Toxicogenomic Data Submissions: Regulatory Considerations

The Toxicology Forum:
30th Annual Winter Meeting

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Overview

- Why FDA is Getting Involved
- FDA's Critical Path and Toxicogenomics
- Pharmacogenomics Guidance
- Voluntary Genomic Data Submissions
- Genomic Biomarkers
- Means to an End – FDA Research Projects
- Conclusions

Key Message

- Toxicogenomics has the potential to be used as key decision tool in drug development and review.
- The question is, how do we get all the pieces in place.
- The field is too complex for a single stakeholder to conquer.
- This has led to the development of new paradigms in research-, development- and review-practices.
- This is good.

Why Does FDA Get *Actively* Involved ?

"Today, as never before, we face a tremendous potential for new medicines to prevent and cure diseases, but fewer new products are actually reaching the FDA. With so much promising technology in development in the clinical labs … we need to turn the process of bringing these technologies to patients from a costly and time-consuming art form to a well-understood science."

Dr. Mark McClellan
Former FDA Commissioner
March 16, 2004

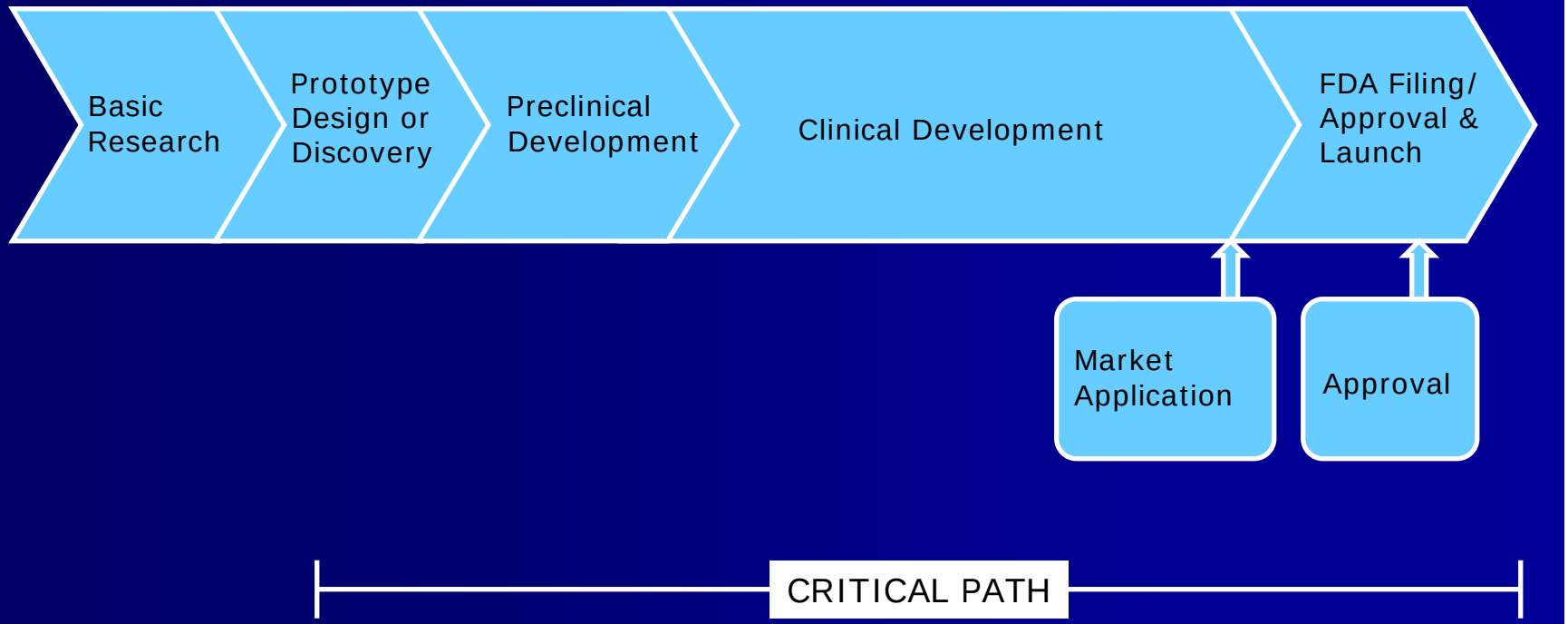
FDA's Mission to Facilitate Drug Development

- FDA's mission is to protect and advance public health …
- … by helping to speed innovations that make medicines and foods more effective, safer and more affordable.
- This mission is reflected in the **Critical Path** Initiative

