Challenges in Biomarker and Drug Co-Development and Regulation: *The Regulatory View for Drugs*

AACC 2006 Annual Meeting

Chicago, IL – July 24, 2006

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

Outline

- Introduction: Pharmacogenomic-based drug therapy
- (Genomic) Biomarkers
  - A scheme to categorize biomarkers
  - Biomarker validation
- Drug-Test Co-Development:
  - What it is
  - What it means
  - Issues around the concept
- Closing Remarks

Pharmacogenomic-based Drug Therapy

- The use of pharmacogenomic information in the care of patients is intimately linked to clinical assays that measure one or more genomic biomarkers
- This knowledge is valuable during drug development and it can also be important once a drug is on the market
- Success is dependent on the analytical and clinical validity of the genomic biomarker and its test

FDA's Framework for the Use of Genomic Biomarkers in Regulatory Decision Making

- Broad concept of using genomic biomarkers in the context of new innovations along the CRITICAL PATH: a key opportunity
- Regulatory Guidance and Information
  - Guidance: Pharmacogenomic Data Submissions
  - Drug-Test Co-Development Concept Paper
  - Device-specific guidances from CDRH
  - Others in development (e.g. clinical trial design, etc.)
- Implementation procedures for guidances (MaPPs)
- Actual review infrastructure
  - Interdisciplinary Pharmacogenomic Review Group
  - Clinical Review Divisions
  - Voluntary Genomic Data Submissions
  - Hardware, software, databases

Genomic Biomarkers

- **A genomic biomarker is defined as a DNA or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other intervention.**

  Proposed Definition
  ICH E-15, PGx Working Group

Classification of (Genomic) Biomarkers

- **Known valid**
  - Accepted by scientific community at-large to predict clinical outcome
- **Probable valid**
  - Appears to have predictive value but not yet replicated or widely accepted

- Classification leads to specifications for validation in the context of **intended use** for biomarker

Classification of (Genomic) Biomarkers, cont'd

- **Exploratory Biomarkers**
  - Lay groundwork for probable or known valid biomarkers
    - Hypothesis generation
  - Fill in gaps of uncertainty about disease targets, variability in drug response, animal – human bridges and new molecule selection
    - Learn and improve success in future drug development programs
  - Can be "de novo" or "sidebar" study embedded in (pivotal) clinical efficacy trials

The Categorization of (Genomic) Biomarkers is about Knowledge …

"Reports that say that something hasn't happened are always interesting to me, because as we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns -- the ones we don't know we don't know."

Donald Rumsfeld

“Not yet discovered, non-valid biomarker” (not part of this presentation)

Known Valid

Probable Valid

Exploratory

- Examples:
  - Safety:
    - Gene panels used for preclinical safety evaluation
  - Efficacy:
    - APOE4 (Donepezil, Alzheimers)
    - VEGF (several anticancer agents)
    - Adiponectin mutations (rosiglitazone, type 2 diabetes)

Probable Valid

Exploratory

- Examples:
  - Safety:
    - Kim1 ~ preclinical (nephrotoxicity)
    - Gene panels used for preclinical safety evaluation
  - Efficacy:
    - EGFR mutations (Iressa)
    - CYP2D6 (Tamoxifen)
    - OncotypeDx gene panel (radiation therapy)

Known Valid

Probable Valid

Exploratory

- Examples from drugs labeled in U.S.:
  - Safety:
    - TPMT (6-MP, azathioprine)
    - UGT1A1 (irinotecan)
    - CYP2C9/VKORC1 (warfarin)
    - CYP2D6 (Strattera)
  - Efficacy:
    - EGFR status (Erbitux, Tarceva)
    - Her2/neu status (Herceptin)
    - Philadelphia chromosome ~ Bcr-abl (Gleevec)
    - C-kit (Gleevec)

Genomics at FDA

Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Pharmacogenomic information is contained in about ten percent of labels for drugs approved by the FDA. A significant increase of labels containing such information has been observed over the last decade. In order to provide a reference for genomic biomarkers in labels of FDA-approved drug products, we created the table shown below. Genomic biomarkers can play an important role in identifying responders and non-responders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety. In the context of drug labels, these genomic biomarkers can be classified on the basis of their specific use, for example:

- clinical response and differentiation,
- risk identification,
- dose selection guidance,
- susceptibility, resistance and differential disease diagnosis,
- polymorphic drug targets.

