Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies

Mike Pacanowski, PharmD, MPH
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

EMA
8 Oct 2012

Application of metabolic data to the evaluation of drugs.

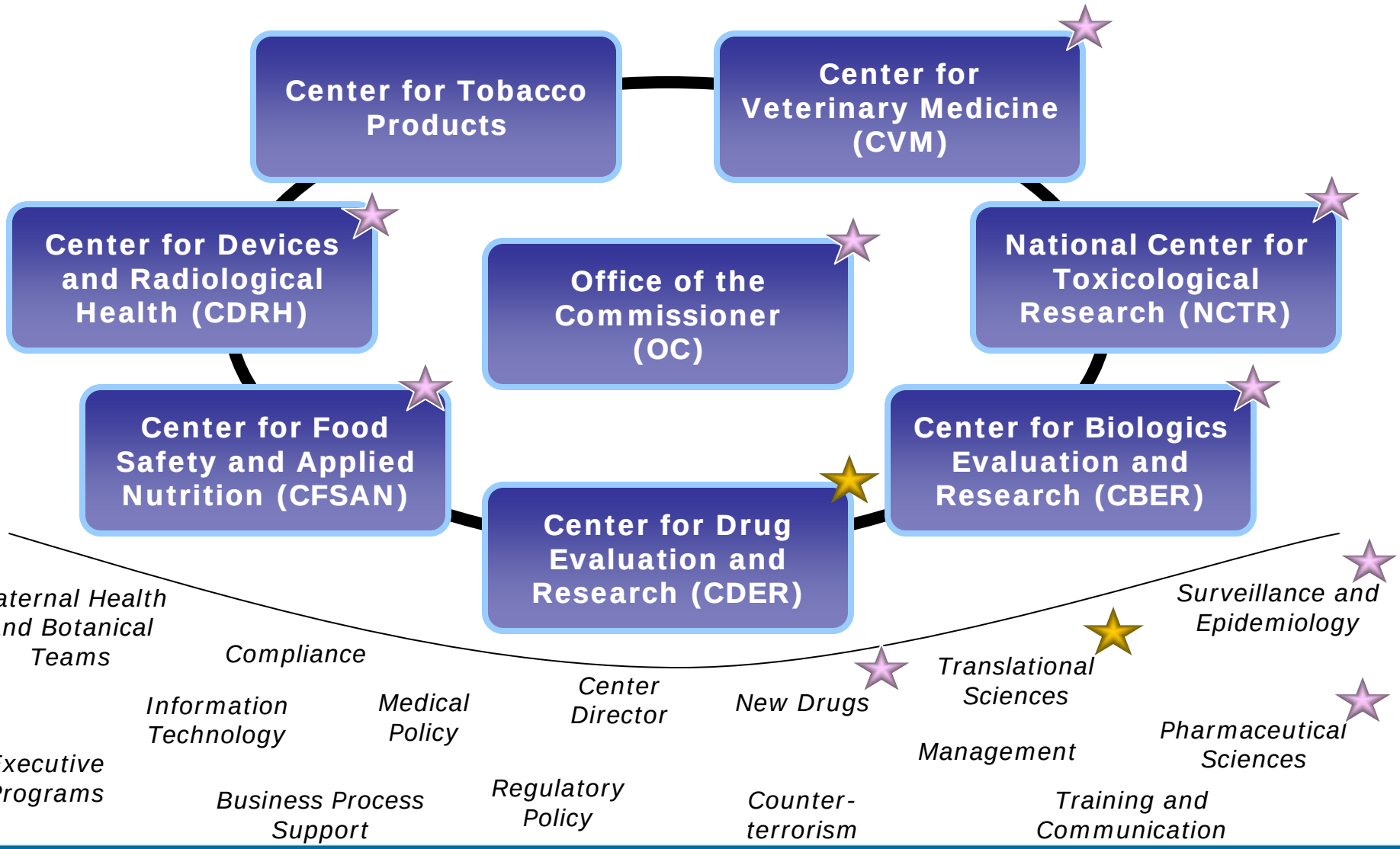
"Differences in individual ability to metabolize drugs must be considered in carrying out clinical pharmacologic studies...A universally safe drug, completely incapable of unusual or unexpected effects, is unobtainable."

