Clarifying the Current Regulatory Position on the Validation and Standardization of Biomarkers for Approval and Ongoing Patient Care

Workshop:

Developing Robust Decision Criteria for the Development and Use of Biomarkers – Learning from Regulatory and Industry Experience To Date

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Overview

Theme:

How do we create the knowledge to make a decision whether or not a new biomarker is qualified for a specific use?

- Genomic biomarker information in drug labels
- Voluntary Data Submissions (VXDS)
- Drug-Test Co-Development
  - How to integrate biomarkers into clinical trial designs
- Conclusions

Defining how much we know

"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

Disclaimer: Unknown, non-valid biomarkers are not part of this presentation

“Known knowns”: information about biomarkers that made it into drug labels

- If a qualified biomarker exists (useful for a specific context of interest), we want to know what to do with the information once the biomarker status is known
- This information can
  - Be critical for prescribing the drug, or
  - Be useful to make a better treatment decision
- This information is conveyed in the dug label as tests that are
  - Required, or
  - Recommended
- In addition, there is biomarker information that is deemed important enough to be in the label, but no specific action is recommended (information only)

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 li… …harmacogenomic data, taking into account multiple regulatory contexts in which these biomarkers were approved. Most drug labels in this table provid… …with no immediate recommendation for a specific action (i.e. genetic testing); however a few labels recommend or require genetic testing thereby specif… …reaching a therapeutic decision.

The table includes:

- Context-specific biomarker (column 1)
- Reference drug label information about the bio… …ug was approved (column 2 subsection 1)
- Test criteria (column 2 subsection 2)
- Prototypic drug associat… …ing the biomarker context (column 2 subsection 3)
- Other drugs in…
- Pa…

…ntext 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 t… …under the right side of the drug name. All approved drugs in this table are linked to labels at Drugs@FDA 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.

The information provided in "label context" is taken from different sections of the actual drug labels.

The term "valid" biomarker has been defined in the "Guidance for Industry: Pharmacogenomic Data Submissions". Therein, a valid biomarker is described as a "biomarker that is measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results." The classification of biomarkers is context specific.

A critical aspect of many of these drugs is the role they play in drug-drug interactions. This list does not address drug-drug interactions. More information on drug-drug interactions, please see Drug Development and Drug Interactions.

Reference is made to the requirement of testing for the biomarker:
1 = test required;
2 = test recommended;
3 = information only

Biomarker	Label Context	Examples of other	References

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Biomarker	Label Context			Examples of other Drugs Associated with this Biomarker	References (PubMed ID)
	Representative 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 c-kit mutation." "Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)."	3	Imatinib mesylate		12851888 16226710 16294026
CYP2C19 Variants	**CYP2C19 Variants (Poor Metabolizers-PM and Extensive Metabolizers-EM) with genetic defect leads to change in drug exposure**. "*In vivo* studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCτ) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts."	3	Voriconazole	Omeprazole[m1] Pantoprazole [m2] Esomeprazole[m3] diazepam[m4] Nelfinavir[m5] Rabeprazole[m6]	12867215 11866669
CYP2C9 Variants	**CYP2C9 Variants PM and EM genotypes and drug exposure**; "Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance."	3	Celecoxib	Warfarin[m7]	16118328 15637526 15714076 15037866 14558433
CYP2D6 Variants	**CYP2D6 Variants** "Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs)."	3	Atomoxetine	Venlafaxine;[m8] Risperidone;[m9] Tiotropium bromide inhalation;[m10] Tamoxifen;[m11] Timolol Maleate;[m12]	
CYP2D6 with alternate Context	**CYP2D6 PM and EM Variants and drug exposure and risk**- "population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6. Fluoxetine, like other agents that are metabolized by P450IID6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by the P450IID6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks."	3	Fluoxetine HCL	Fluoxetine HCL and Olanzapine;[m13] Cevimeline hydrochloride[m14] Tolterodine;[m15] Terbinafine;[m16] Tramadol + Acetamophen [m17] Clozapine[m18] Aripiprazole;[m19] Metoprolol;[m20]	16472103 16384813; 15063083; 16271013 16236141 15828850 15492763 15037866 14639062 10431214 1302039

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)

Known Valid

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)