The table portrays a view on valid genomic biomarkers in the context of FDA-approved drug labels. It provides a comprehensive list of these markers and links to pharmacogenomic data, taking into account multiple regulatory contexts in which these biomarkers were approved. Most drug labels in this table provide pharmacogenomic information with no immediate recommendation for a specific action (i.e. genetic testing); however a few labels re[commend] or require genetic testing thereby specifying the use of these markers for reaching a therapeutic decision.

The table includes:

1) context-specific biomarker (column 1)
2) reference drug label information about the [context within which the drug was approved (column 2 subsection 1)]
3) test criteria (column 2 subsection 2)
4) prototypic drug associated with the [the biomarker context (column 2 subsection 3)]
5) other drugs in a similar context (c
6) pertinent references (column 4)

Drugs sharing [the context of] labels have had their pharmacogenomic informa[tion] information can be accessed [by clicking t]der the right side of the drug name. All approved d[rug] labels at Drugs@FDA [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/] which can be accessed by clicki[ng] left side of the drug name. The t[able] basis.

Biomarker	Label Context			Other Drugs Associated with this Biomarker	References
	[Label]	Test	Drug		
C-KIT expression	**Gastrointestinal stromal tumor *c-Kit* expression** "*In vitro*, imatinib inhibits proliferation and induces apoptosis in gastro-intestinal stromal tumor (GIST) cells, which express an activating	**3**	Imatinib mesylate		PMID: 12851888; PMID: 16226710 PMID: 16294026

Valid Genomic Biomarkers in the Context of Approved Drugs - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Search Favorites Media Links

Address C:\Documents and Settings\fruehf\Desktop\Biomarker table example.htm Go

5) other drugs in a similar context (column 3)
6) pertinent references (column 4).

Drugs sharing the context of a specific biomarker in their labels have had their pharmacogenomic information extracted into this table. This information can be accessed by placing the mouse over the symbol under the right side of the drug name. All approved drugs in this table are linked to labels at Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) which can be accessed by clicking over symbols under the left side of the drug name. The table will be updated on a quarterly basis.

SHOULD BE LIVE IN A WEEK OR TWO...

WWW.FDA.GOV/CDER/GENOMICS

	subjects have shown that poor metabolizers have, on averag... fold higher voriconazole exposure (AUCτ) than their hom... extensive metabolizer counterparts. Subjects who are ... extensive metabolizers have, on average, 2-fold hig... voriconazole exposure than their homozygous e... metabolizer counterparts."			
CYP2C19 Variants with alternate Context	**CYP2C19 Variants, drug exposure in... metabolism**- Lansoprazole is metabo... P450 system, specifically through th... isozymes. Studies have shown that lan... clinically significant interactions with othe... cytochrome P450 system. Because of the s... direction of the effect on theophylline clear... unlikely to be of clinical concern. Nonetheless, ... may require additional titration of their theophyllin... lansoprazole is started or stopped to ensure clinical... blood levels.		illin,Clarithromycin, brazole;[m7] brazole and Naproxen Pro anil and Atovaquone [m9] Delavirdine [m10]	PMID: 12680476 PMID: 12495367 PMID: 12809821; PMID: 16413249; PMID: 16413245 PMID: 15871633; PMID: 15496214 PMID: 14664653

