Pharmacogenomics: Experience with Voluntary Submissions and Regulatory Development

International Conference on Drug Development

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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

Overview

- FDA's Critical Path and Pharmacogenomics
- Pharmacogenomics Guidance
  - Voluntary Genomic Data Submissions
  - Interdisciplinary Pharmacogenomics Review Group
  - Experience
- Drug/Test Co-development Guidance
- Genomic Biomarkers
- FDA's Activities in Pharmacogenomics
- Conclusions

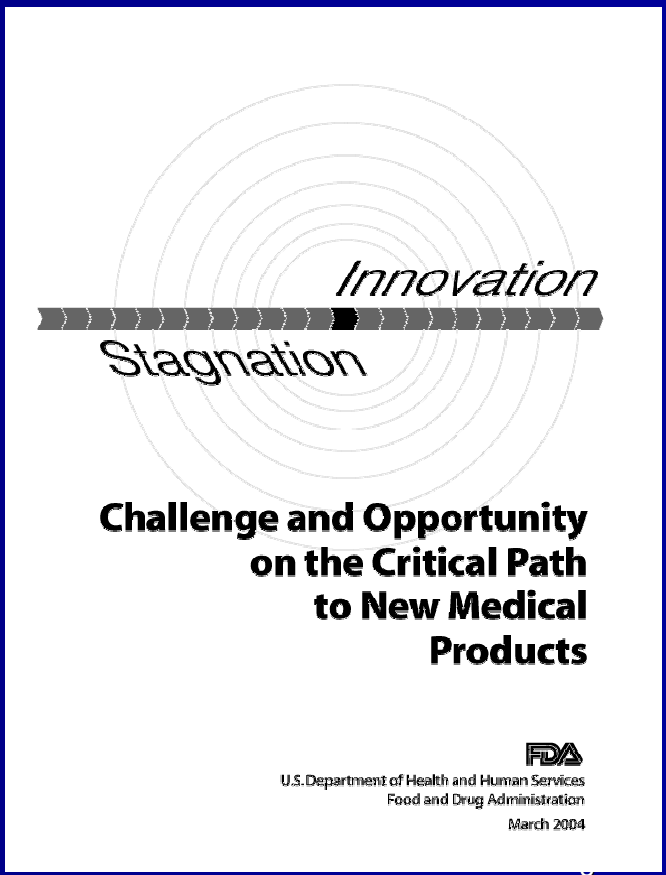
FDA's Mission to Facilitate Drug Development

- 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

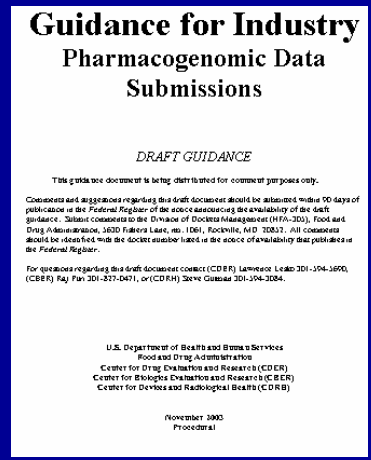
The Critical Path white paper lists opportunities on the "critical path" to new medical products:

Opportunity: "The emerging techniques of pharmacogenomics and proteomics show great promise for contributing biomarkers to target responders, monitor clinical response, and serve as biomarkers of drug effectiveness. *However*, much development work and standardization of the biological, statistical, and bioinformatics methods must occur before these techniques can be easily and widely used. Specific, targeted efforts could yield early results."



Regulatory Framework: Growing Genomics Guidance Family

- 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 dev.)
  - Concept paper by April 2005
  - CDER, CBER, CDRH
  - Draft early 2005



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 301-594-5650, (CBER) Raj Puri 301-827-0471, or (CDRH) Steve Gutman 301-594-2084.