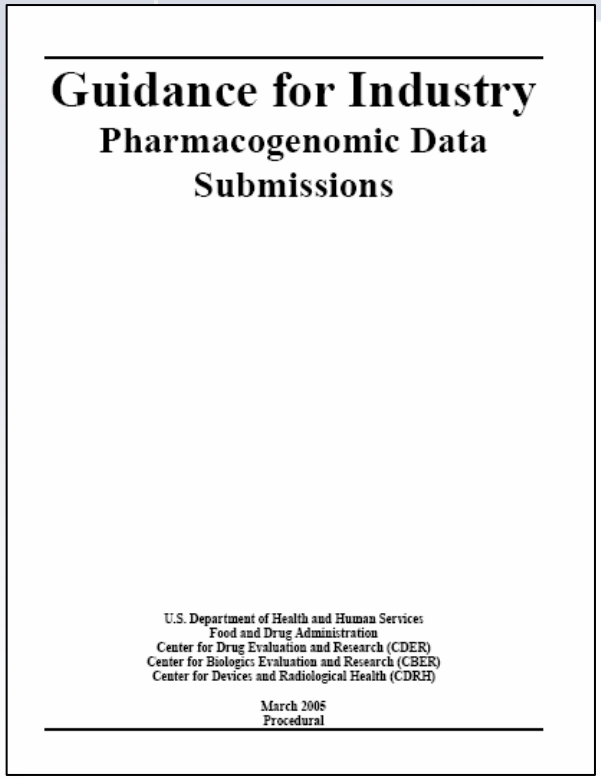
Known Valid

Probable Valid

Exploratory

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

The "Validity" of a Biomarker Has Regulatory Implications



Guidance for Industry

Pharmacogenomic Data Submissions

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

March 2005
Procedural

Submitting data to an:	IND	New (Unapproved) NDA, BLA, or Supplement	Previously Approved NDA or BLA
Known Valid Biomarker	Must be submitted, pursuant to 21 CFR 312.23 (a) (8), (9), (10) (iv) or (11).	Must be submitted, pursuant to 21 CFR 314.50 and 601.2. See section IV.B. of the guidance.	Must be submitted pursuant to 21 CFR 314.81 in annual report and should be submitted pursuant to § 601.12 as synopses or abbreviated reports.
Probable Valid Biomarker	Does not need to be submitted.[9] The FDA welcomes voluntary submission of such data in a VGDS.	The FDA recommends submission, using algorithm in section IV.B. of the guidance.	Must be submitted pursuant to 21 CFR 314.81 in annual report and should be submitted pursuant to § 601.12 as synopses or abbreviated reports.
Exploratory or Research Pharmaco-genomic Data	The FDA welcomes voluntary submission of such data in a VGDS.	The FDA recommends submission, using algorithm in section IV.B. of the guidance. The FDA welcomes voluntary submission of such data in a VGDS.	The FDA welcomes voluntary submission of such data in a VGDS.

VGDS: A Novel Data Submission Path

- "Safe harbor" idea for exchanging early stage or exploratory pharmacogenomic data that is *not ready for use in regulatory decision making* regardless if subject of an active IND, NDA, or BLA
- 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
- Intent to build expertise and foundation for developing scientifically sound regulatory policies
- VGDS creates a forum for scientific discussions with the FDA outside of regular review process
- Data not used for regulatory decisions

FDA's Voluntary Genomic Data Submission (VGDS) Program

- Two year anniversary – approx. 30 VGDS received
- Program respected in industry and FDA – meetings are well attended with high-level representation
- Increasing complexity of data submitted reflects comfort level of industry sharing this type of information with regulators
- Broad coverage of therapeutic areas and genomic topics
- Preclinical, clinical and Phase IV submissions
- Bilateral meetings with EMEA
- Program expanded to "**VXDS**" (X = exploratory) to include a broader variety of exploratory biomarkers, including proteomics, metabolomics, imaging, and other areas

VGDS Examples

- Candidate gene approach vs. whole genome SNP scan to identify efficacy biomarkers
- Gene expression profile in peripheral blood
- Gene expression pattern as genomic biomarker to predict responders and non-responders
- Use of registries to identify novel biomarkers
- Toxicogenomics approaches
- “Panomics” (genomics → proteomics → metabolomics)

VGDS Submission Types

- **Therapeutic Areas:**
  - Cancer (multiple types)
  - Alzheimer's Disease
  - Hypertension
  - Hypoglycemia
  - Depression
  - Obesity
  - Rheumatoid Arthritis

- **Scientific and PGx Areas:**
  - Biomarkers
  - Genotyping Devices
  - Microarrays
  - Analysis Software
  - Databases
  - Metabolic Pathways
  - Biostatistics
  - Enrichment design
  - Registry design
  - Toxicology