Direct link to Popup provides PGx label information

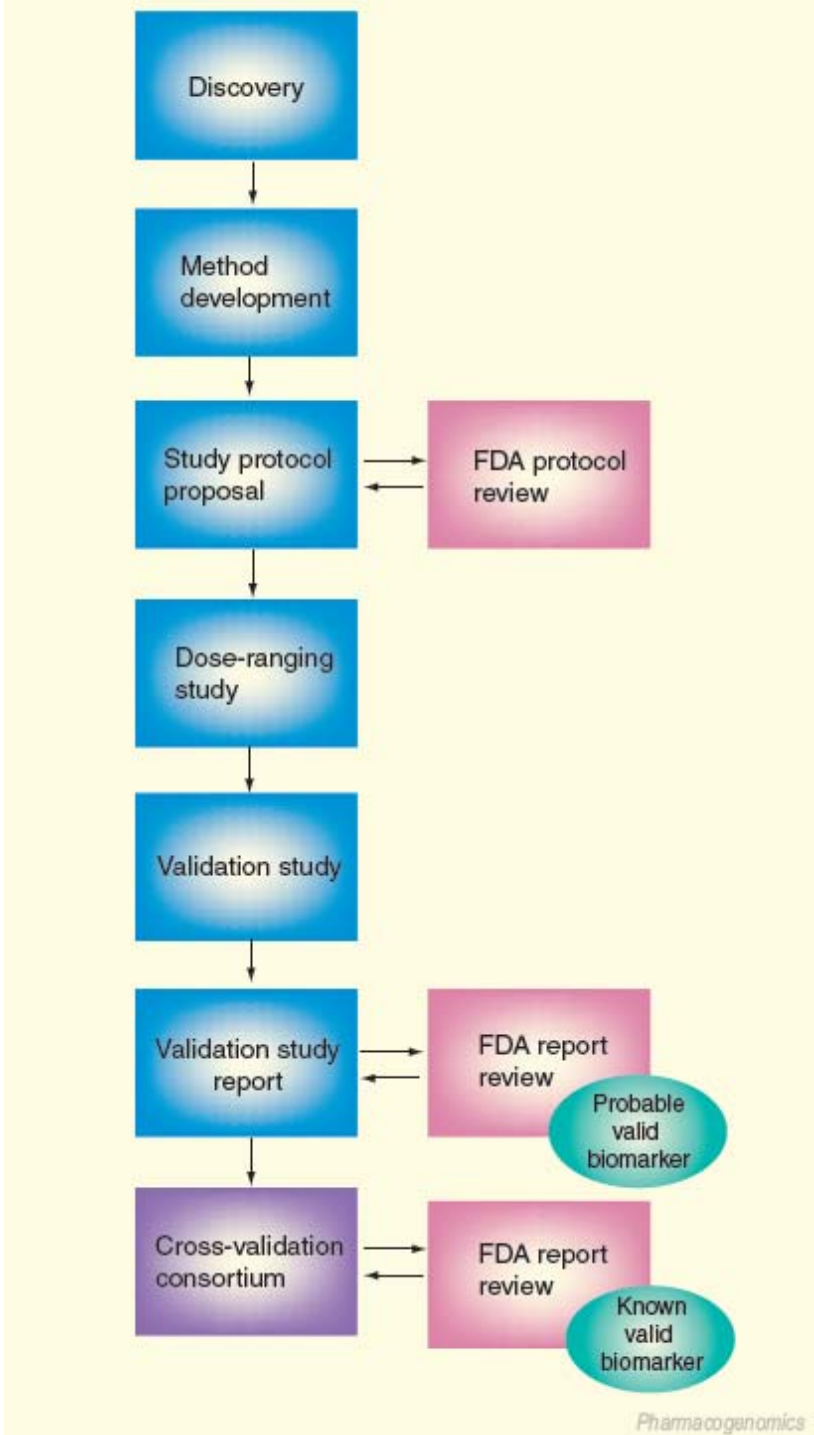
My Computer

How does an exploratory marker become probable or known valid ?

- Most “known” valid biomarkers have been “validated” by accumulating data over many years
- Markers for “targeted therapies” become known valid when treatment is approved: they are used to demonstrate efficacy during clinical drug development (drug-test co-development)
- FDA Pharmacogenomics guidance does not provide information about marker validation
- Short of clinical trials in drug development process, there are no established processes for marker validation
- Can retrospective data be persuasive for marker validation or are prospective studies required?
- A validation path for pre-clinical markers has been proposed

Biomarker Validation: A Proposal

- Validation of **pre-clinical** genomic biomarkers for drug safety
- CRADA
- Pre-clinical safety testing consortium
- Goal: Regulatory buy-in



Goodsaid and Frueh
Pharmacogenomics, in press

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | FDA Centennial

FDA News

FOR IMMEDIATE RELEASE
P06-40
March 16, 2006

Media Inquiries:
301-827-6242
Consumer Inquiries:
888-INFO-FDA

FDA and the Critical Path Institute Announce Predictive Safety Testing Consortium

Consortium Will Share Tests to Understand Safety of Potential New Drugs Earlier

The Food and Drug Administration (FDA) and The Critical Path Institute (C-Path) today announced the formation of the Predictive Safety Testing Consortium between C-Path and five of America's largest pharmaceutical companies to share internally developed laboratory methods to predict the safety of new treatments before they are tested in humans. The FDA, while not a member of the Partnership, will assist it in an advisory capacity. This unprecedented sharing of potential early indicators of clinical safety may streamline the cost and time of preclinical drug safety evaluation and better inform the use of "personalized medicine". The Consortium was announced today at a press conference detailing the release of the Critical Path Opportunities List – 76 initial research priorities that, if accomplished, will modernize the drug development process by 2010 and help get new medical discoveries to Americans faster and at a lower cost.