NAS-NRC, CPT 1969

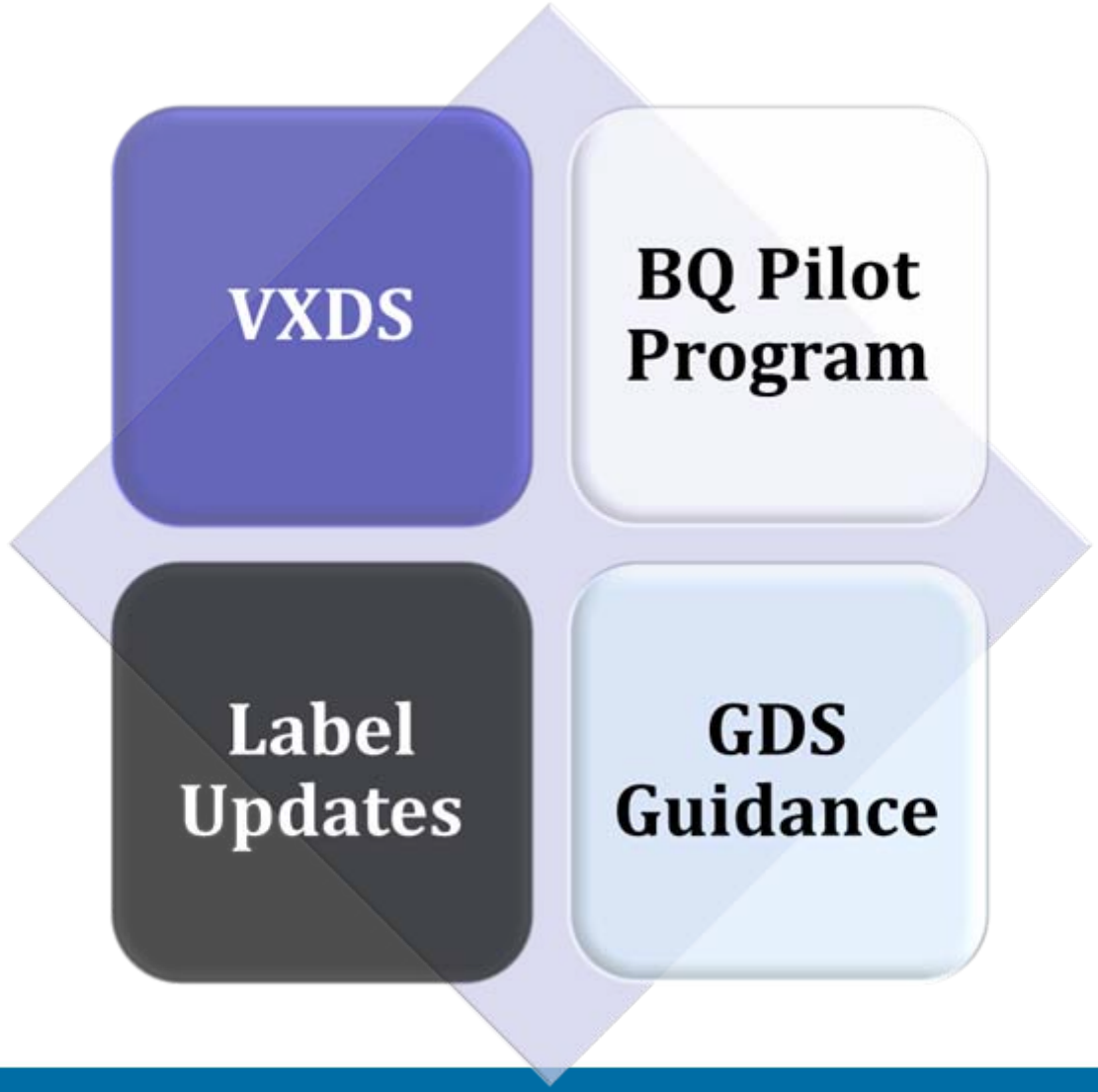
"It is no longer possible to prescribe drugs rationally on the basis of a memorized schedule of dosages and contraindications."

Azarnoff, JAMA 1970

FDA's Personalized Medicine Universe



Innovation at CDER: Early Focus Areas and Programs



Present State – PG Elements of NME NDAs/BLAs FY2011

Drug	Approval	Issue(s)
Crizotinib	8/26/11	Co-developed (ALK status)
Vemurafanib	8/17/11	Co-developed (BRAF status)
Ticagrelor	7/20/11	PD/efficacy by CYP2C19 status; exploratory safety
Indacaterol	7/1/11	PK by UGT1A1 status
Belatacept	6/15/11	Safety by EBV/CMV status
Ezogabine	6/10/11	PK by UGT1A1 and NAT2 status
Telaprevir	5/23/11	Efficacy by IL28B, safety by HLA
Boceprevir	5/13/11	Efficacy by IL28B, safety by ITPA
Ipilimumab	3/25/11	PGx of safety
Belimumab	3/9/11	Efficacy by SLE biomarkers
Roflumilast	2/28/11	Safety potential by human vs. animal genome
Vliazodone	1/21/11	PGx of efficacy and safety
Dabigatran	10/19/10	Differential PK/outcome by ABCB1, VKOR/2C9

34 NME approvals in FY11

U.S. Regulatory Guidance

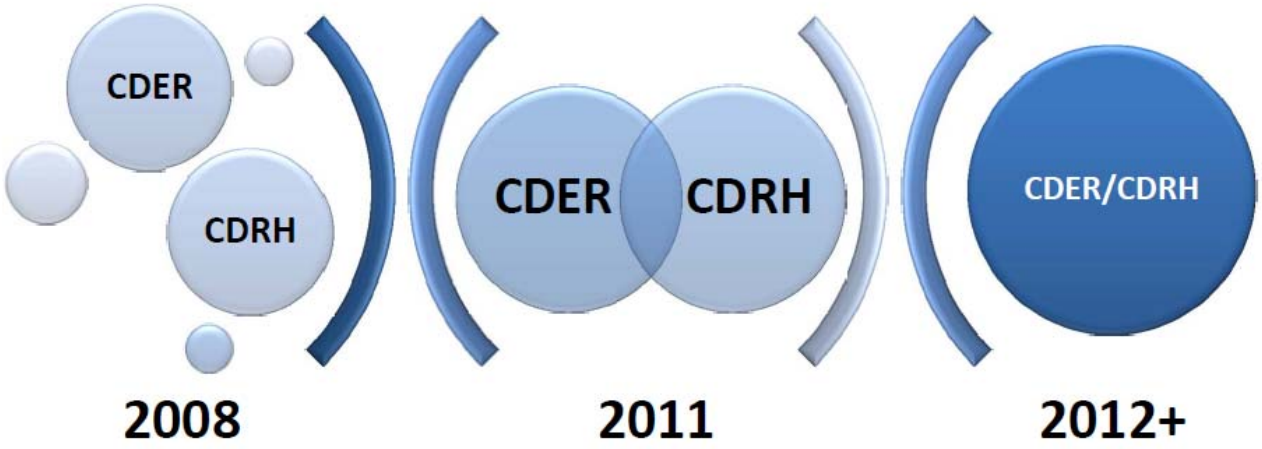
2005	Guidance on PG Data Submissions
	Concept Paper on Drug-Diagnostic Co-Development
2007	Companion Guidance on PG Data Submissions
	Guidance on PG Tests and Genetic Tests for Heritable Markers
2010	ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards
	Guidance on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment
	Guidance on Qualification Process for Drug Development Tools
2011	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies
	Guidance on in vitro Companion Diagnostic Devices
In Process	Guidance on Clinical Trial Designs Employing Enrichment Designs to Support Approval of Human Drugs and Biological Products