Data based on 25 submissions

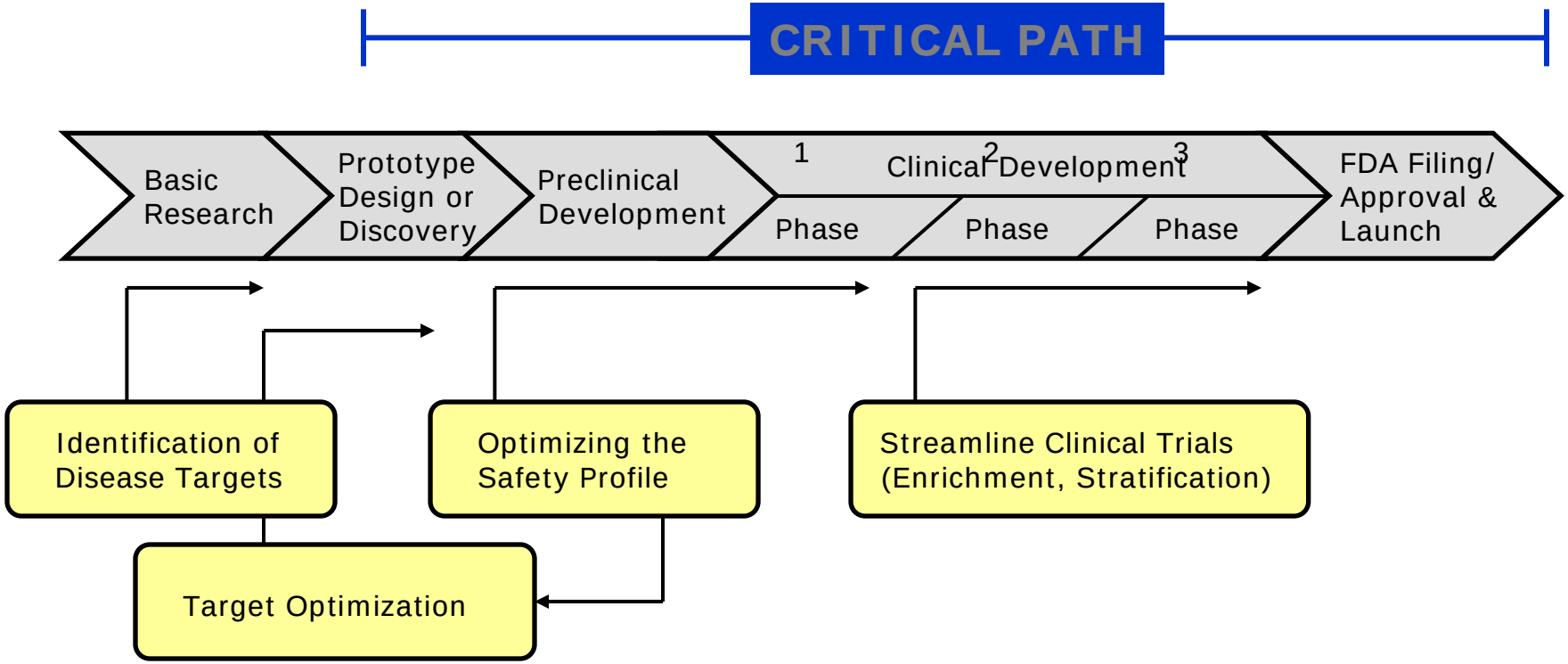
OK, but how do we get (*clinical* genomic) biomarkers qualified ?

- **3** key ingredients:
  - Good science
  - A business case
  - A supportive regulatory environment
- **2** options for qualifying a biomarker:
  - Wait long enough until we believe it
  - Don’t wait, but have a good strategy
- **1** such strategy is drug-test co-development
  - Question is how to do it