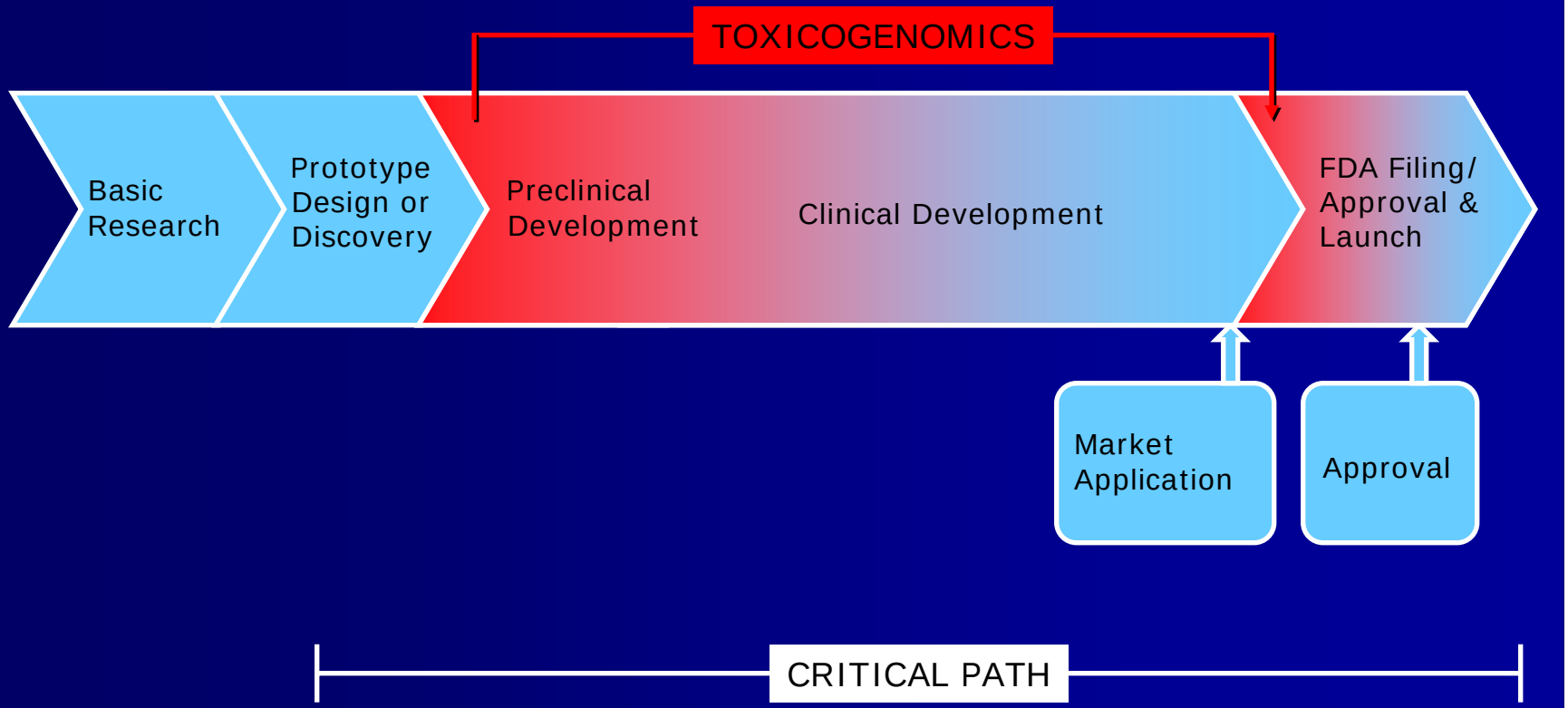
Stagnation → Innovation

- The Critical Path white paper lists opportunities on the "critical path" to new medical products
- Toxicogenomics is identified as a key opportunity
- *CP, Opportunity #1:*
  "Proteomic and toxicogenomic approaches may ultimately provide sensitive and predictive safety assessment techniques…"

Stagnation → Innovation



Stagnation → Innovation



Toxicogenomics

- **Definition:**

  Study of drug-related safety / toxicity and pathology at the gene expression level in preclinical studies

  Combination of toxicological sciences with gene expression analysis

- **Rationale:**

  Gene expression changes occur early and are direct consequences of drug treatment

- **Goals:**

  Deeper mechanistic understanding of toxicity / pharmacology at the molecular level

  Discovery, identification and qualification of predictive markers of toxicity (i.e. gene signatures)

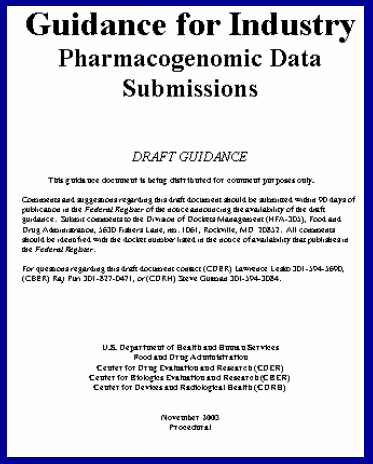
  Use of predictive markers to rank, select, and evaluate compounds early in development

Toxicogenomics: The Promise To...

- Reduce the time and resources needed to screen new therapeutic candidates,
- Improve the process of lead candidate selection in drug discovery,
- Reduce the “bottleneck” phenomenon prevalent in preclinical drug safety evaluation,
- Reduce the amount of test compound for testing,
- Provide insights into mechanisms of toxic lesion development useful for troubleshooting drug safety problems,
- Predict toxicity earlier.

Regulatory Framework: Growing Genomics Guidance Family

- ***FDA Critical Path White Paper (March 2004)***
  - *http://www.fda.gov/oc/initiatives/criticalpath/*
  - *Pharmacogenomics identified as a key critical path opportunity*
- **Pharmacogenomic Data Submissions (Draft, 2003)**
  - http://www.fda.gov/cder/guidance/5900dft.pdf
- **Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns (Draft, 2003)**
  - www.fda.gov/cdrh/oivd/guidance/1210.html
- **Drug/Test Co-development Guidance (in development)**
  - CDER, CBER, CDRH
  - Draft early 2005
- ***EPA White Paper on "Potential Implications of Genomics for Regulatory and Risk Assessment Applications at EPA" (December 2004)***
  - http://www.epa.gov/osa/pdfs/EPA%20Genomics%20White%20Paper.pdf



Guidance for Industry

Pharmacogenomic Data Submissions

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Lawrence Lesko 301-594-5600, (CBER) Raj Puri 301-827-0471, or (CDRH) Steve Gutman 301-594-3084.

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)

November 2003
Procedural

Yes, it will be out !