Rational Drug Development Successes…Ushering in the Next Generation

CAPSULES
XALKORI®
CRIZOTINIB

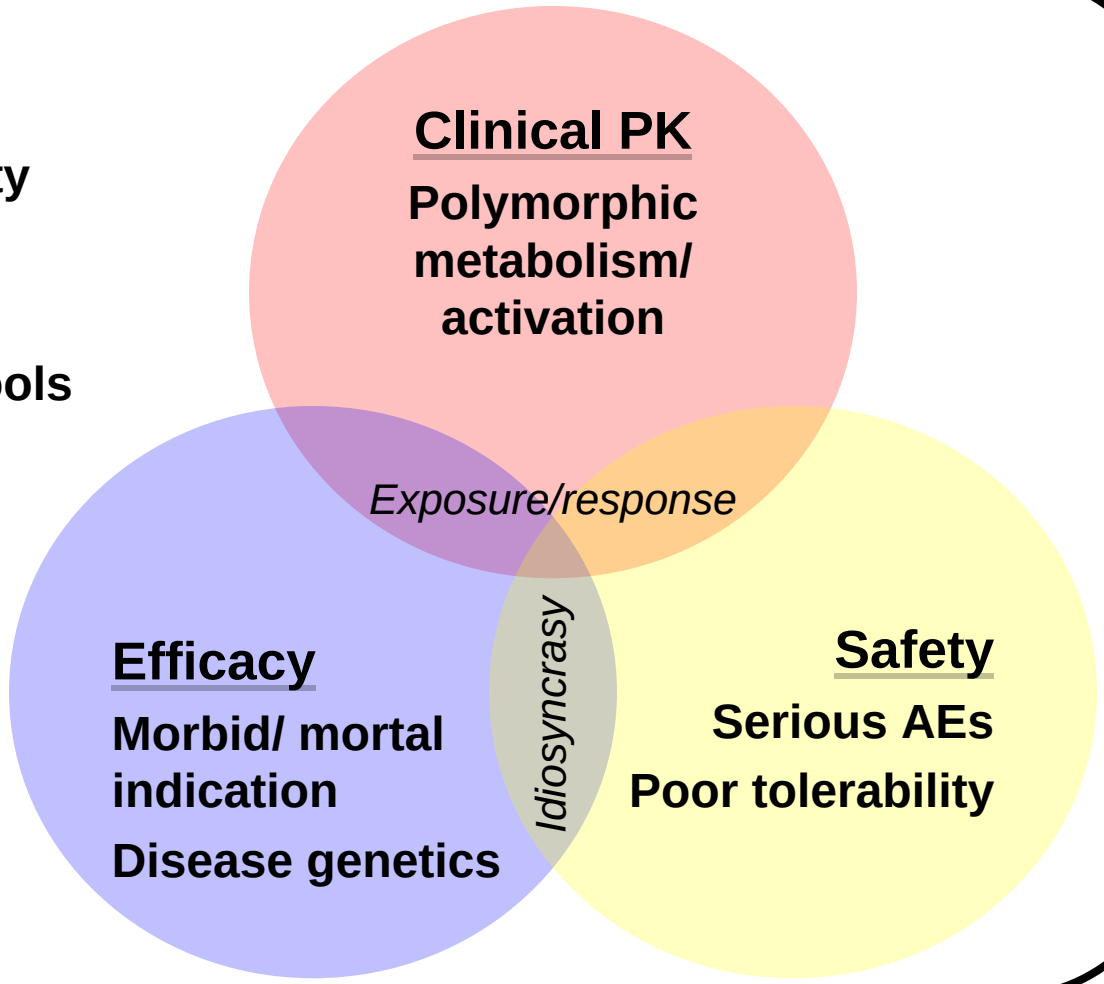
ZELBORAF™
(vemurafenib) tablets

kalydeco™
(ivacaftor) tablets



Problem Drugs

High variability
Disproportionality
Race effects
Outliers
No monitoring tools



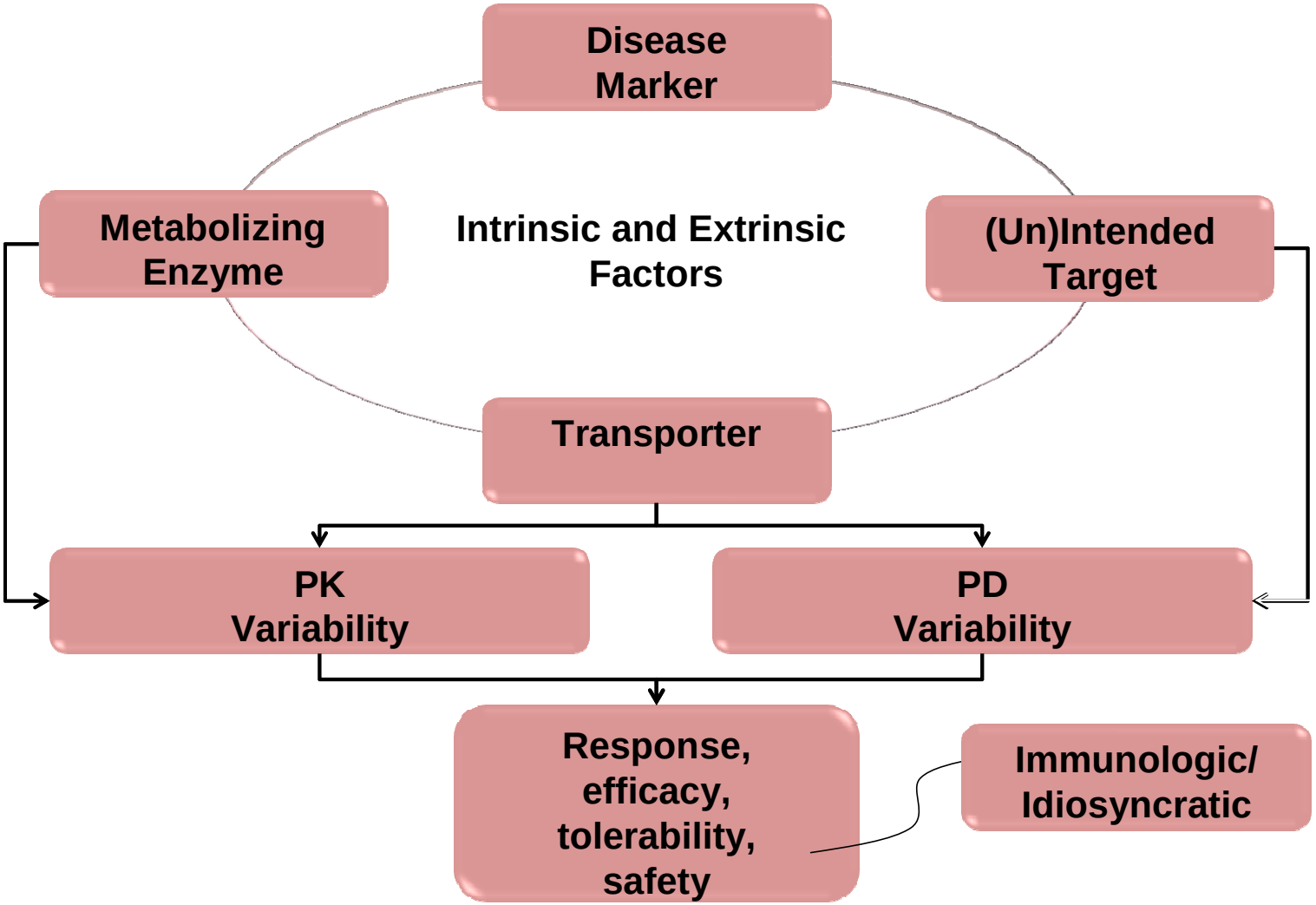
FDA Guidance: Clinical Pharmacogenomics in Early Phase Studies

- Purpose is to guide industry on when to consider how human genomic variation (specifically DNA) affects a drug's PK, efficacy, or safety
- Provides general principles of study design, data collection, data analysis and labeling for PG studies
- Scope: Early phase clinical trials (exploratory and observational studies)