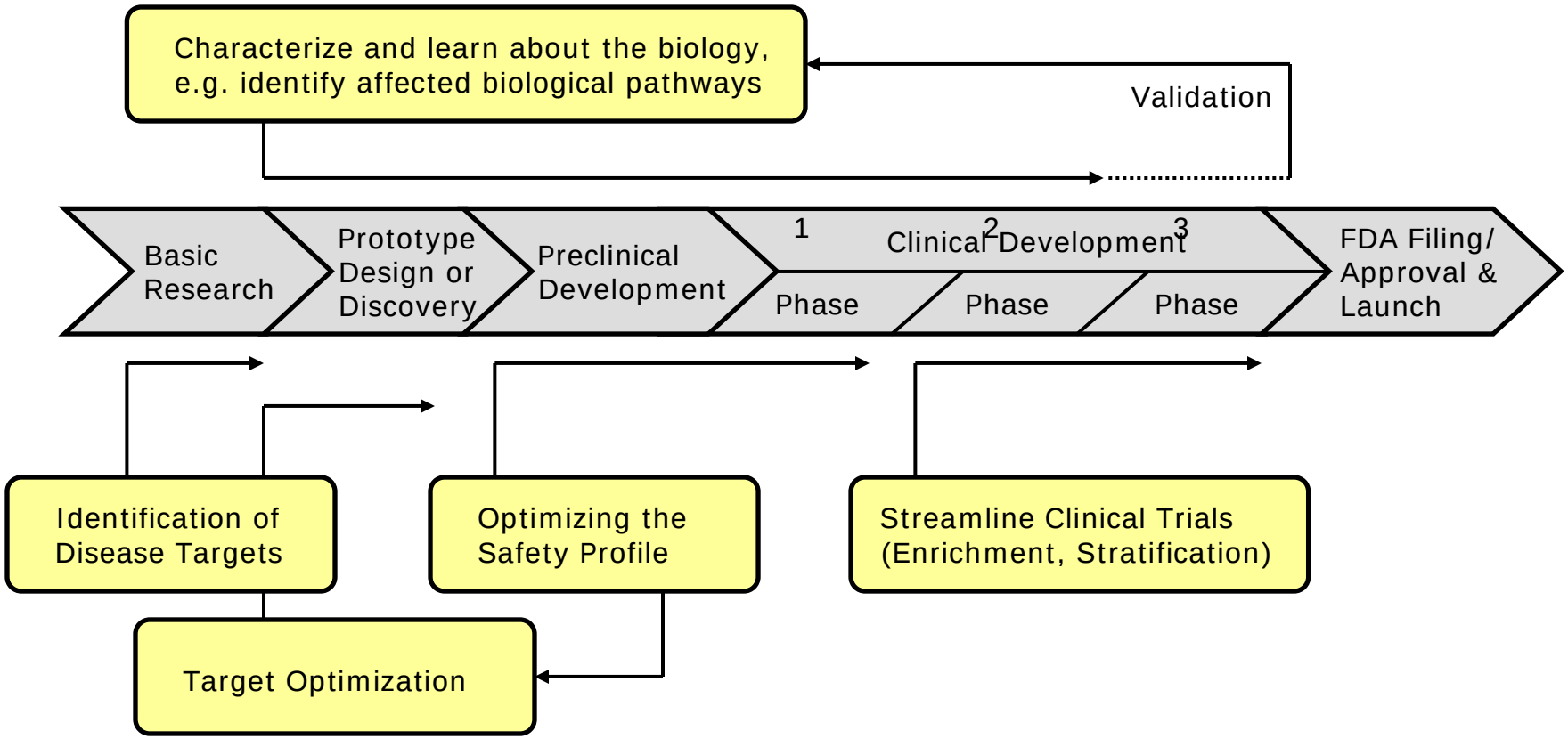
Drug-Test Co-Development: What is it ?

- 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

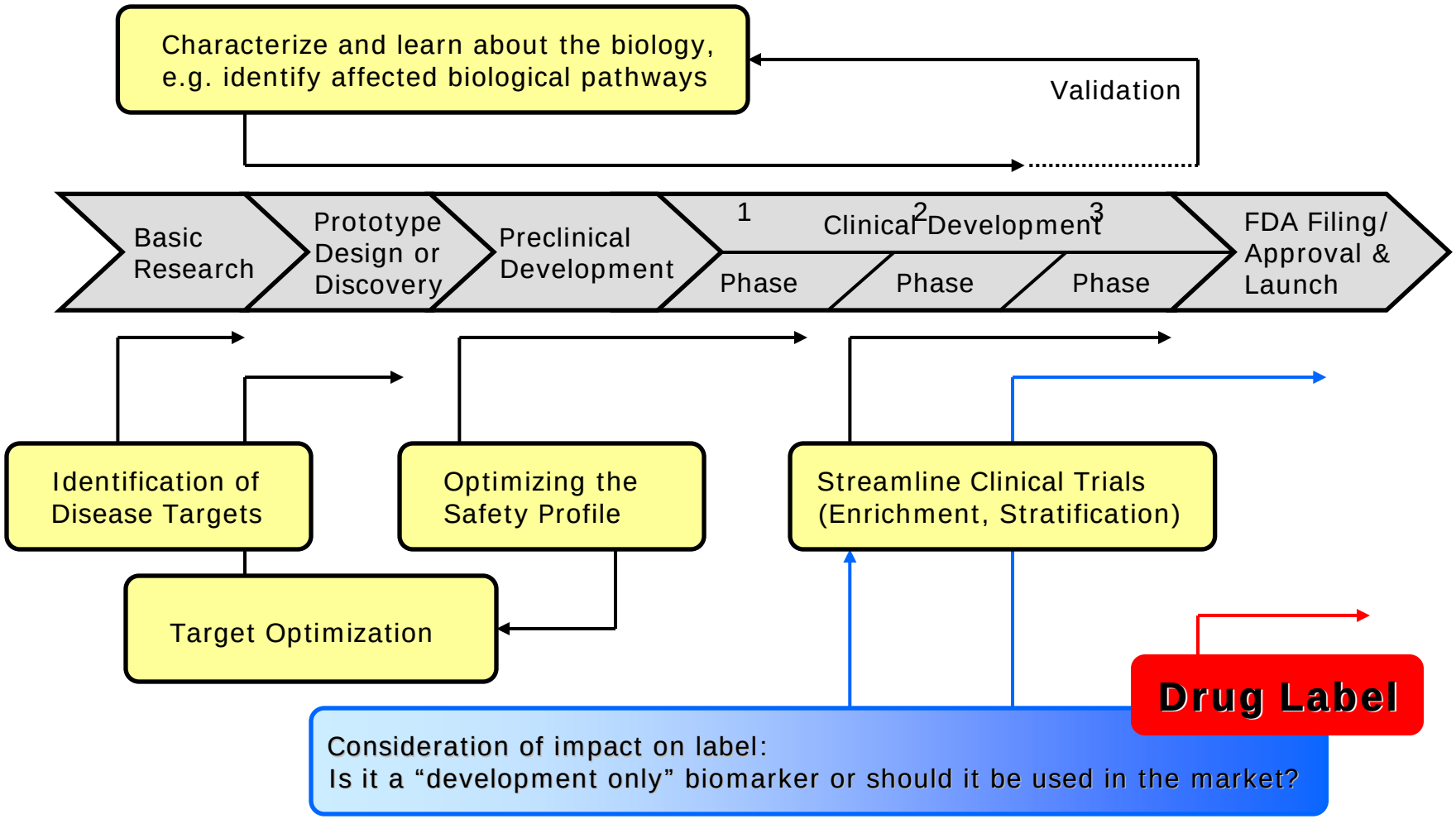
Use of (clinical) biomarkers during drug development