Three Documents Pertinent to PG Guidance

- Guidance on PG Data Submissions
  - Appendix with examples/scenarios
- Charter for the IPRG
- MAPP for the VGDS Process

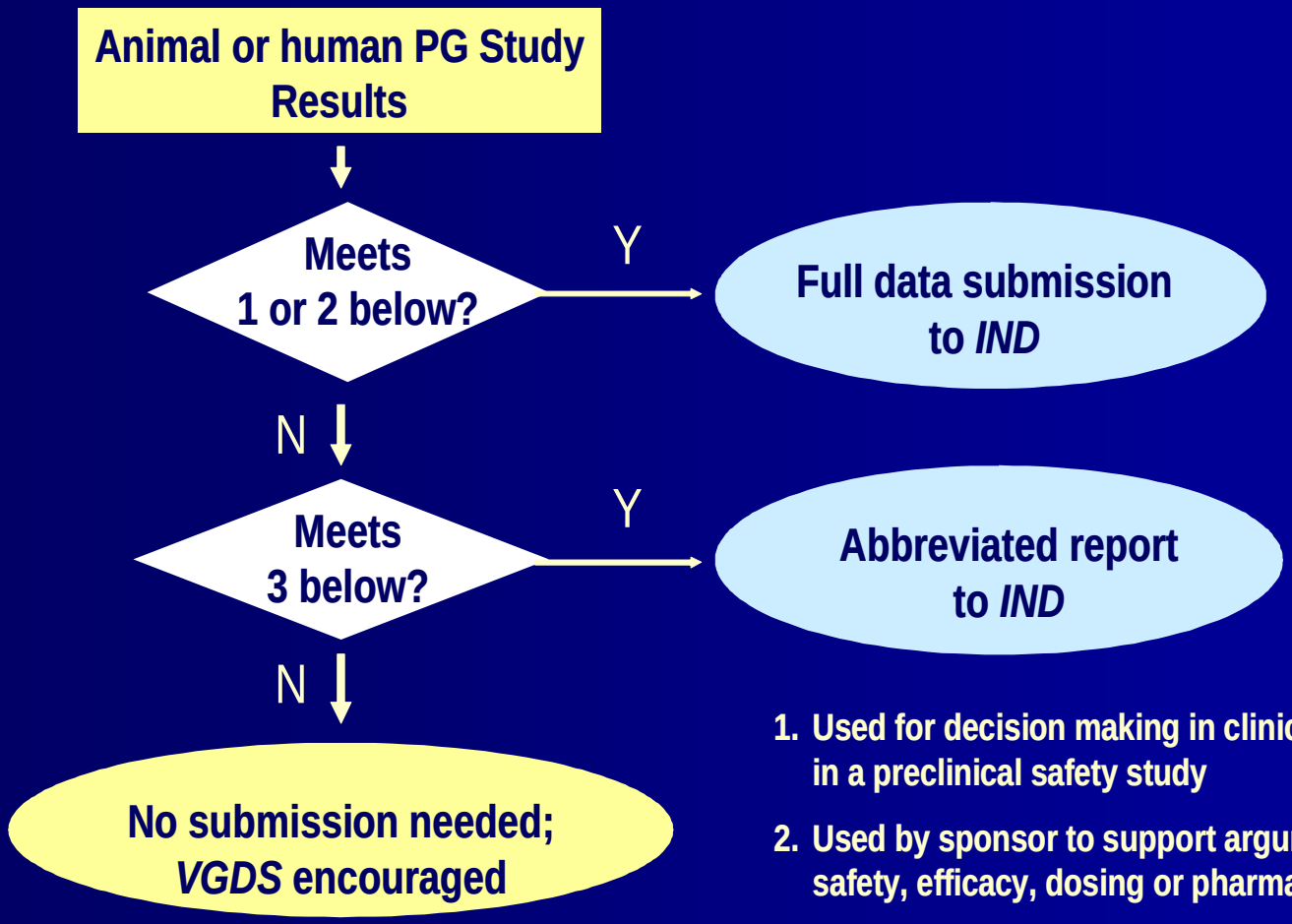
A special FDA website is being created. These documents will be available publicly on this site along with other useful information and any special forms.

FDA Guidance for Industry: Pharmacogenomic Data Submissions

- Provides recommendations on:
  - What PG data to submit
  - The format of submissions
- Explains:
  - Submission process
  - How the data will be used in regulatory decision making

- The guidance is intended to facilitate scientific progress in the area of pharmacogenomics.

Example: Submission of Data to an IND



1. Used for decision making in clinical trial or in a preclinical safety study
2. Used by sponsor to support arguments on safety, efficacy, dosing or pharmacology
3. Is a ***known valid biomarker***

(Changes in the Guidance)
Decision Trees in Appendices

- Submission to an IND (Appendix A)
- Submission to an new NDA/BLA/Supplement (Appendix B)
- Submission to an approved NDA/BLA/Supplement (Appendix C)
- **All are unchanged**

Incentives to Submit a VGDS

- Provides opportunity to have informal meeting with FDA PG experts
  - receive and benefit from informal peer-review feedback on PG issues and/or questions
  - gain insight into current FDA thinking about PG that may assist in reach strategic decisions
  - familiarize FDA with PG experiments, data analysis and interpretation approaches
- Pave the way for time- and cost-savings by familiarizing FDA with PG and avoiding future delays in review
- Impact FDA thinking and help build consensus around PG standards, policies and guidances

More to VGDS than Genomics

- Create a generalized pathway for accelerating development of new technologies
  - Proteomics, metabolomics, non-genomic biomarkers including imaging
- New biomarkers can lead to tests that facilitate development of new therapeutics
  - Prognostic (protein signatures), diagnostic (cellular biochemistry), selective (enrichment) and predictive (responder subsets)