  - Not statistical considerations for later phase RCTs intended to draw conclusions from genomic subgroup effects or co-development
  - Does not address tumor genomics specifically

Background

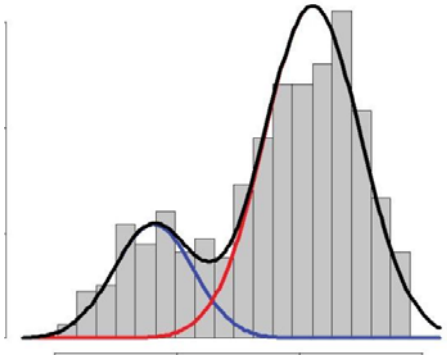
- Uses for genomic data
  - Basis for PK/PD outliers, intersubject variability
  - Investigating molecular/mechanistic basis for lack of efficacy, AEs
  - Estimating magnitude of potential DDIs
  - Subgroup effects and enrichment
- Potential clinical outcomes
  - Select patients based on risk/benefit profile
  - Modify dosing to avoid extreme exposures
  - Intensify AE monitoring

Genetic Factors of Interest

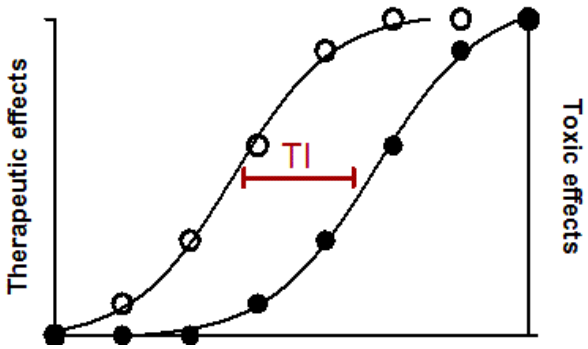


Modified from Expert Opin Drug Metab Toxicol. 2008 May;4(5):529-44.

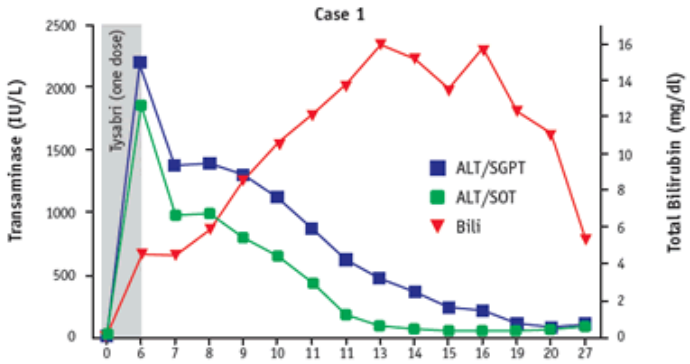
Foundational Principle: No PG without DNA