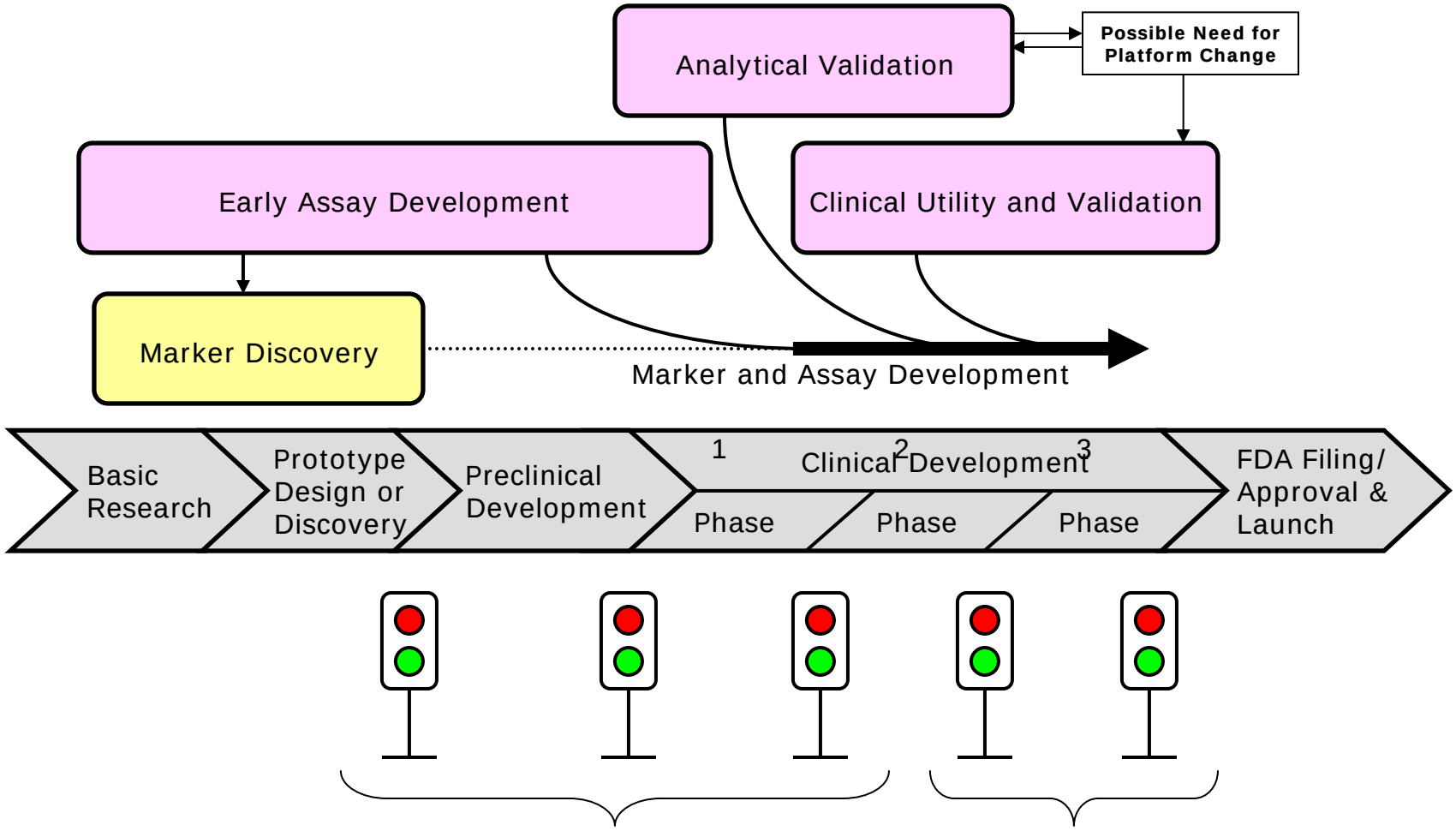
Qualification of Clinical Biomarkers



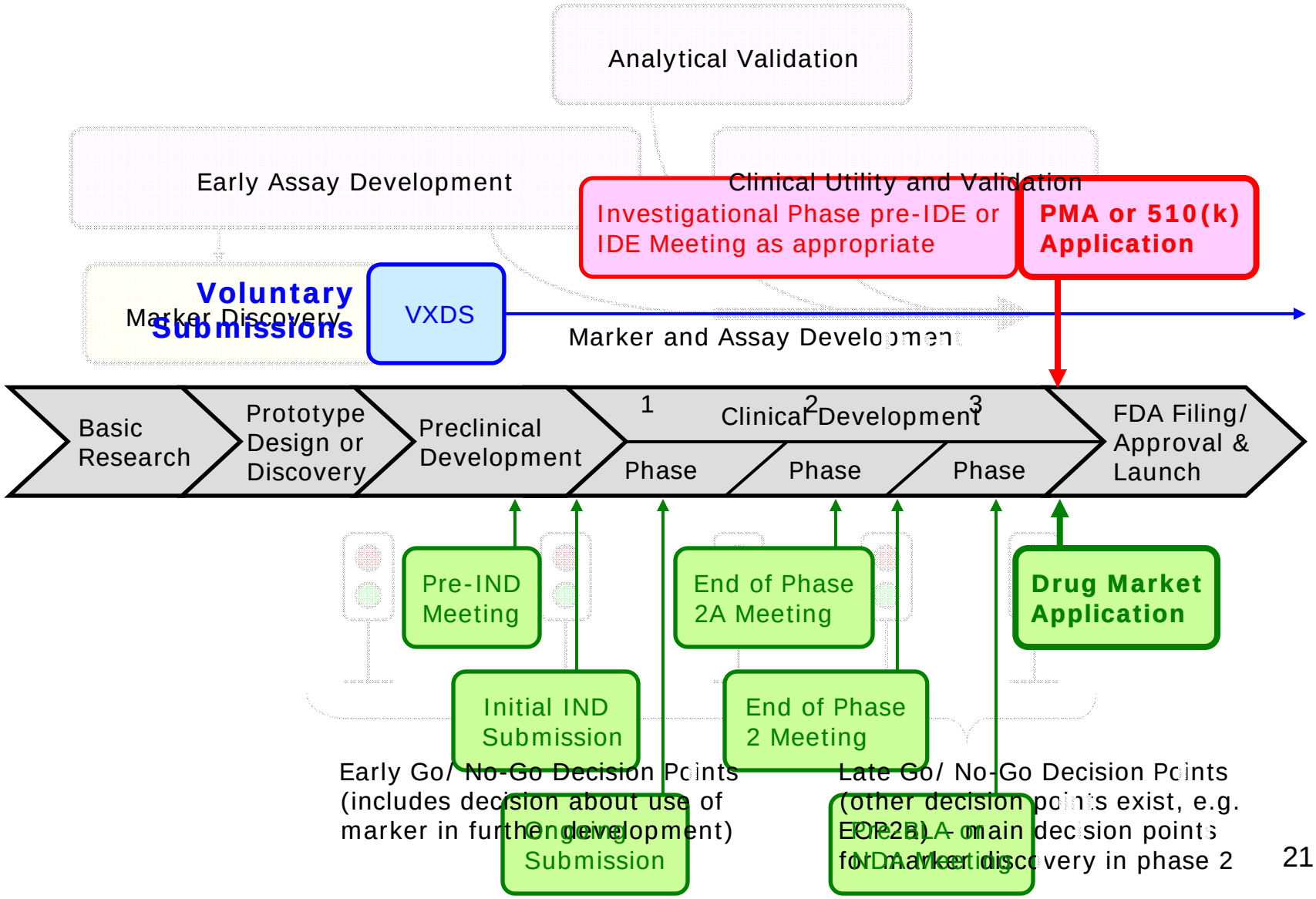
Impact of Biomarkers on Drug Label



Biomarker and assay development process



Sponsor – Regulator Interactions



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)
- New innovative (e.g. adaptive) clinical trial designs (**this is the clinical validation of the biomarker**) are needed