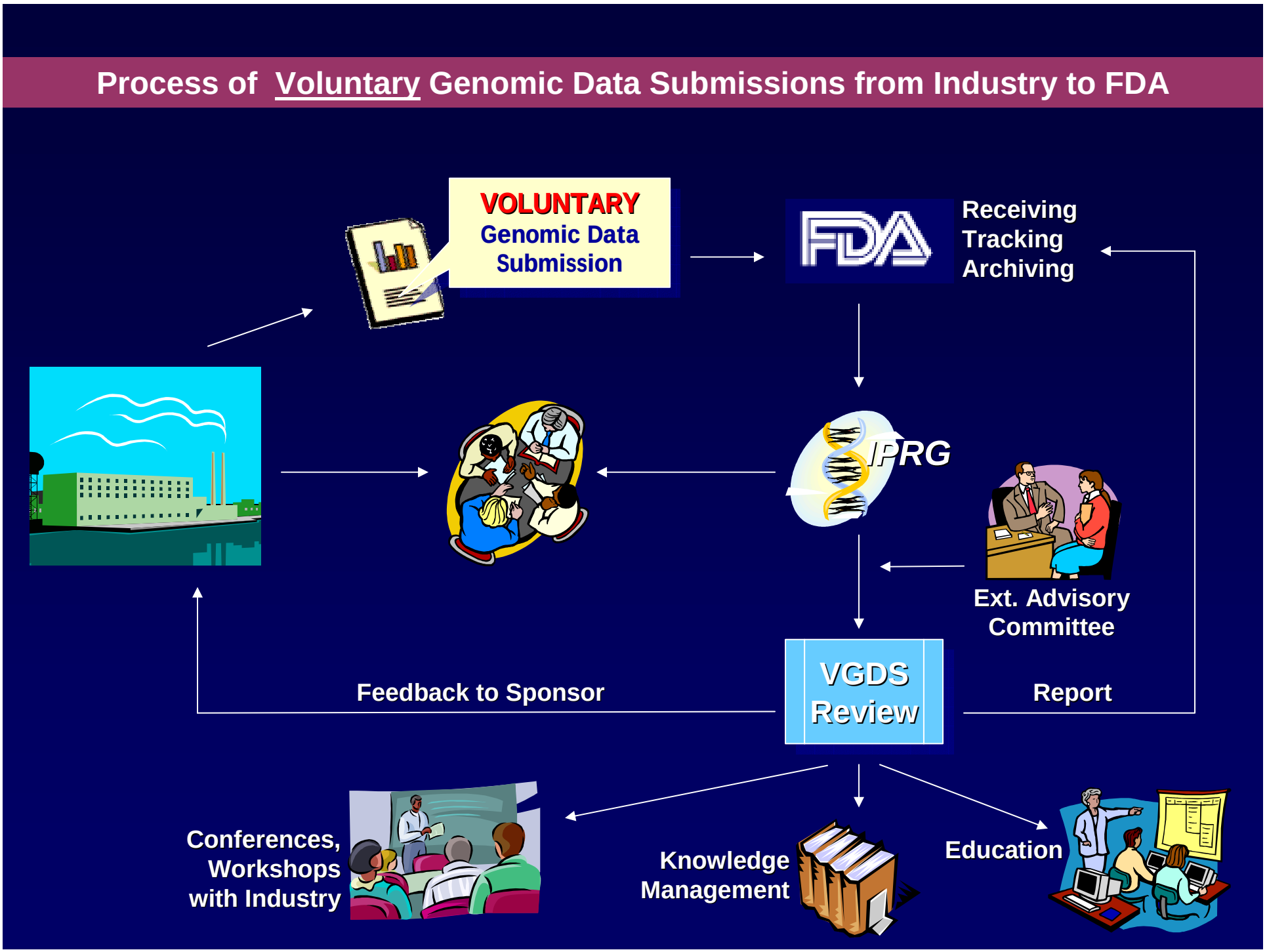
Regulatory Use of (Toxico)Genomic Data

- **May 2001: "Is this useful?"**
  ~ Industry uncertain how FDA will treat PG data
  ~ No regulatory framework available
  - How does a regulator treat data that cannot be interpreted?
  - How does a regulator treat data that some are anxious to report and other to withhold?
  - What data to submit?
  - How does submission of genomic data affect outcome of approval?
- **Today: "*How* is this useful?"**
  ~ Series of FDA-Industry workshops
  ~ PG guidance
  ~ VGDS experience
  - May 2002, November 2003, July 2004 and April 2005
  - Fostered dialogue, led to publications and to guidance for industry

A Novel Data Submission Path: Voluntary Genomic Data Submission (VGDS)

- Submission of exploratory PG data on (candidate) drugs whether or not the drugs are currently the 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
- According to the regulations, sponsors are not required to submit these data to their INDs or NDAs; however, the VGDS process is to provide the FDA access to emerging pharmacogenomic data so that a foundation can be built for developing scientifically sound regulatory policies.
- The VGDS process provides a forum for scientific discussions with the FDA outside of the application review process.
- **This includes Toxicogenomics !**

Process of Voluntary Genomic Data Submissions from Industry to FDA



A New Review Group: Interdisciplinary PG Review Group (IPRG)

- FDA-wide group (CBER, CDER, CDRH, CVM, NCTR)
- Reviews VGDS for questions and issues related to science, standards, policies and providing general guidance
- Consults for review divisions in genomic related questions
- Provides advice to industry (VGDS and non-volutary GDS)
- Creates a data repository to identify gaps in knowledge, e.g., validation, analytic methods, study design
- Presents educational/professional development courses within FDA and organizes public workshops

Examples of VGDSs

- Candidate gene approach vs. whole genome SNP scan
  - Statistical approach feasible?
  - Which SNPs to take forward?
  - Mechanistic explanation?
- Gene expression profile in peripheral blood
  - Can expression profile be obtained?
  - Is it predictable?
- Gene expression pattern as genomic biomarker to predict responders and non-responders
  - Hypothesis vs. validation
  - Statistics
  - Clinical utility

