Qualification of Genomic Biomarkers for Regulatory Decision Making

Session 4

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- The views expressed in this presentation are the ones of the author and may not necessarily reflect the position of the U.S. Food and Drug Administration.

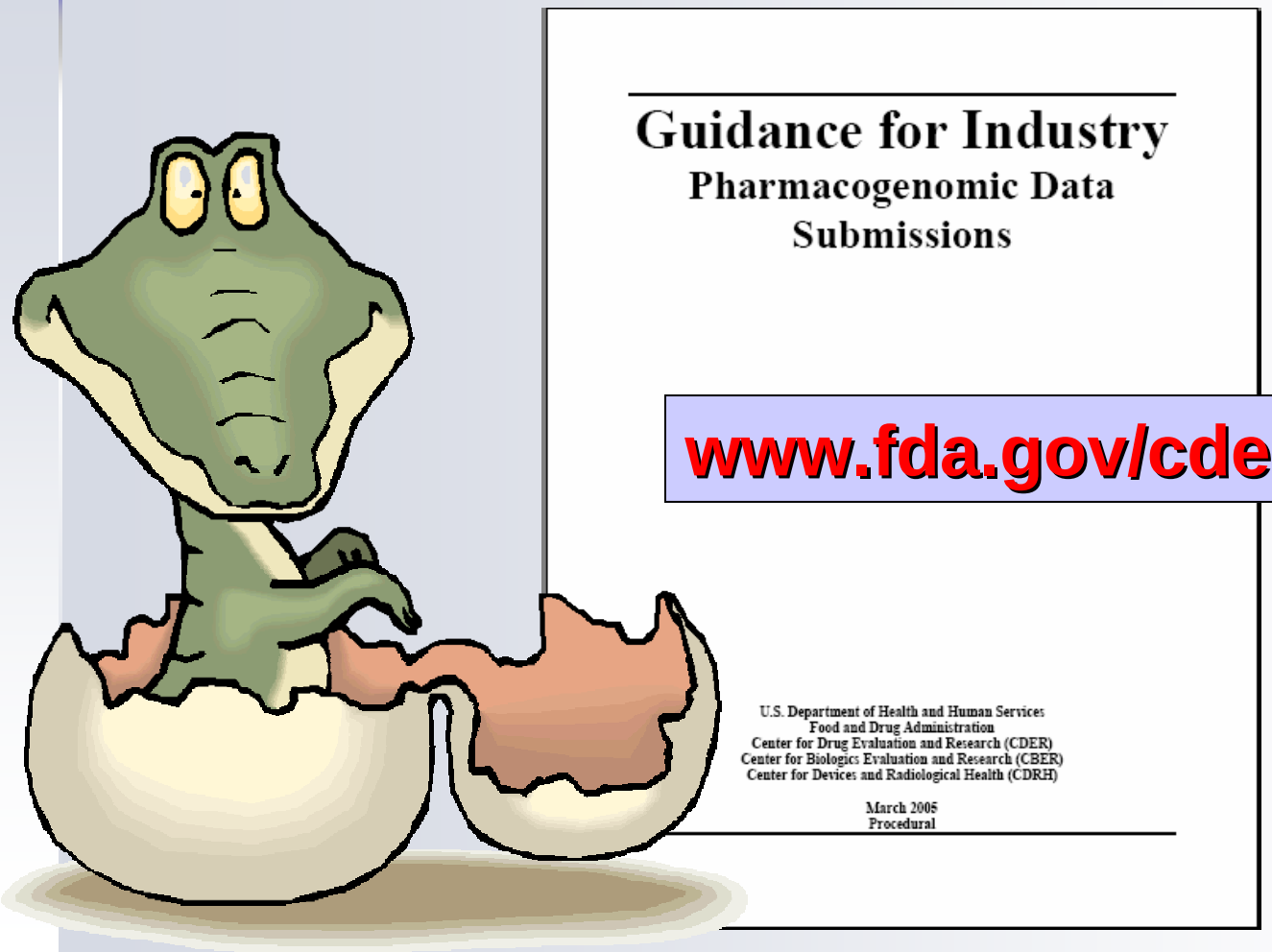
Outline

- Regulatory framework
- Biomarker categories
- Biomarker qualification
- Voluntary genomic data submission program at FDA
- Summary

Framework for Use of Genomic Biomarkers in Regulatory Decision Making in the U.S.