Key Questions and Decision Criteria About Biomarkers During Clinical Development

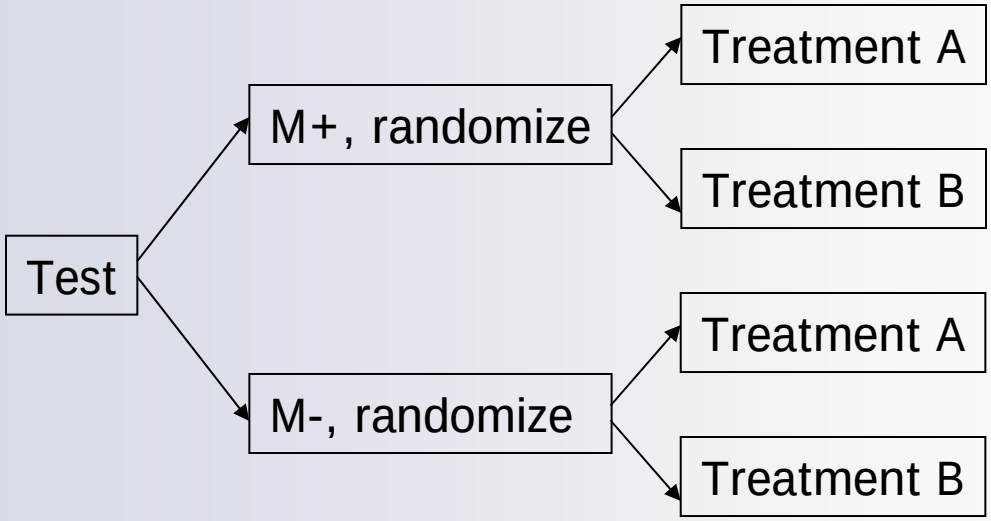
- What is the marker being used for?
  - Efficacy prediction or efficacy measurement
  - Safety
- Is it a prognostic (i.e. outcome related to disease, but not necessarily to drug therapy) or a predictive (i.e. outcome related to therapeutic intervention) marker and how does it, in either case, affect 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