- Current membership: 12 large pharmas
- Co-directed by C-Path and pharma representatives

Timeline of Predictive Safety Testing Consortium (PSTC)

- Initial discussions started in March 2005 between reps. from OCP Genomics Group and industry, series of informal telecons
- Structural framework proposal by C-Path in July 2005
- Legal framework completed in March 2006
- Four working groups initiated in March 2006 at the SOT Meeting in San Diego
  - Nephrotoxicity, Hepatotoxicity, Vasculitis, Genotoxic and Non-Genotoxic Carcinogenicity
- Launch by Secretary of HHS on March 16, 2006

Assembly of new FDA review teams (umbrella: IPRG) to ensure appropriate regulatory expert review of PSTC data

Validation of *Clinical* Genomic Biomarkers

- Less obvious, but basically two options:
  - Wait long enough, and we might believe it
  - Don't wait, but have a good strategy, e.g., drug-test co-development
- Problem: sometimes hard to extrapolate, e.g. EGFR:
  - Tarceva: only EGFR+ patients respond
  - Erbitux: only EGFR+ patients respond (or so we thought…)
  - Iressa: EGFR mutations play a role (really?)
- Even if a marker is valid, the variability of the *test* can be significant (e.g. Herceptest)
- Unlikely that we can create a standardized validation pathway, but some general rules may apply

Where Will *Clinical* Genomic Biomarkers Be Validated?

- Consortia:
  - Biomarker for predicting adverse events (common, and, perhaps, idiosyncratic – depends on what we learn)
  - Biomarkers in specific therapeutic areas (e.g. oncology: development of tests for pathways, etc.)
  - Markers that cut across indications ("biomarker trials")
- Individual companies/ organizations:
  - Clinical trials and Drug-Test Co-Development
    - Ideally, early use and integration of marker in drug development program
    - Coordinated effort between the development of the drug and the test, e.g. trial data will support both drug and test approval
    - Test (use of marker) required

Where Will *Clinical* Genomic Biomarkers Be Validated?

- Consortia:
  - Biomarker for predicting adverse events (common, and, perhaps, idiosyncratic – depends on what we learn)
  - Biomarkers in specific therapeutic areas (e.g. oncology: development of tests for pathways, etc.)
  - Markers that cut across indications ("biomarker trials")
- Individual companies/ organizations:
  - Clinical trials and Drug-Test Co-Development
    - Ideally, early use and integration of marker in drug development program
    - Coordinated effort between the development of the drug and the test, e.g. trial data will support both drug and test approval
    - Test (use of marker) required