Experience with VGDS

- **Submission:**
  Summary of studies, goals, data, analytic issues and questions
- **Sponsor – IPRG Meeting:**
  Informal, free exchange of ideas, partial answers to questions
  - "qualification" of genomic biomarkers, potential pathways of diagnostic/test development, alternative predictive models, performance criteria of diagnostics, statistical dilemmas (replication, subsets, multiple test corrections)
- **Follow-Up:**
  Meeting minutes, evaluation of benefits of meeting, ways to improve, what could have been done better

VGDS Feedback

"Our thanks to you and the rest of the Interdisciplinary Pharmacogenomics Review Group for meeting with us. The meeting was quite useful for us. We are proceeding with the study and the VGDS being careful to acknowledge the limitations."

"Thanks for a very productive meeting - I got a lot of positive feedback, even from folks who were not there which means the attendees were indeed happy and felt both [company] and FDA scientists benefited. We need to work on the follow up and use this a case example for our workshop."

"As we proceed with our activities, we fully intend to continue our most productive dialogue."

Biomarkers (Definitions PG draft Guidance)

- Known valid biomarker: *"A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results."*

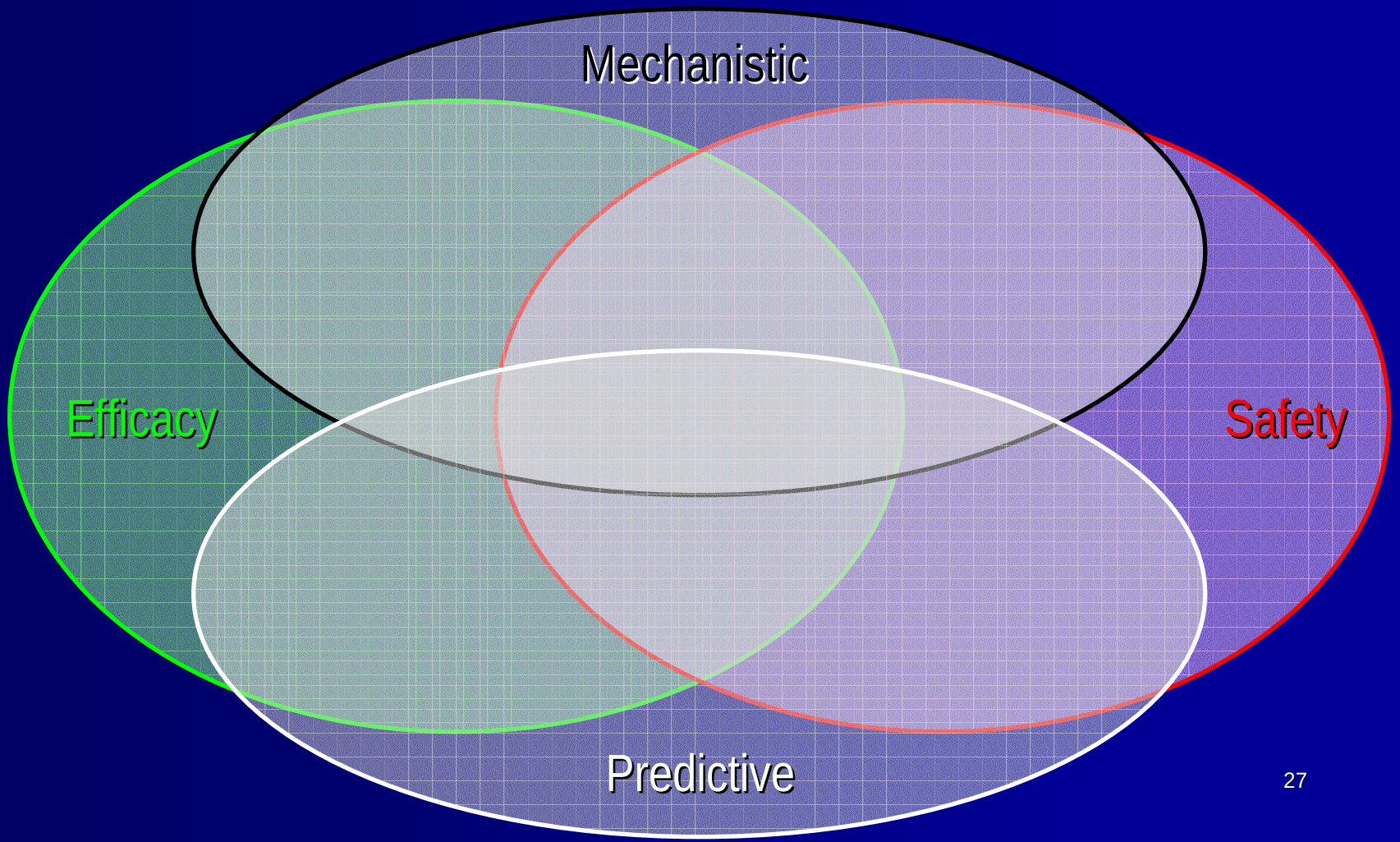
- Probable valid biomarker: "*[…] scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.*"
  - The data elucidating its significance may have been generated within a single company and may not be available for public scientific scrutiny.
  - The data elucidating its significance, although highly suggestive, may not be conclusive.
  - Independent verification of the results may not have occurred.