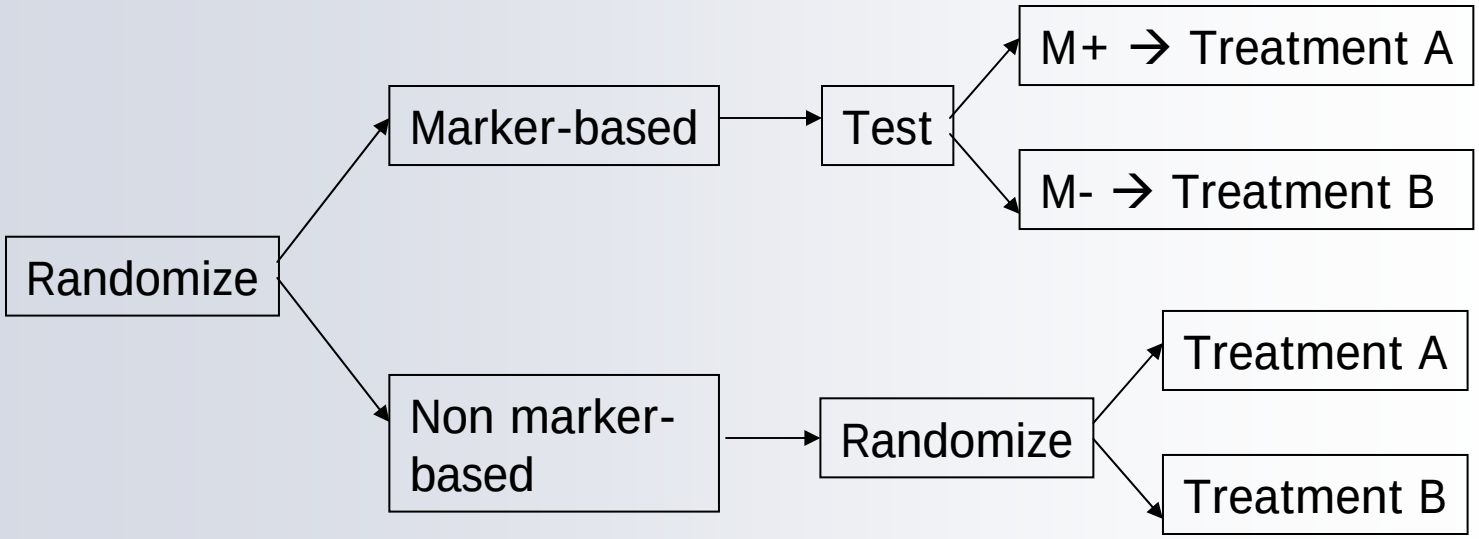
A. Upfront Stratification – Example

- Produces data on all patients
- Completely prospective



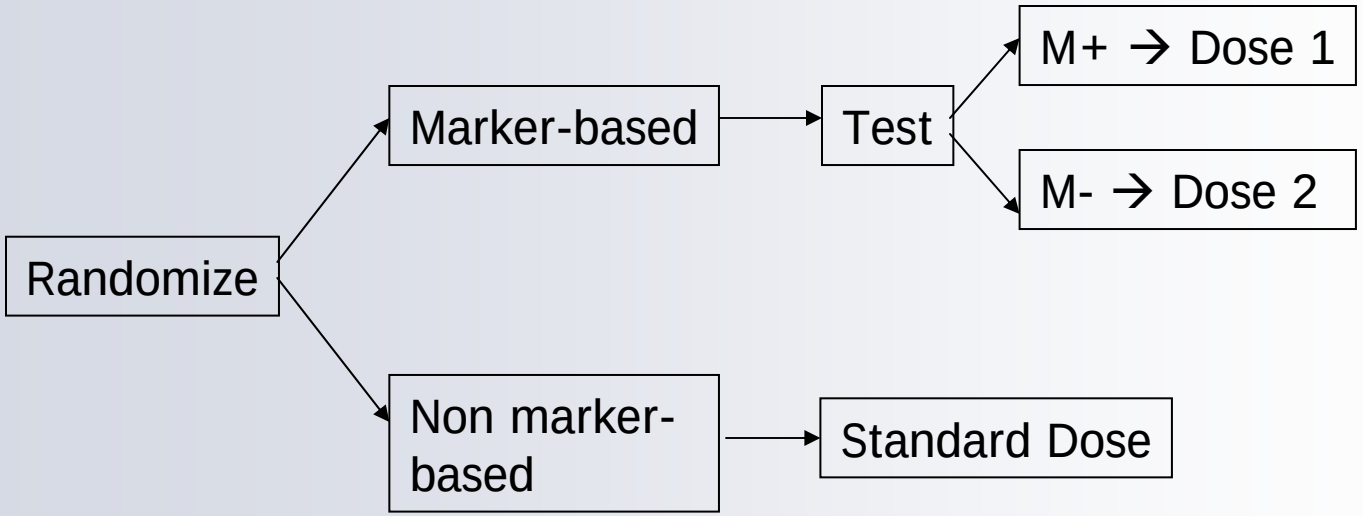
B. Biomarker-based Strategy – Example 1

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



B. Biomarker-based Strategy – Example 2

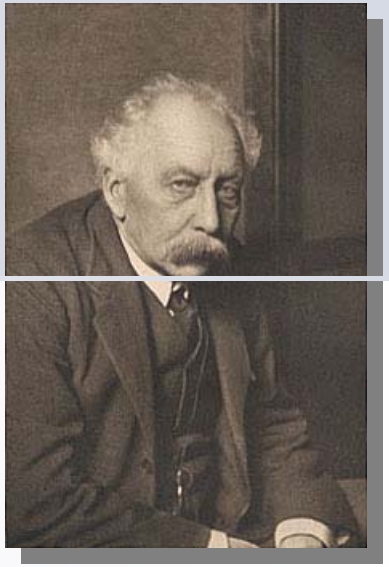
- May not produce data for all patients (although it can)
- Example 2: Dose selection



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

- 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 without having regulatory implications
- 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 – not expected to be easy
- It is also a process that challenges the regulatory system: new regulatory pathways and review processes are being established
- (All of this is far, far away from surrogacy, but that wasn't really the point here anyway)

100 years later …



“I expect a century must elapse before the […] complete union of science and practice will be achieved.”

- ***William Bateson*** at the **1906** Royal Horticultural Society conference, at which he suggested for consideration…:

“…the term *Genetics*, which sufficiently indicates that our labours are devoted to the elucidation of the phenomena of heredity and variation […]”

www.fda.gov/cder/genomics

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