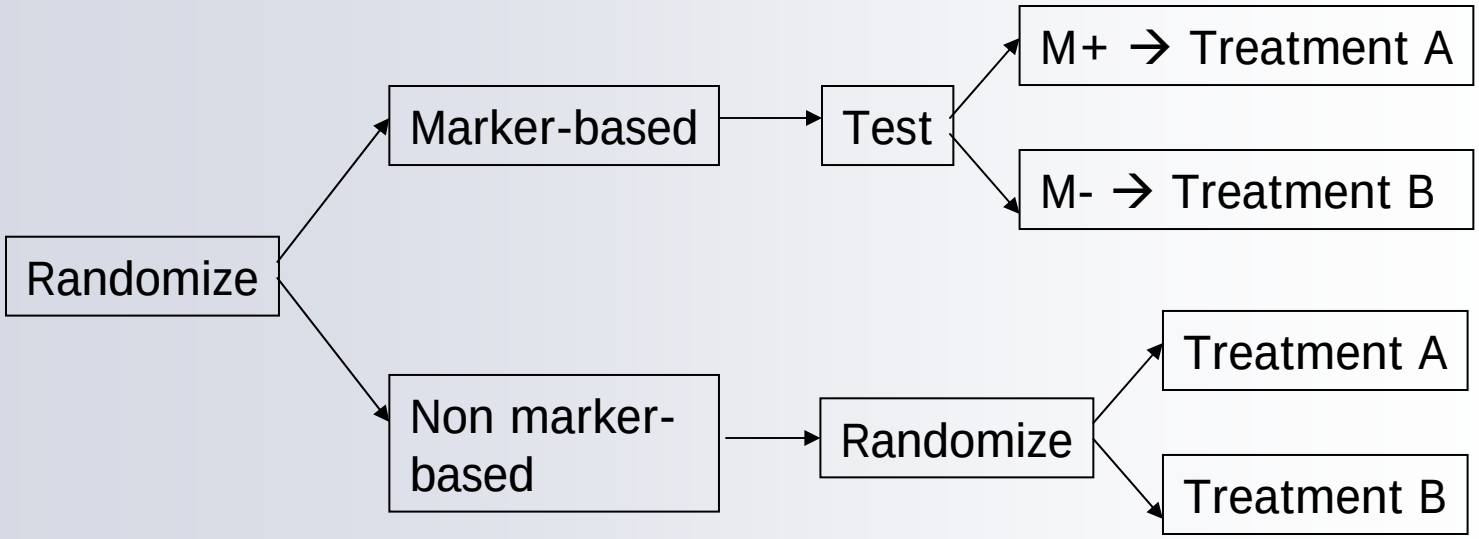
A. Upfront Stratification – Example

- Produces data on all patients
- Completely prospective



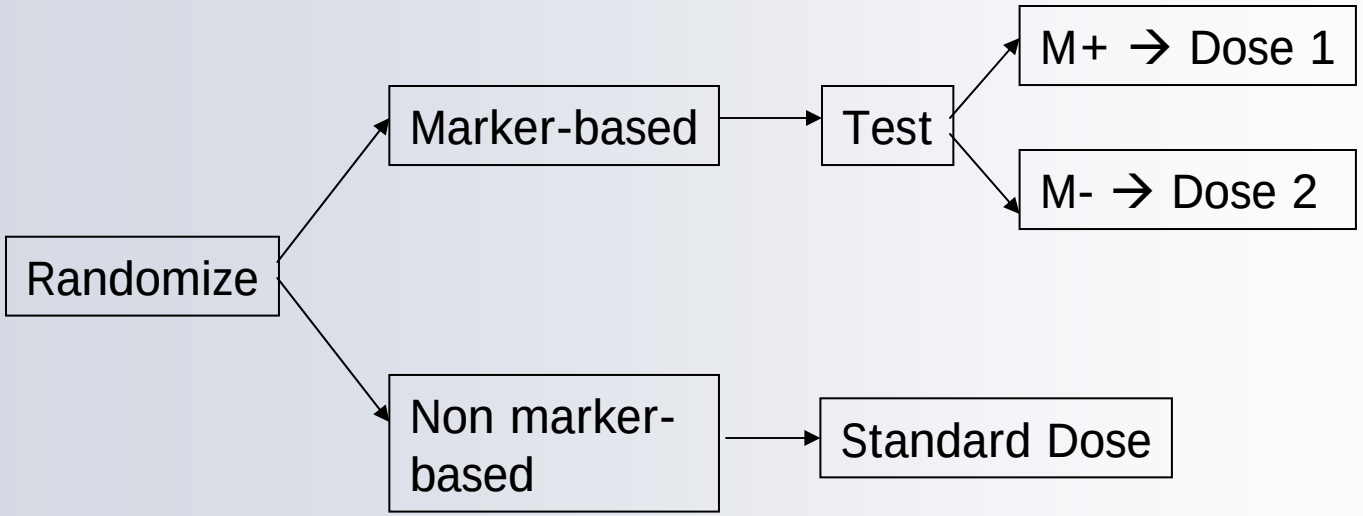
B. Biomarker-based Strategy – Example 1

- May not produce data for all patients (although it can)
- Can include retrospective design aspects
- Example 1:

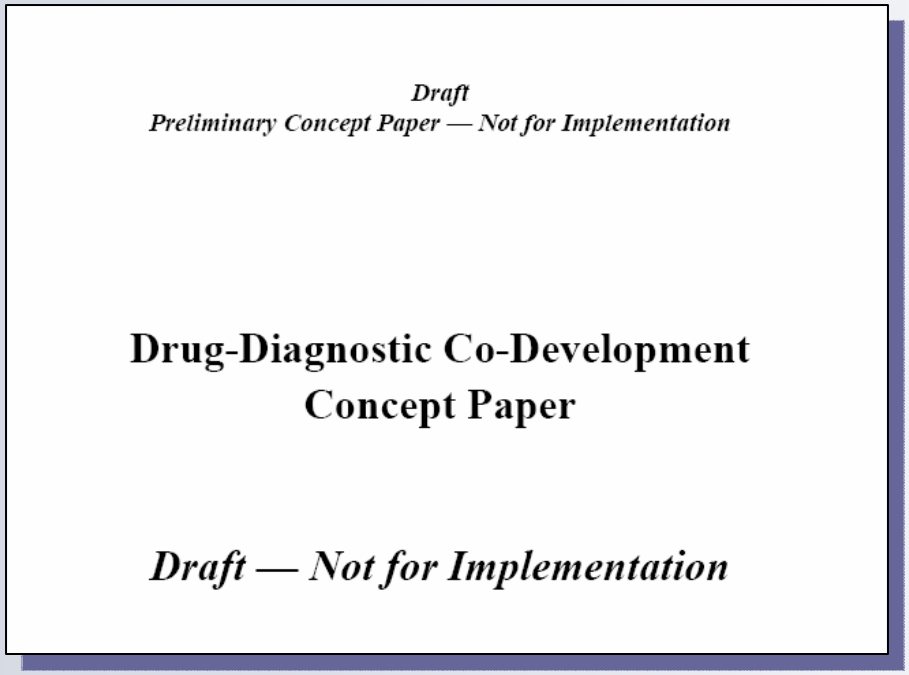


B. Biomarker-based Strategy – Example 2

- May not produce data for all patients (although it can)
- Example 2: Dose selection



FDA Guidance / Concept Paper



Draft
Preliminary Concept Paper — Not for Implementation

Drug-Diagnostic Co-Development
Concept Paper

Draft — Not for Implementation

April 2005

Updated Concept Paper expected to be available Dec 2007

Upcoming Workshop Addressing Co-Development

Register for back-to-back workshops and SAVE $175!

4th Workshop in a Series on Pharmacogenomics

Biomarkers and Pharmacogenomics in Drug Development and Regulatory Decision Making

DECEMBER 10-12, 2007 | Hyatt Regency Bethesda, Bethesda, MD, USA

STEERING COMMITTEE CHAIR

FELIX FRUEH, PHD
Associate Director for Genomics, Office of Clinical Pharmacology, CDER, FDA

ORGANIZING COMMITTEE CHAIRS

FELIX FRUEH, PHD
CDER, FDA

RICHARD DEANE HOCKETT, MD, PHD
Director, Genomic Medicine
Eli Lilly and Company
See page 2 for a complete list of Steering and Organizing Committee members.

TARGET AUDIENCE

This workshop is intended for scientists and clinicians working in industry, academia, clinical practice or government and engaged in drug development, regulatory assessment or clinical practice. It includes those with an interest in the role of pharmacogenetics and pharmacogenomics in small molecule and/or biological drug development, and in the co-development of small molecule and/or biological products along with molecular diagnostic tests that are necessary for their use.