Changes in the Guidance: Glossary – Definition of Valid Biomarkers

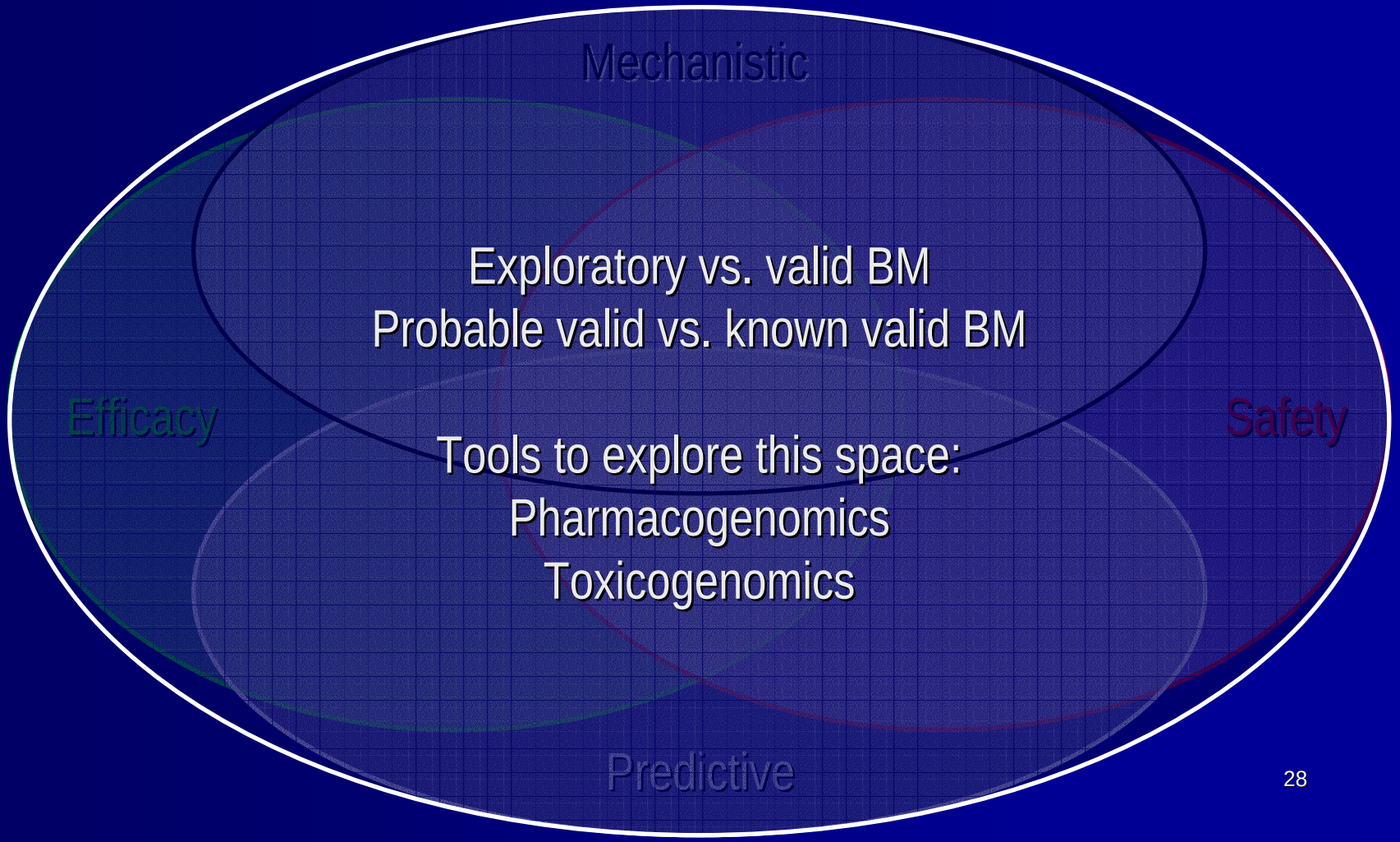
- Change: Expanded definition with the following addition

"The classification of biomarkers is context-specific. The degree of validity will change depending on the specific application. The clinical utility and use of epidemiology and/or population data are examples of approaches that may be used to determine the specific context."

Genomic Biomarkers



Genomic Biomarkers



Issues

- **Biomarker Qualification / Acceptance**

  E.g., mechanistic vs. “predictive” biomarkers = low vs. high bar for qualification?

- **Sensitivity**

  Genomics vs. phenotype = high vs. low sensitivity

  (But is it meaningful ? E.g., has DOSE been studied?)

- **Exposure**

  Genomics vs. phenotype = early vs. late prediction

  (But is it meaningful? E.g., has TIME been studied?)

- **Species Differences**

  Extrapolation from animal studies to humans

  (What if humans have phenotype, but animals don’t or vice versa ?)

More Issues

- **Data Standardization**

  Health Level Seven (HL-7)

  Clinical Data Interchange Standards Consortium (CDISC)

  Minimum Information About a Microarray Experiment (MIAME)

  MIAME/Tox (European Bioinformatics Institute, NCT, HESI)

- **Controls**

  Internal (e.g. duplicates, blanks, mismatches, cross-contamination, etc.)