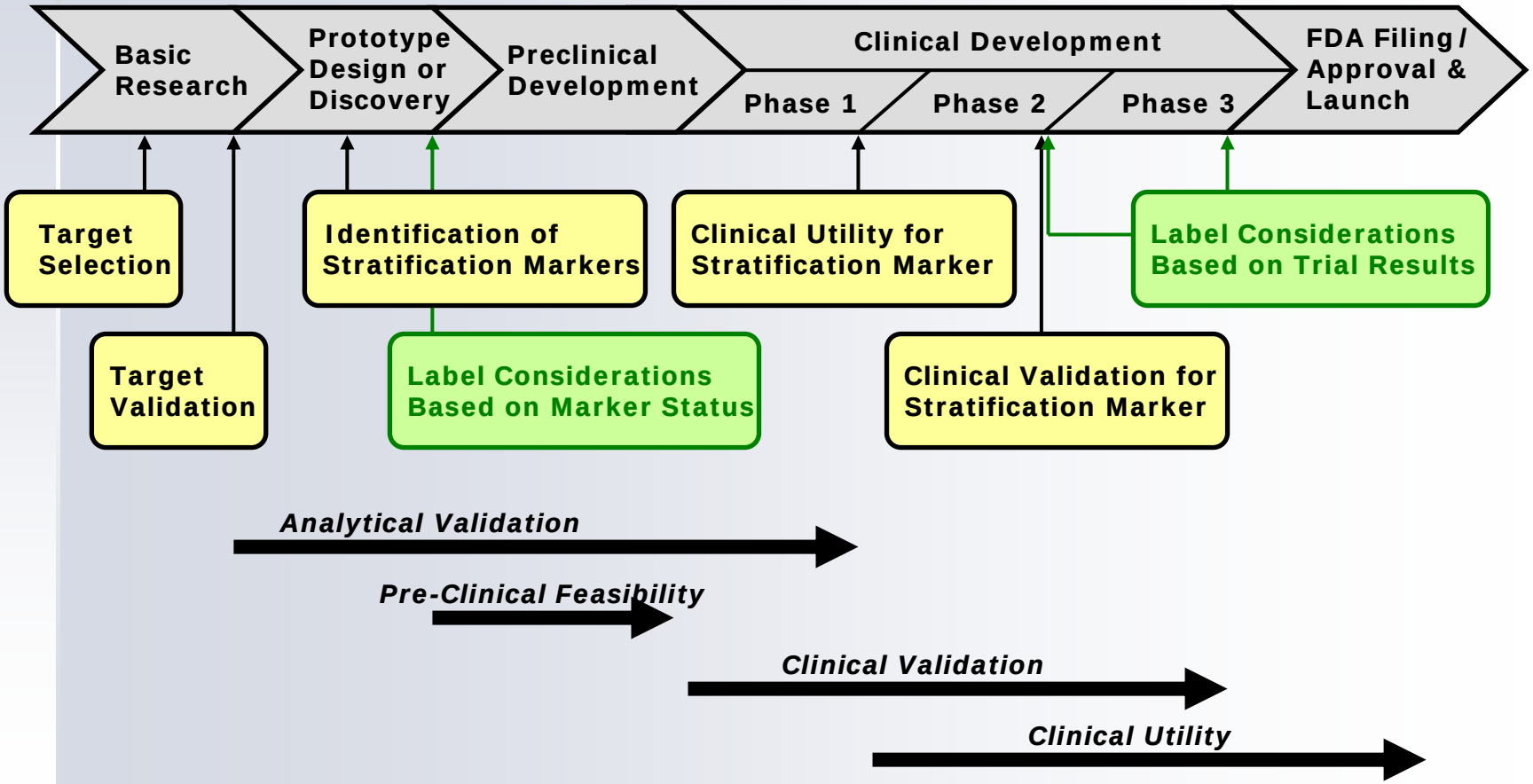
Drug-Test Co-Development: What is it ?

- Drug and test are investigational (biomarkers are “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