- 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
- Implementation procedures for guidances (MaPPs)
- Actual review infrastructure
  - Interdisciplinary Pharmacogenomic Review Group
  - Clinical Review Divisions
  - Voluntary Genomic Data Submissions
  - Hardware, software, databases

Guidance for Industry: Pharmacogenomic Data Submissions



www.fda.gov/cder/genomics

March 22, 2005

What Does the PG Guidance Do?

- Introduces a classification for genomic biomarkers
- Clarifies what type of genomic data needs to be submitted to the FDA and when
- Introduces a new data submission pathway to share information with the FDA on a voluntary basis
- Encourages the voluntary submission of exploratory genomic data
- Introduces new agency-wide PG review group (IPRG)
- Clarifies how the FDA will review genomic data submissions

What Does the PG Guidance *Not* Do?

- Does not provide information on how to validate genomic biomarkers
- Does not provide information on how to use genomic biomarker during drug or device development process (scientific vs. regulatory guidance)
- Does not expand into other "-omics' areas such as proteomics or metabolomics
- Does not equal genomic data with voluntary data
- Does not create new processes for the review of required data submissions

Classification of 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 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

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)

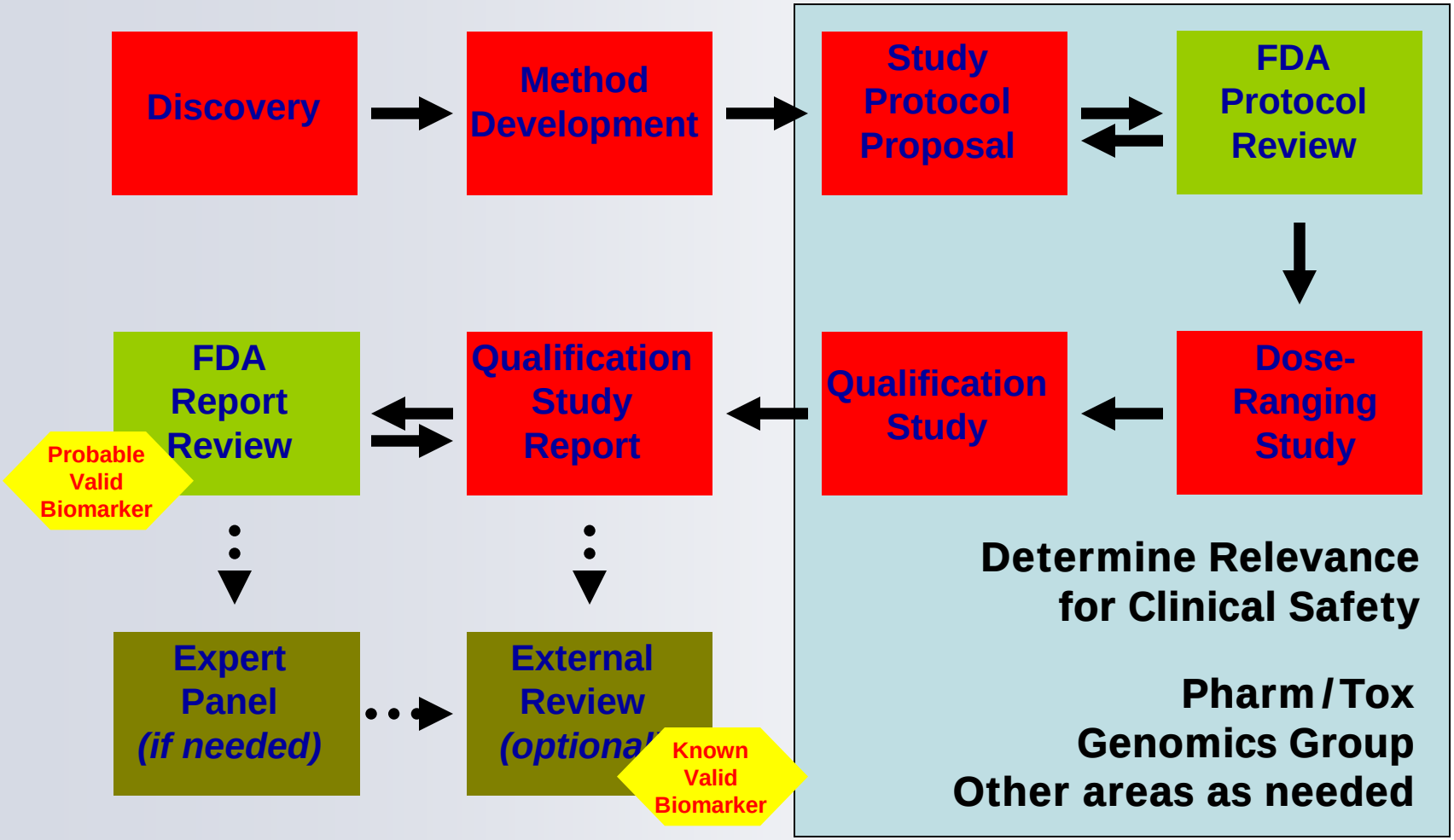
Known Valid
Probable Valid
Exploratory

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

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

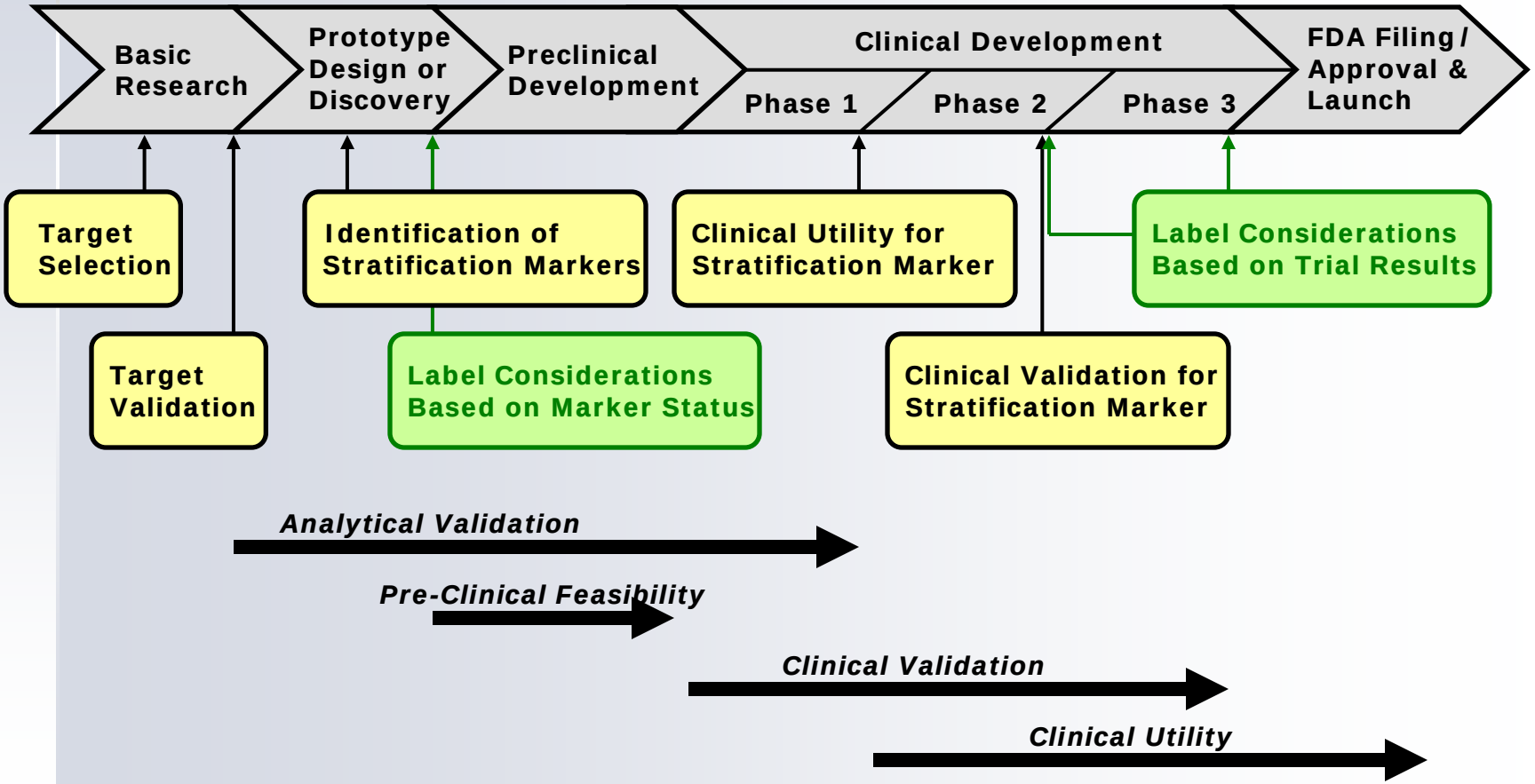
Proposed Biomarker Validation in *Preclinical* Drug Safety Assessment