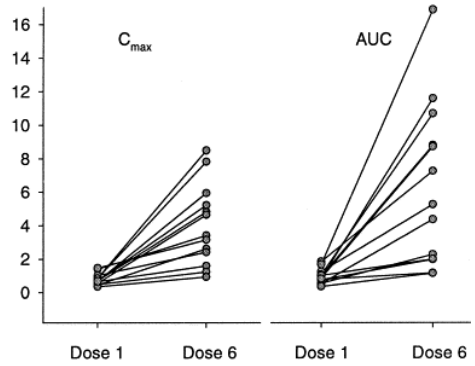
Multimodal PK



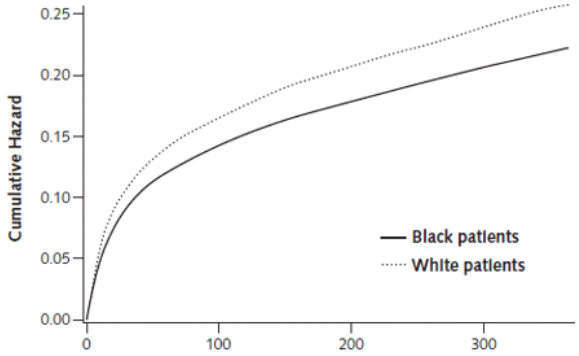
NTI



Safety



High Variability



Race Effects

DNA in all if hypothesis

DNA in all if no hypothesis (where possible)

If not all, many (+ targeted from “cases”)

If not all, why not

DNA Collection and Storage: General considerations

- Obtain broad consent
- Collect before randomization to minimize bias
- Retain samples to allow post-approval assessment
- Document reasons for incomplete sampling
- Provide information to support sample quality and integrity, in addition to QC/QA in CSR

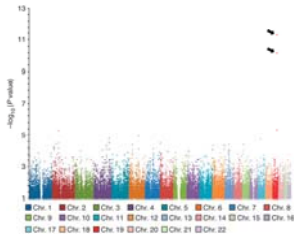
Applied Clinical Evaluation: Genotyping Strategies

- Hypothesis testing: Candidate gene
  - Test well-characterized, functional variants in ADME genes or drug target
- Hypothesis-generating: ADME or genome-wide chips
  - Useful for unresolved variability in exposure and/or response
  - High rate of false-positives – confirm findings in vitro or in additional clinical studies
- Marker selection
  - Appropriate to racial/ethnic group being studied

Applied Clinical Evaluation: PG Study Design

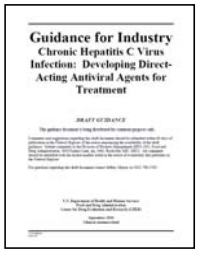
- Retrospective genotyping
  - Subgroup analysis, meta-analysis, case-control
  - Generally exploratory; appropriate for PK and safety endpoints
- Prospective genotyping
  - Stratified randomization/intervention, enrichment (inclusion/exclusion, over-enrollment)
  - Indicated for thorough PG assessments, dose-adjusting or excluding at-risk/non-responsive subjects from early trials, evaluating stratified dosing or efficacy in late phase trials, reducing noise in DDI studies

Paradigm Change and the "Progressive Reduction of Uncertainty"

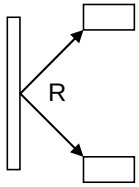


GWAS IL28B predicts Peg-IFN/RBV response

Dozens replicate



FDA HepC guidance



Standard analysis in RCTs

New NDAs

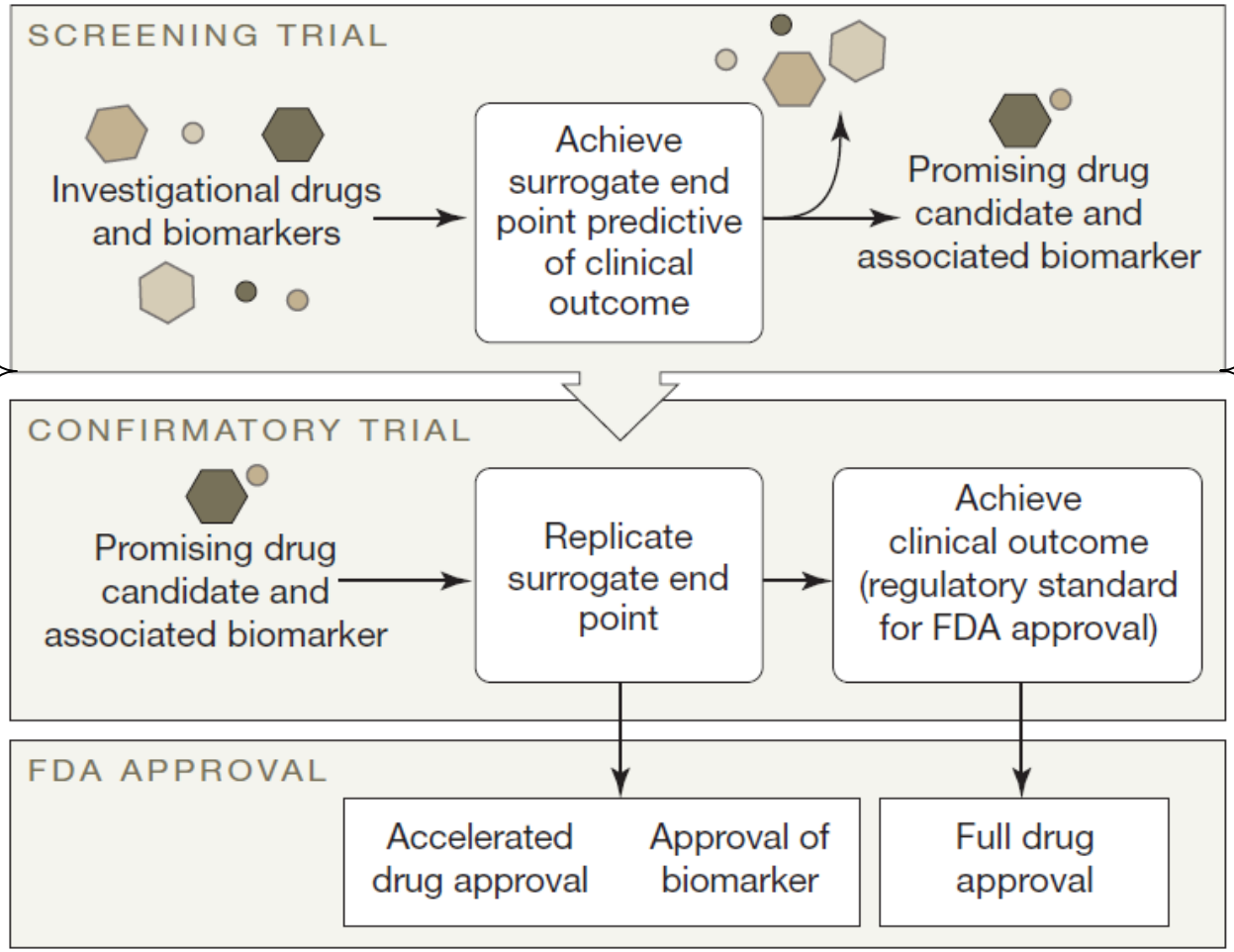
Seamless "Learn/Confirm" Paradigms May Provide a Path