  External (e.g. external RNA control consortium, ERCC, NIST)

- **Regulatory Acceptance of Methods**

  Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

Means to an End – FDA Research Projects: "Critical Steps" along the "Critical Path"

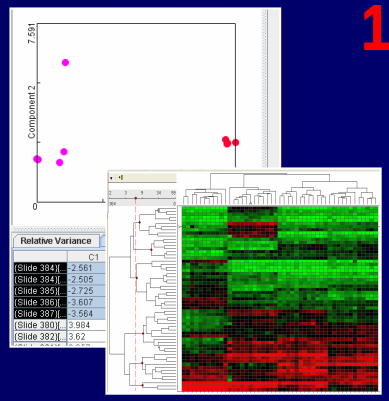
1. Review Tool for Toxicogenomic Data Submissions: ArrayTrack
   - Management, mining, and visualization of two- and one color microarray data
2. Use and Analysis of Microarray Data
3. Qualification of Genomic Biomarkers
   - Qualification process
   - Guidance development
4. Prospective Clinical Safety Study

1. ArrayTrack: Integrated Environment for Microarray Data

Developed at FDA/NCTR (online link here)

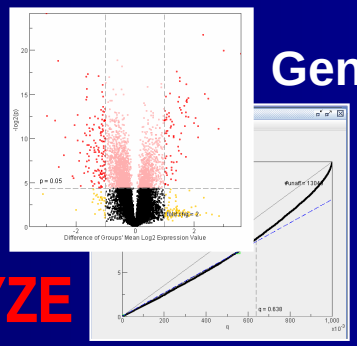
Raw data

1. STORE



Exploring

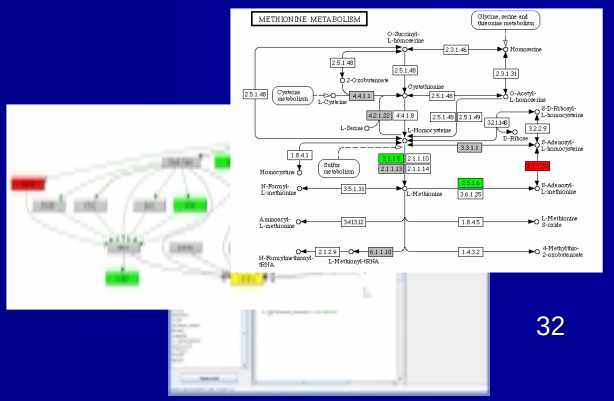
2. ANALYZE VISUALIZE



Gene selection

3. UNDERSTAND

Interpretation



FDA Project – PI: Dr. Weida Tong, NCTR

2. Use and Analysis of Microarray Data
Or: How Good Is the Data ?

Platform comparison

Tan et al. (2003)
Nucleic Acids Research
31, 5676-5684

Marshall (2004)
Science
306, 630-631

Low cross-platform concordance puts hybridization results in question.

How important is this? -- Which answer is the correct answer?

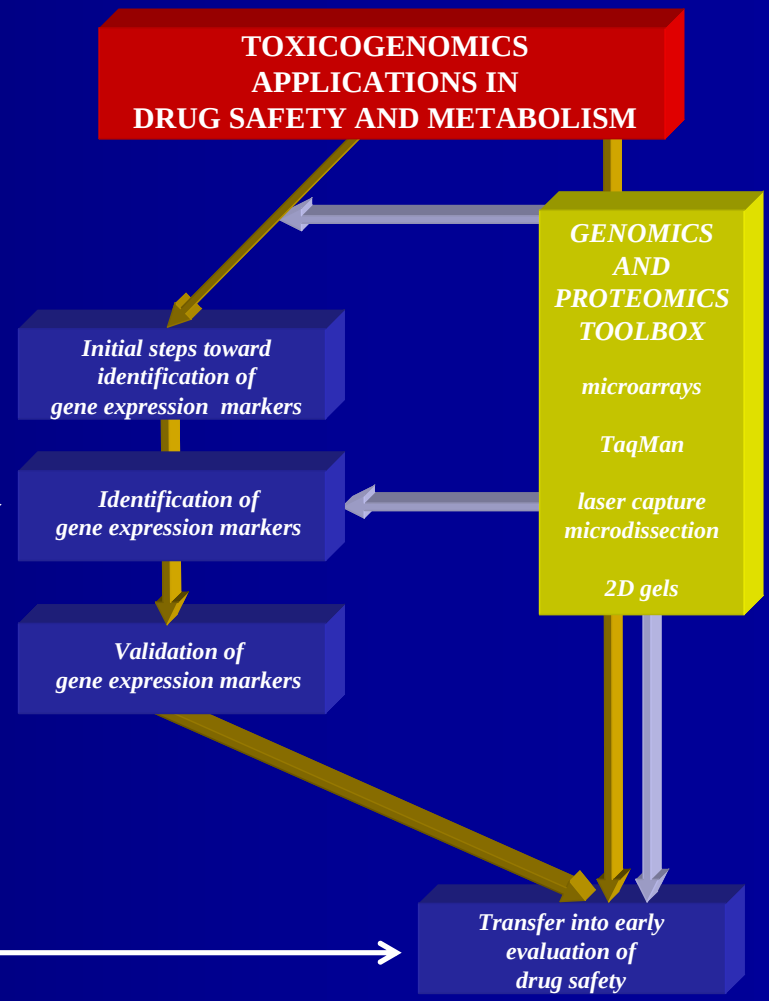
2. Use and Analysis of Microarray Data
Microarray Cross-platform Comparison

- **Sample Quality:**
  - Low quality starting material can cause variability in hybridization results
- **Platform Characteristics and Protocol:**
  - Intra-platform consistency
  - Have proper handling procedures been followed?
  - Each platform might provide a unique picture, which in itself can be meaningful
- **Data Analysis:**
  - Data normalization and gene selection method
  - Statistical approach
  - *IN FACT, reanalysis of Tan's data set, shows a significantly higher concordance* ***FDA Project – PI: Dr. Leming Shi*** *(manuscript in preparation)*
- **What Is Needed:**
  - Well characterized reference data set
  - Spike-in controls

3. Qualification of Genomic Biomarkers: Path to Implement

- Create list of toxicants and non-toxicants
- Identify models (*in vitro, in vivo*)
- Use candidate vs. whole genome
- Determine test method
- Identify best analytical approach