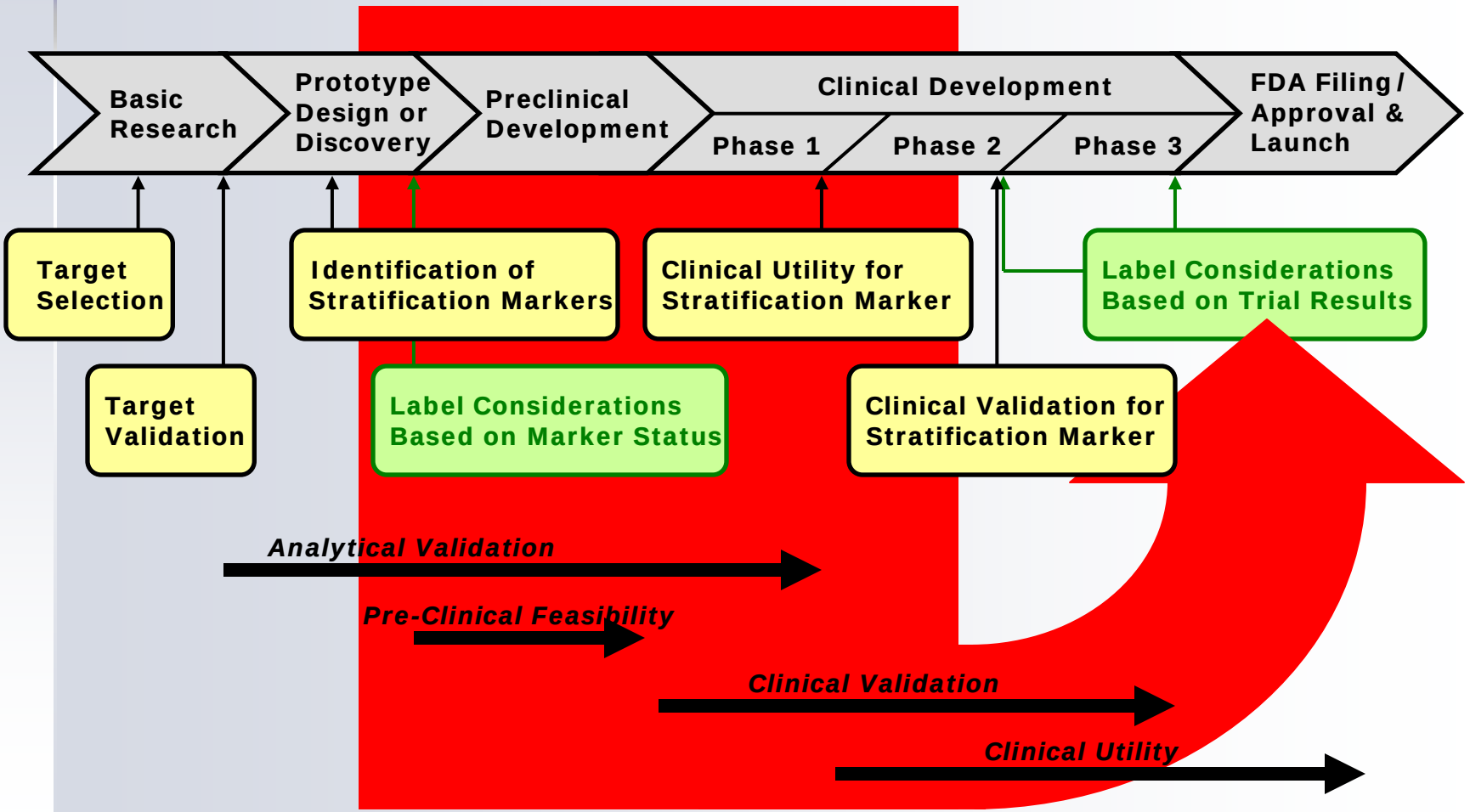
Why Validation is Needed: Issues around *Preclinical* Biomarkers