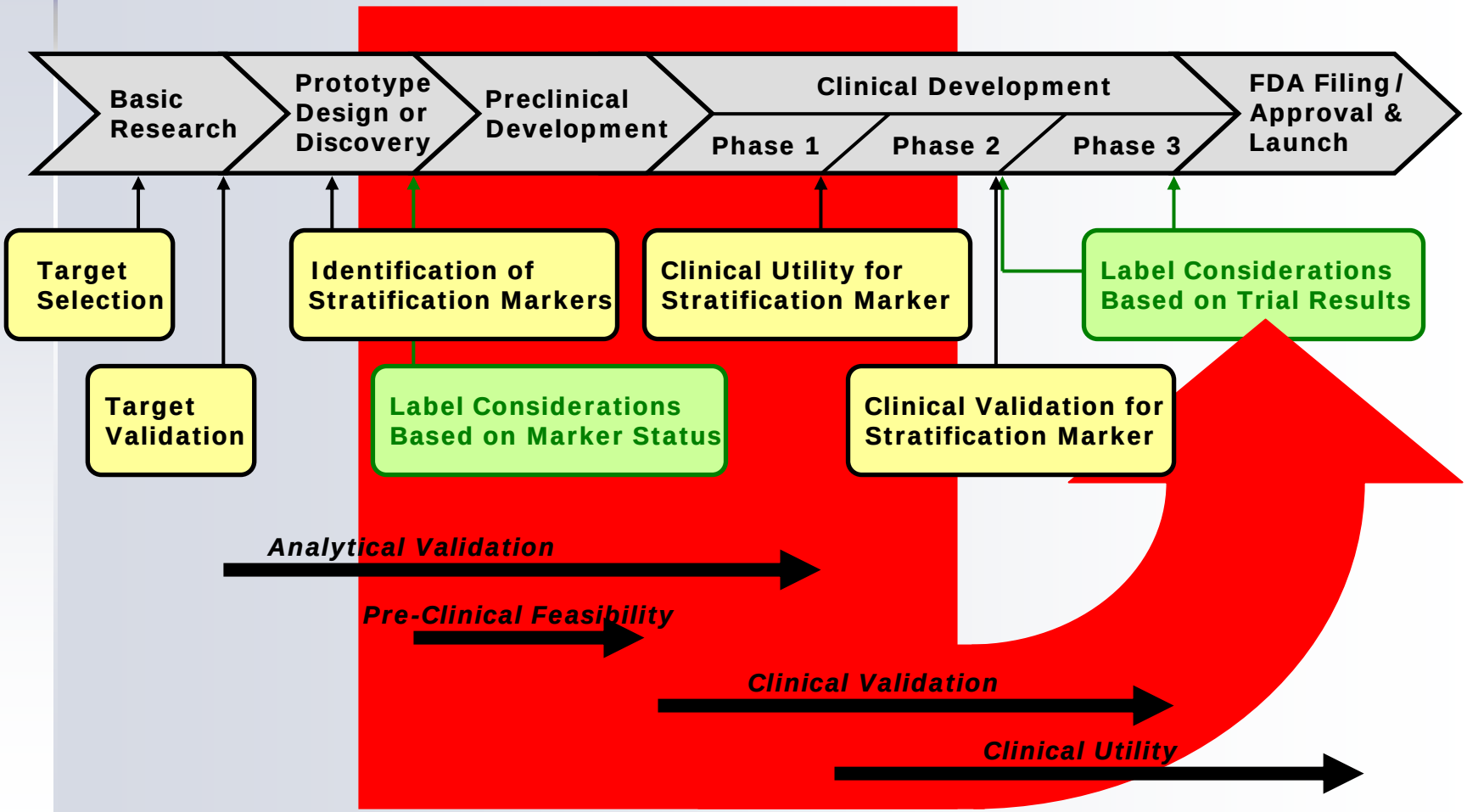
Why Drug-Test Co-Development?

- Move therapy from non-mechanistic (i.e., trial and error) approach to scientifically based prediction
- Refine definitions of disease (i.e., disease subtypes)
- Avoid certain adverse drug event and therefore improve benefit/risk analysis
- Select patients for therapy based on better predictions of response – or avoidance of non-response and at risk for toxicity

Drug-Test Co-Development



Drug-Test Co-Development: Strategic Considerations



Yes, it's all about the Biomarker…

- 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
- This makes it difficult to generalize findings and impossible to propose one specific pathway to validate clinical markers
- What happens if a marker is not as good as we thought? What if it is better (i.e. more predictive)?
- Do the current clinical trial designs acknowledge this dilemma?

Bottleneck in Drug-Test Co-Development: Integration of PGx Into Clinical Trials – Need for More Informative Trial Designs

- Randomized controlled clinical trial addresses bias and the impact of "random" variability – basis for many advances in modern medicine
- Qualification of clinical biomarkers is dependent on clinical trial data (ideally prospective, but to some extent also possible retrospective)
- Current clinical trial designs are limiting the extent of information that can be derived from a trial:
  - However, this trial design answers only 1 questions at a time, yet there are many questions about the appropriate use of medical products – and these questions evolve over time
    - (What if wrong question is asked? – Little flexibility)
  - Binary outcome (success or failure) is determined by p-value – limits information gain

More Informative Trial Designs

- Approach: Pair diagnostic with therapeutic
  - Identify responders and non-responders
  - Prevent toxicity
  - Monitor response
- Flexibility using adaptive designs
  - Answer series of questions, e.g.,
  - Which dose is correct for which sub-population?
  - Which sub-population should be treated?
- Can provide recipe to success when low efficacy overall
- Can provide important information when efficacy is compared to competitor drug: which drug to use for which group?

FDA-ZBI Pharmacogenomics Clinical Trial Design Tool

NEW !