Those who should attend this workshop include:

- Physicians
- Statisticians
- Clinical pharmacologists
- Biologists
- Molecular biologists
- Clinical scientists
- Human geneticists
- Regulatory affairs personnel
- Nurses
- Clinicians
- Healthcare providers
- Reimbursement specialists
- Legal community

Save Time & Money!

Back-to-back with Clinical and Laboratory Genomic and Genetic Standards

December 13-14, 2007
Hyatt Regency Bethesda, Bethesda, MD, USA

See pages 3 & 4 for details about this workshop and discount opportunities.

Co-sponsors

DIA Drug Information Association

FDA US Food and Drug Administration

BIO Biotechnology Industry Organization

PhRMA Pharmaceutical Research and Manufacturers of America

PWG Pharmacogenetics Working Group

OVERVIEW

An open dialogue among regulatory, drug development and academic scientists on the use of pharmacogenomics in drug development was recognized in 2002 *(Lesko and Woodcock. Pharmacogenomic-guided drug development. The Pharmacogenomics Journal (2002) 2, 20-24).* Since then, the FDA in collaboration with Industry has co-sponsored three major workshops followed by publications of the proceedings from these workshops. This interaction between regulators and stakeholders facilitated drafting the FDA "Guidance for Industry: Pharmacogenomic Data Submissions", published in final form in March 2005.

Smaller, focused workshops were held such as an adjunct workshop in 2004 to discuss issues concerning the co-development of drugs and pharmacogenomic tests and a 2006 workshop on Best Practices and Development of Standards for the Submission of Genomic Data to the FDA. Many other recent activities and initiatives, such as the formation of a variety of biomarker-focused consortia, several new regulatory guidance documents, the introduction of legislative bills, and high-profile safety concerns continue to illustrate the prominent role biomarkers and pharmacogenomics play, or will play in moving drug development and therapy from a population-based to an individualized paradigm.

This fourth major workshop in the series of FDA/DIA Pharmacogenomics Workshops will focus on the implementation and integration of biomarkers and pharmacogenomics from the early to late stage clinical phases of the development of new drugs, biologics and associated devices. An important focus of the workshop will be on ways to facilitate the translation of biomarkers and pharmacogenomics into medical product development and clinical practice.

Recent activities and initiatives, such as the formation of a variety of biomarker-focused consortia, new regulatory guidance documents, the introduction of legislative bills, and high-profile safety concerns continue to illustrate the prominent role biomarkers and pharmacogenomics play, or will play in moving drug development and therapy from a population-based to an individualized paradigm. These and other pertinent issues such as drug-test co-development, biomarker qualification and reimbursement will be discussed and illustrated with a series of interactive case studies.

Topics for this 4th workshop in the series will include but are not limited to:

- Challenges and solutions to the use of pharmacogenomics and biomarkers in drug development and clinical use including where progress has been made in safety biomarkers
- How much evidence is needed for safety and efficacy decisions based on novel biomarkers
- Strength of data needed to get a claim using a genetic test
- Co-development
- Postmarketing considerations
- Perspective of third party payors

VISIT WWW.DIAHOME.ORG FOR A COMPLETE SCHEDULE OF EVENTS!
DIA, 800 Enterprise Road, Suite 200, Horsham, PA 19044, USA tel: +1-215-442-6100 fax: +1-215-442-6199 email: dia@diahome.org

Conclusions:
Developing Robust Decision Criteria for the Development and Use of New Clinical Biomarkers

- Guiding decision criteria should be the *impact of using versus not using the marker* (compare: required versus recommended tests)
- Not all biomarkers need to be *formally* qualified – many biomarkers will be used during drug development only, i.e. without the intent to be used as a diagnostic
- Science keeps evolving
  - Biomarkers can be discovered throughout the development of a drug – scientific and regulatory flexibility to integrate this new knowledge in the drug development process must exist
  - Keep open mind about the use of the biomarker even after development, in market place (e.g. re-labeling)
- Drug-test co-development requires integrating two very different, complex processes – drugs and devices – and is not expected to be easy

At the end of the day… it's the science, stupid!

(… and if it's obvious, why not just do it?)

THANK YOU !

www.fda.gov/cder/genomics

Felix.Frueh@hhs.fda.gov
Office of Clinical Pharmacology
FDA/CDER