Enrichment

Prognostic

Predictive

Practical



Companion Diagnostic

Esserman, Woodcock. JAMA 2011 [PMID: 22187281]; Temple. CPT 2010 [PMID: 20944560]

FDA Guidance: Companion Diagnostics

- Defines “companion diagnostic”
  - Test essential for safe and effective drug use
  - Prediction, prognosis, selection, dosing, monitoring
- Describes FDA’s policies for approval and labeling of a therapeutic/diagnostic product pair
  - Pre-market review, risk-based regulation
  - Analytical validity of tests used for critical treatment decisions to be reviewed
- Does not describe how to co-develop products

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017

IX. ENHANCING REGULATORY SCIENCE AND EXPEDITING DRUG DEVELOPMENT

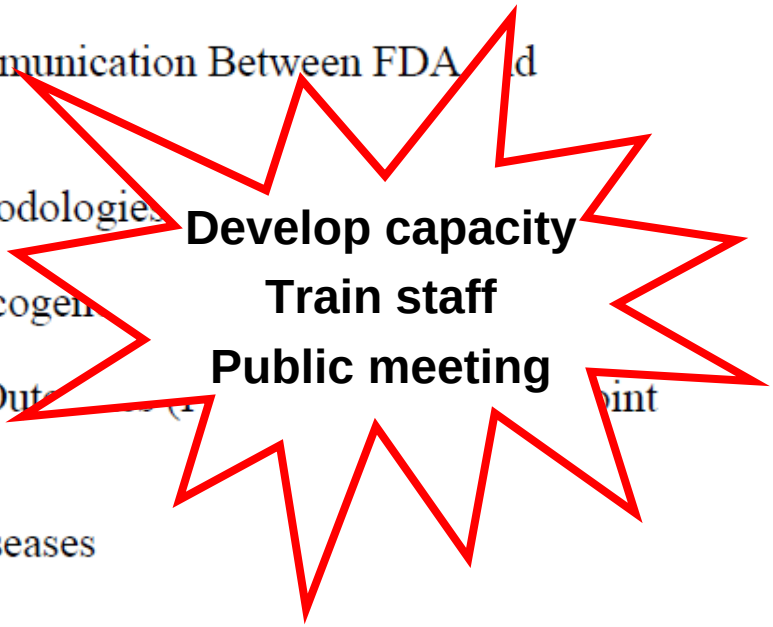
A. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development