- Design and compare all-comers and enriched studies
- Off-the-shelf: MS Excel and Visual Basic
- Scalable: plan to expand into more complex designs (currently in prototype version 0.2)
- In standard mode, tool produces same results as nQuery and NCI online tool (R. Simon), but it is adapted specifically to accommodate PGx input
- Remembers settings, allows to run multiple scenarios
- Accommodates binary and time-to-event endpoints

- Available for free: fdagenomics@fda.hhs.gov

Zurich Biostatistics, Inc.

ZBI Pharmacogenomic ClinicalStudyDesign - Main Screen - [Study Characteristics - Chi Square Test for Two Independent Proportions]

File Edit Windows Help

SCENARIO BUILDER - Input Area

Alpha level : 0.050 **1 or 2-sided test ? :** 1 **Power % (0<power %<100) :** 80

	Placebo response rate (0<=pc<1)	Response rate for the biomarker negative subjects (0<=pc+delta0<1)	Treatment effect for the biomarker negative subjects (0<=delta0<1)	Response rate for the biomarker positive subjects (0<pc+delta1<=1)	Treatment effect for the biomarker positive subjects (0<delta1<=1)	All-comers proportion that is biomarker negative (0<gamma<1)	All-comers proportion that is biomarker positive (1-gamma)
Scenario - 1	0.680	0.680	0.000	0.830	0.150	0.300	0.700
Scenario - 2							

Output Area

	Treatment effect for the all-comers (gamma*delta0+ ((1-gamma)*delat1)	Treatment response rate for all comers (gamma*delta0+ ((1-gamma)*delat1)+pc	Sample size per group for the all-comers study	Treatment effect for the assay positive stratum ((1-PPV)*delta0 + PPV*delta1)	Treatement response rate for assay positive stratum ((1-PPV)*delta0 + PPV*delta1)+pc	Sample size per group for the assay positive study	Ratio of sample sizes for all-comers relative to assay positive
Scenario - 1	0.105	0.785	238	0.150	0.830	114	2.088
Scenario - 2							

User Notes

Test calculation for prospective warfarin trial

Help

Treatment effect for the biomarker positive subjects (δ_1):

The addition to the placebo response rate expected from the treatment in the biomarker positive subjects, a value that is > 0, <= 1.

Generate Import Save Plot Print Close

(Regulatory) Mechanisms for Discussing Biomarker Validity

- **Regulatory:**
  - Typical regulatory meetings (e.g. IND meetings such as EOP2 meeting)
  - New types of meetings
    - VGDS
    - EOP2A
  - Device-oriented meetings (e.g. pre-IDE)
- **Non-Regulatory (likely not drug-specific)**
  - Consortia
  - Collaborative efforts

Example: Voluntary Genomic Data Submission (VGDS)

- Submission of **exploratory** PGx data submission regardless if subject of an active IND, NDA, or BLA
- Biomarker data may result from, e.g., DNA microarrays, single or limited gene expression profiles, genotyping or SNP profiling, or from other studies using evolving methodologies
- Forum for scientific discussions with the FDA outside of regular review process
  - Data not used for regulatory decisions

NEW! VXDS (X= exploratory)

"X" could be proteomics, metabolomics, imaging, ... great interest also in "bridging" between fields

Voluntary Data Submissions: What We Are Interested in

- Biomarker discovery and qualification, e.g., use of repositories, biobanks
- Cover broad clinical areas to illustrate impact of genomics in all therapeutic fields
- Immediate impact, e.g. active drug development program-related submissions, toxicogenomics, etc.
- Associated with active drug development programs
- Interesting designs for e.g., stratification/enrichment
- Challenging data analysis (tools, statistics, etc.)
- New technologies and “bridging” studies
- Follow-on submissions

Voluntary Data Submissions: Questions of Interest

- Statistical approach feasible?
- Which biomarker(s) to take forward?
- Mechanistic explanation?
- Can expression profile be obtained?
- Is the profile predictable for outcome?
- How can we test the hypothesis and how can it be validated?
- Will this approach provide us with a clinically useful answer?