- Toxicogenomic markers need to be characterized (validated) rigorously in the context of safety and toxicity:
  - In the context of toxicity, we want to avoid excluding potentially good drug candidates (issue of false positives).
  - In the context of safety, we want to confirm that the absence of a signal corresponds to a safe compound (issue of false negatives).
- Therefore, key questions to address include:
  - Which toxic compounds should be tested?
  - Which controls should be used?
  - How many toxic and control compounds should be included?
  - Which dose (range) should be tested?
  - Which time points should be chosen?
  - How many replicates are needed?
  - Which genes should be included?

Development of Biomarkers for *Clinical* Use (Drug-Test Co-Development)



Strategic Considerations for *Clinical* Biomarker Development



(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** PG data submission 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

VGDS Typical Questions

- Statistical approach feasible?
- Which SNPs 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?

Drivers to Accept a VGDS

- 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
- Follow-on submissions
- Biomarker discovery and qualification, e.g., use of repositories, biobanks

VGDS: Limitations

- Not a regulatory decision tool
- Not a standard submission: individual considerations
- Amount of data submitted
- Involvement of Clinical Review Division (priority)
- It's voluntary: we may not see all there is to see

VGDS Program at FDA so far

- **VGDS statistics:**
  - 25 submissions received
  - 15 sponsor meetings held (2 bilateral with EMEA)
- **Impact:**
  - Strategic use of VGDS meetings
  - New policy development, best practices
  - Education
  - New pathway for communication
- **Success Measures:**
  - Overall feedback: 4.5 out of 5 (formal survey)
  - Multiple (and follow-on) submissions from single sponsor

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

VGDS: Value and Benefits

- Sponsor:
  - Opportunity to have informal, scientific meeting with FDA PG experts
  - Eliminate uncertainty about PG data submissions and review at FDA
  - May assist in reaching strategic decisions
  - Receive and benefit from informal peer-review feedback on PG issues and/or questions
  - Gain insight into current FDA thinking about PG
  - May avoid future delays in review
- FDA:
  - Familiarize with PG experiments, data analysis and interpretation approaches
  - Education
  - Ensure data driven development of new policies and guidances
  - Build consensus around PG standards
- Both:
  - New strategies for using PG in drug development
  - Learn about benefits and limitations
  - Discuss analysis approaches

VGDS Goes Global

- So far, 2 meetings held
- Videoconference, presentations from both locations
- What we learned:
  - FDA and EMEA evaluated, with only minor differences, the submission similarly, no dispute over science
  - Pre-meeting dialogue between FDA and EMEA resulted in better review product
  - Both agencies adjusted their usual format to accommodate the requirements necessary for a joint event

- **Guiding Principles Document** between FDA and EMEA for bilateral VGDS has been developed – available at **www.fda.gov/cder/genomics (after March 13)**

Aspects of Joint Meetings

- Global science
- Local regulations
- Unique opportunity for consensus building and step towards harmonization
- Educational

- Complex in planning and setup
- Time difference
- Presentations and interaction via videoconference
- No longer “informal”

Summary

- Evolving regulatory framework to promote pharmacogenomics in drug development
- The use and characterization of (genomic) biomarkers is key (and we need tools to use them...: Session 5)
- Strategies / paths for biomarker validation are needed
- Industry participation (e.g. VGDS program, collaborative research, consortia, etc) supportive of regulatory initiatives
- International scope of pharmacogenomics
- THE GLASS IS HALF FULL !

Acknowledgements

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