B. Advancing the Science of Meta-Analysis Methodologies

C. Advancing the Use of Biomarkers and Pharmacogen

D. Advancing Development of Patient-Reported Out int Assessment Tools

E. Advancing Development of Drugs for Rare Diseases

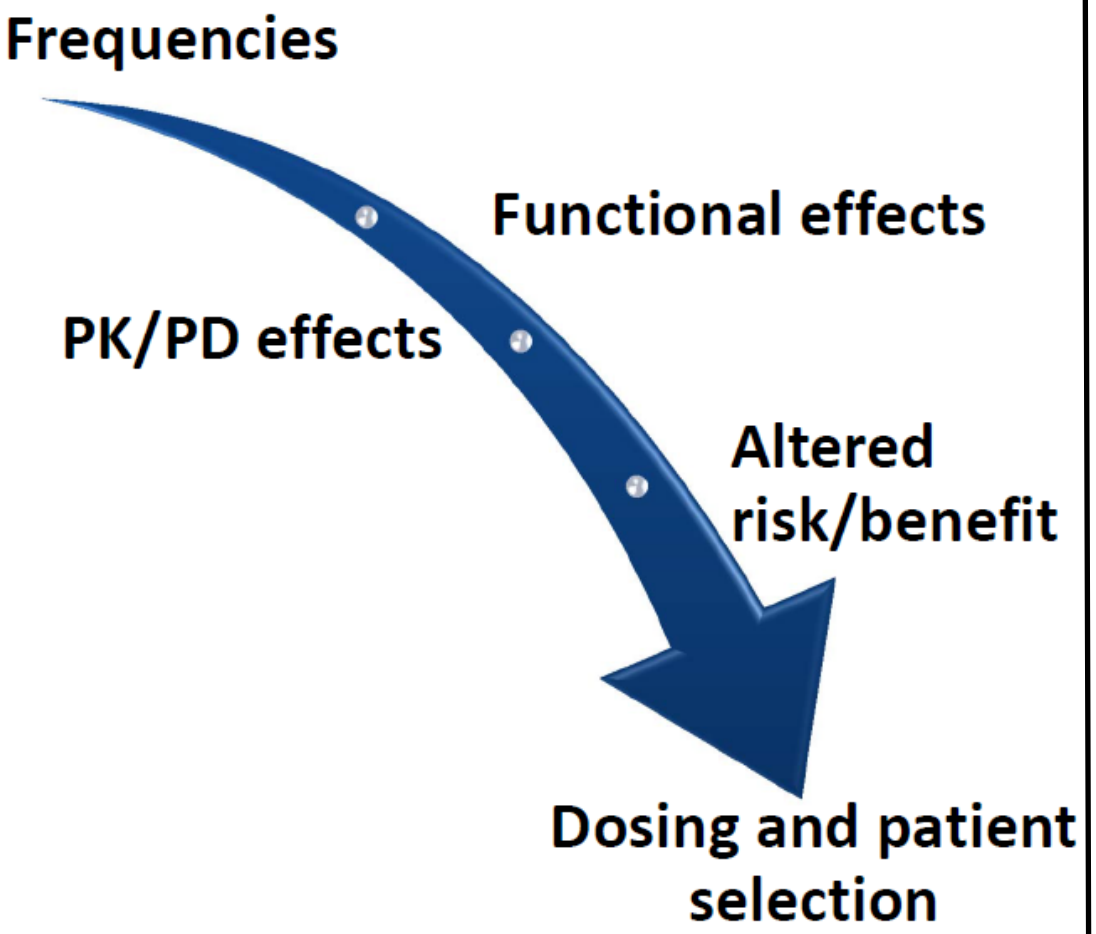


Summary and Conclusions

- Protecting and promoting public health are equally important charges to the FDA
- The role of PG in drug development is evolving, extends beyond drug-test pairs
- Regulatory policy has attempted to foster use of applied genomics in drug development, reducing uncertainty
- Co-development and Enrichment guidances to address late-phase issues related to biomarker-based drug development

Backup

Labeling: Hierarchy of Action



INDICATIONS AND USAGE

- Patient selection

DOSAGE AND ADMINISTRATION

- Subgroup dosing

BOXED WARNING

CONTRAINDICATIONS

WARNINGS AND PRECAUTIONS

ADVERSE REACTIONS

USE IN SPECIFIC POPULATIONS

- Differential safety

CLINICAL PHARMACOLOGY

- Impact on PK/PD

CLINICAL STUDIES

- Substantial evidence of observed or neutral differences

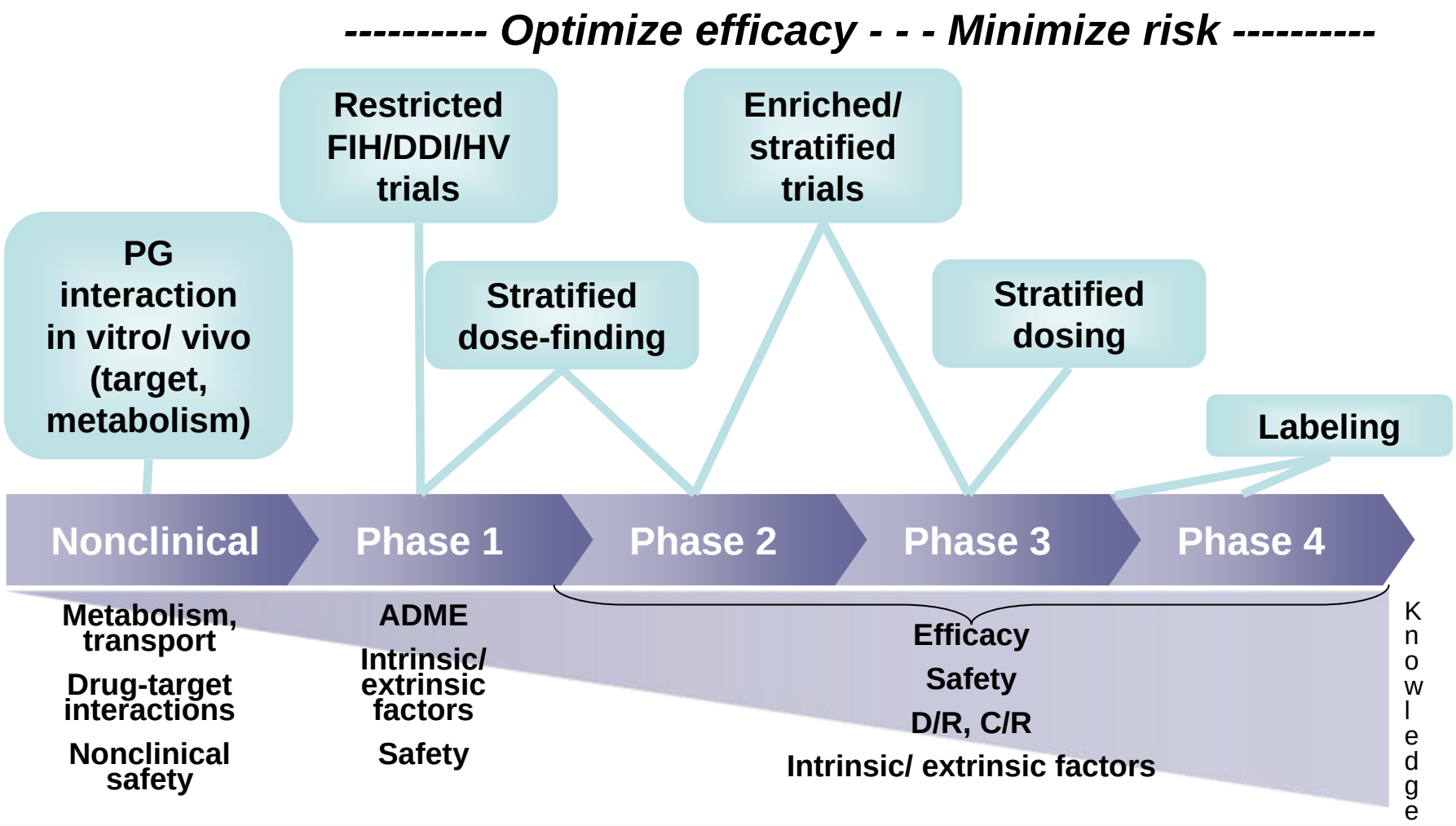
Applied Clinical Evaluation – Additional Considerations