Drug-Test Co-Development: Some of the Issues to Be Addressed

- Drug:
  - When and how to study marker-negative population
  - Adaptive trial designs: when are they appropriate, interim data analysis, etc.
  - How to enroll patients when prevalence of marker is low:
    - How to treat marker-negative patients
    - Morale of physicians conducting trials (i.e. need to reject large number of potential trial participants)
- Test:
  - Data requirements for clinical utility
  - When will a test be required, when recommended
  - Can test be performed in every-day clinical environment
  - Switch from research to production mode
- Drug-Test:
  - Communication and coordination between drug- and test-manufacturers and regulatory authorities

Guidance on Drug-Test Co-Development

- **Drug-test co-development concept paper**
  - Published Spring 2005
  - Focused mainly on technical/analytical issues, not so much on clinical aspects
  - 90 day comment period ~ 20 comments to docket
  - Proposed timeline and strategy for drug and test developments are ideal, but may not be achievable
- **Drug-test co-development draft guidance**
  - Complete re-write of concept paper, to be published in 2006
  - Focus more on clinical aspects
  - Better integration of test (diagnostic) development into drug development process

What About Translating this Information into Clinical Practice ?

- Education is lacking behind the pace of science
- FDA develops and supports a variety of educational efforts, e.g.
  - CDER internal course on pharmacogenomics (slides available at www.fda.gov/cder/genomics)
  - FDA-AMA online course with CME credits (in development); second course (FDA-ACCP) planned
  - Educational videos (irinotecan, warfarin, others) planned
  - Many workshops and publications
  - NACB Laboratory Medicine Practice Guidelines (LMPG) presented here at AACC as two full-day symposia

NACB: Guidelines and Recommendations for Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice. Draft version 60806. Open for comments.

Guidelines and Recommendations for Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice

Guidelines Committee:

Chair:

Roland Valdes, Jr., Ph.D., DABCC, FACB (Kentucky)
rvaldes@louisville.edu

Vice Chairs:

Deborah Payne, Ph.D., DABCC, (Texas)
deborah.payne@utsouthwestern.edu

Mark W. Linder, Ph.D., DABCC, FACB (Kentucky)
wlind01@gwise.louisville.edu

Members:

Gil Burkhart (California) burckart@usc.edu
Danial Farkas (Texas) dfarkas@chondrogene.com
Felix Frueh (Maryland) FruehF@cder.fda.gov
Howard McLeod (Missouri) hmcleod@im.wustl.edu
Jean-Pierre Morrello (Ontario) jpmorello@signaturegenetics.com
Atik Rahman (Maryland) RAHMANA@cder.fda.gov
Gualberto Ruano (Connecticut) g.ruano@genomas.net
Les Shaw (Pennsylvania) shawlmj@mail.med.upenn.edu

Other contributing authors:

Saeed Jortani (Kentucky) sjortani@louisville.edu
Werner Steimer (Germany)
Steven Wong (Wisconsin) shwong@mail.mcw.edu

Primary reviewers (to date):

David Flockhart, Wendel Weber, Jose deLeon, Jeanne Carr, Dennis O'Kane, Elaine Lyons, Julia Kirchheiner , Kristen Reynolds, Alan Wu, Jerry Collins, Allen Rudman

http://www.nacb.org/lmpg/LMPG_Pharmacogenetics.pdf

Closing Remarks

- Evolving regulatory framework in the area of genomic biomarkers and drug-test co-development
- Biomarker validation and clinical trial design are two key areas currently being addressed by regulators
- In many cases, it will no longer be possible for a single entity to create the information needed for marker validation: new collaborative models need to be explored
- Drug-test co-development examples are few and far between:
  - Herceptin® (breast cancer, Her2/neu+, approved 1998 in U.S.)
  - Gleevec® (CML, Philadelphia chromosome (Bcr-abl), 2001; GIST, c-kit, 2003)
  - Erbitux® (colon cancer, EGFR+, 2004)

Closing Remarks, cont'd

- Drug-test co-development is a paradigm change: from one drug for all to more drugs for smaller populations
- To encourage this change, we need a supportive scientific, regulatory and economical environment
- We should think about how to create incentives for the field
- There is an increasing awareness from a public policy perspective: a careful evaluation of the impact of such new policy is needed as much (or more) as the new policy itself
- A transparent approach and an open dialogue are important
- At the end, we all want the same: medical products, which we know will work for us as individuals, not populations
  - The question is how we get there, which is why we're here

THANK YOU !

www.fda.gov/cder/genomics

Felix.Frueh@fda.hhs.gov