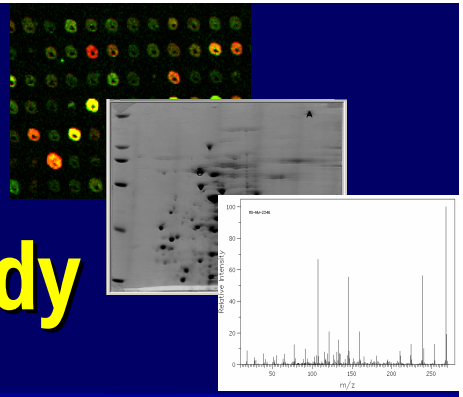
- Repeat
- Ensure consistency with toxicology / pharmacology (phenotype)



3. Qualification of Genomic Biomarkers: Questions the Project Should Answer

- Key toxicological issues facing pharmaceutical development
  - The development of surrogate biomarkers of toxicity for human safety assessment.
  - The implementation of these biomarkers in the drug discovery and development processes.
  - Improved understanding of drug-induced toxicity, including dose-response relationships.
- How many and which genes should be measured to characterize organ-specific toxic responses?
- How will toxic responses be distinguished from physiologically adaptive responses that are not linked to toxicity?
- Can we identify the association of gene expression profiles with specific toxicological outcomes?
- ***FDA Project – PI: Dr. Federico Goodsaid, OCPB, CDER***

4. Taking It One Step Further: Prospective Clinical Safety Study



Preclinical Model	?? →	Prospective Clinical Trial
Rat Dog Monkey other		Human

- Collect blood and urine samples during the course of a clinical trial with an agent that has indicators of toxicity
- RNA: gene expression analysis
- DNA: SNP analysis
- Serum: Proteomic analysis
- Urine: NMR- and MS-based metabonomic analysis
- ***FDA Project – PIs: Yvonne Dragan (NCTR) and John Senior (CDER)***

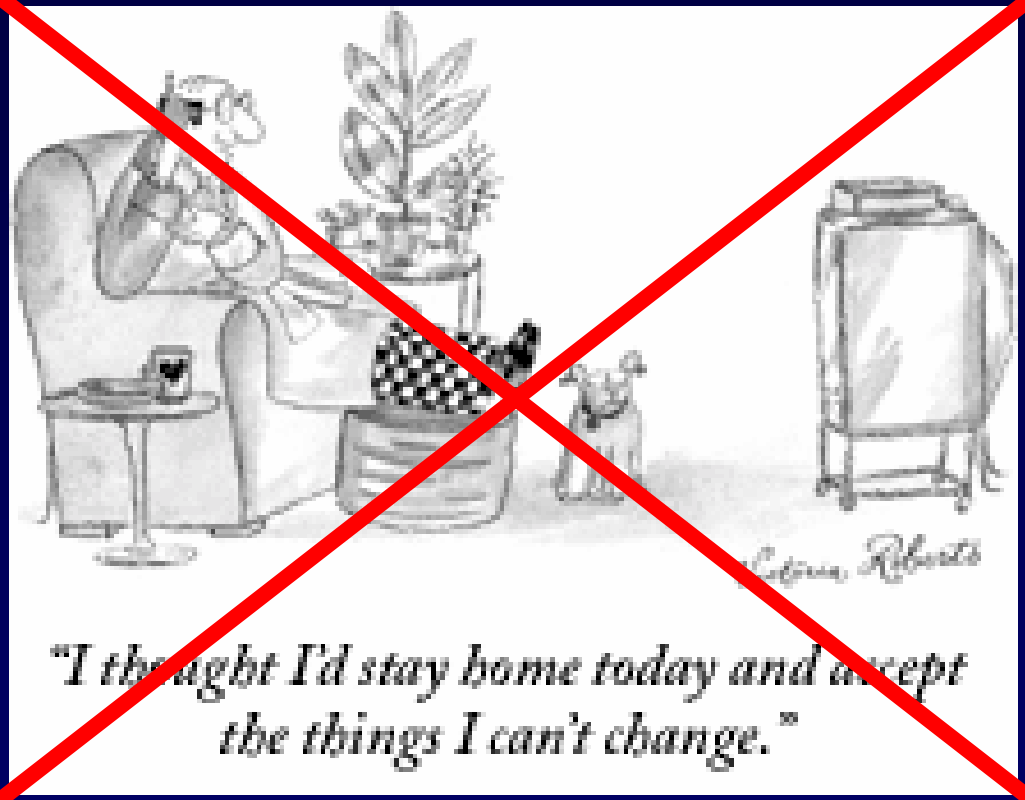
Use of Toxicogenomics in Drug Regulation: Immediate, Most Important Concerns

- **Qualification of Genomic Biomarkers**
  - Focus on the qualification process (path)
  - Can we identify/define a universally applicable qualification process?
  - What are the key decision points?
  - Guidance
- **Database Access and Development**
  - Large databases with qualified (validated) information need to be available
- **Dialogue and Collaborative Efforts**
  - This must be a public effort
  - Interactive workshops, conferences
  - Collaborations (CRADAs and other mechanisms)

Conclusions

- FDA recognizes toxicogenomics as a key opportunity on the Critical Path to develop new medical products
- Guidance documents are being developed
- FDA actively engages in toxicogenomics research

- Toxicogenomics does not replace traditional toxicity studies
- Qualification protocols for genomic biomarkers are needed
- Technological issues need to be addressed
- Data standardization is critical


"I thought I'd stay home today and accept
the things I can't change."

Acknowledgements

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- Dr. Weida Tong, Director, Center for Toxicoinformatics, NCTR
- Dr. Leming Shi, Computational Chemist, Center for Toxicoinformatics, NCTR

- Many industry and academic colleagues who have collaborated to thoughtfully advance the use of pharmaco- and toxicogenomics