- Evaluate PG interactions in context of clinical covariates, particularly race/ethnicity
- PBPK modeling may provide supportive evidence
- Control multiplicity
- Evaluate test performance (e.g., PPV, NPV)
- Address bias in substudies (i.e., differences from overall population, preservation of randomization)
- Establish strength, cohesion, etc
- Replicate
- Assay
  - Establish QC materials, standards, calibrators, and validated protocols to assure continued analytical performance
  - Consult CDRH for imminent test

Summary:
Review Considerations

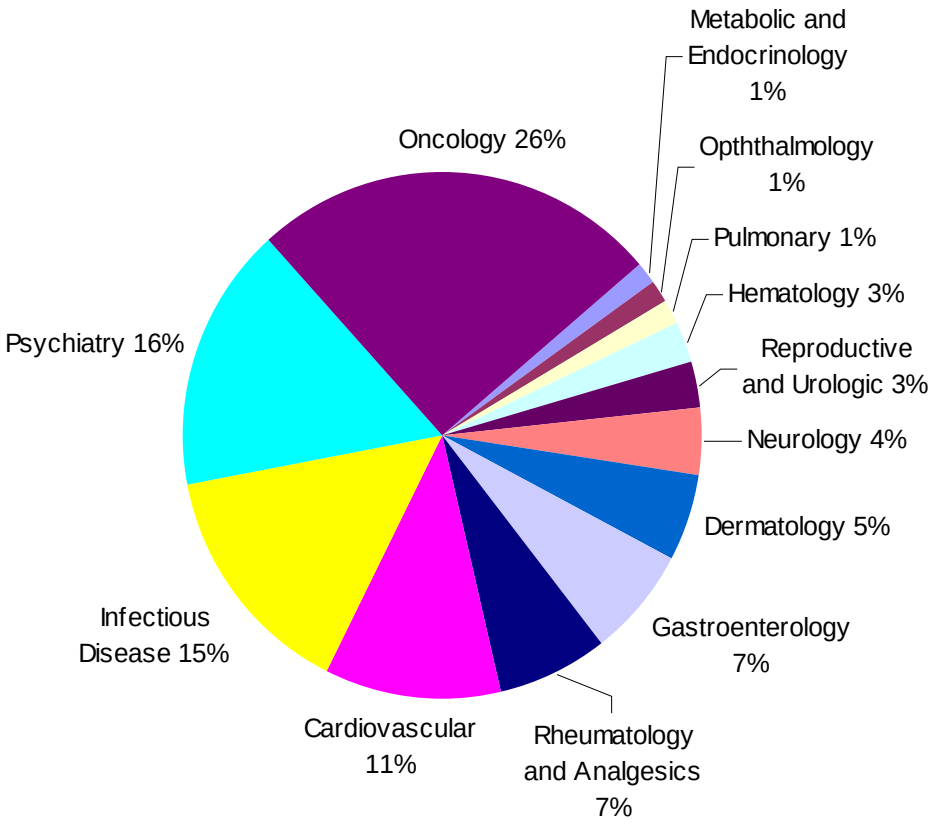
- Is a general plan for DNA collection (for exploratory studies) indicated based on the expected metabolic/PK, efficacy, and/or safety profile?
- Should any markers be tested in *all* subjects?
- Should any subjects be excluded based on the potential for high exposure/toxicity?
- Should only certain subjects be included to reduce noise?
- Are a sufficient number of studies planned to support retrospective analyses?
- Will a dedicated PG study be necessary before Phase 3 (for dose selection)? Approval?
- Are the analytical methods and SAP clearly described?

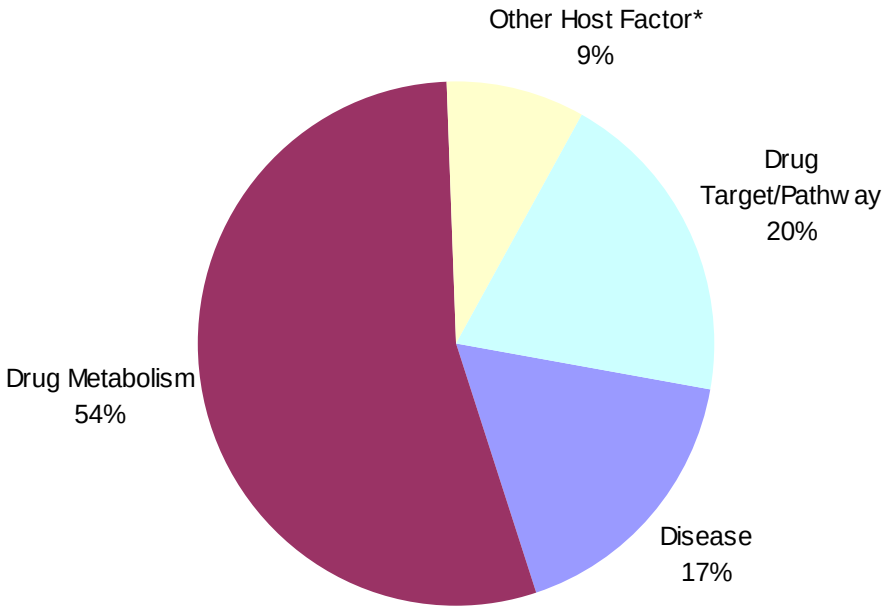
Enhancing Drug Development: Prospective Maneuvers



Zineh and Pacanowski 2011 [Pharmacotherapy]

PG in Drug Labels





Cancer, psychiatric, and infectious disease therapeutics make up more than half of the drugs with PG labeling

Most PG labeling is related to drug metabolism