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

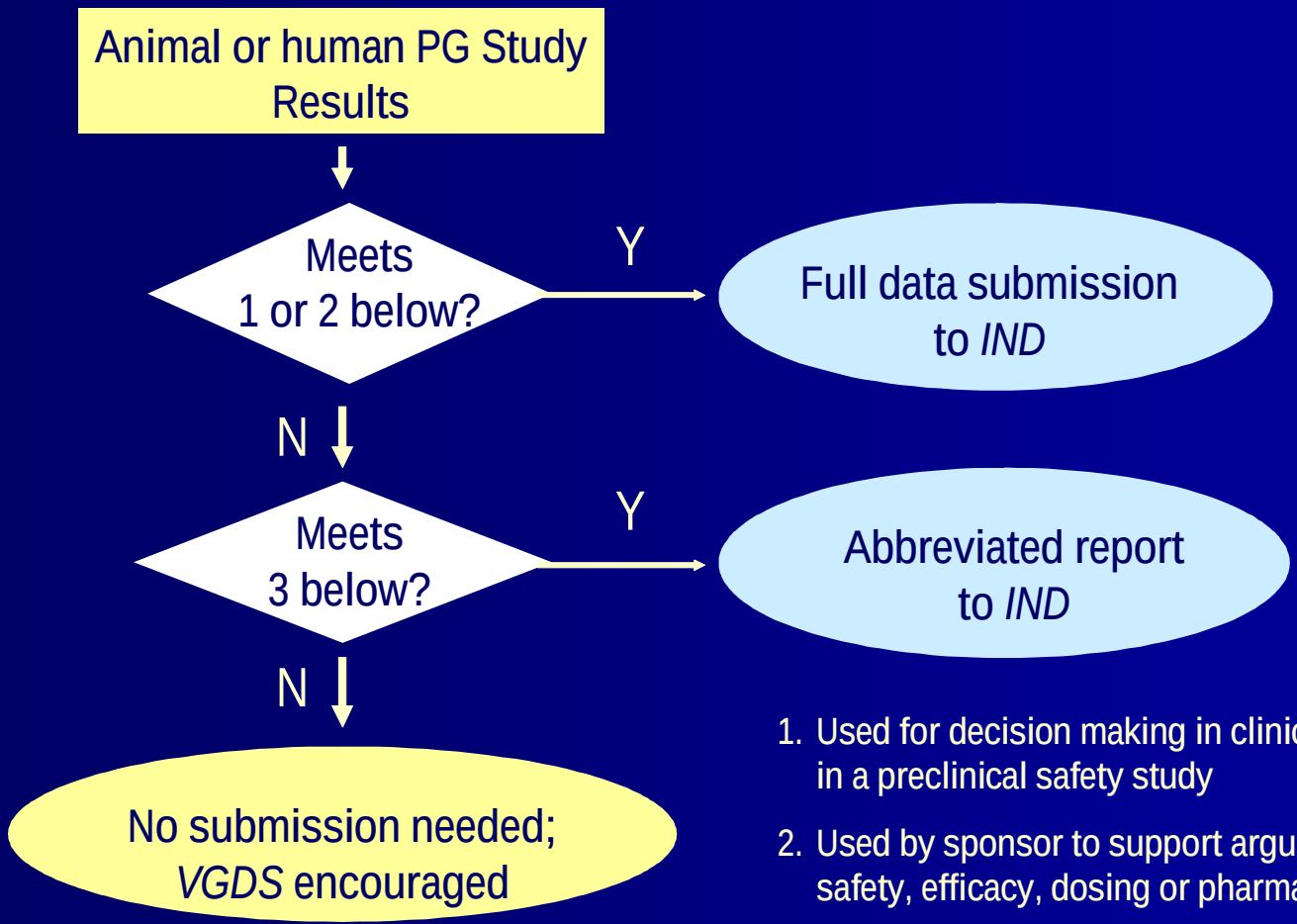
- Guidance on PG Data Submissions
  - Appendix with examples/scenarios
- Charter for the IPRG
- MAPP for the VGDS Process

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

Changes in the Guidance: Clarify "Decision-Making"

- Regulatory decision-making:
  Specific decisions that FDA makes after evaluating *probable or known valid biomarkers* to establish dosing, safety or effectiveness of a drug

- Drug development decision-making:
  Decisions that sponsors make in using *probable or known valid biomarker* in a specific animal safety study or human clinical trial
  - not intended to apply to guiding overall drug development strategy or managing portfolio

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."

Changes in the Guidance: Clarify Incentives to Sponsors to Submit 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)

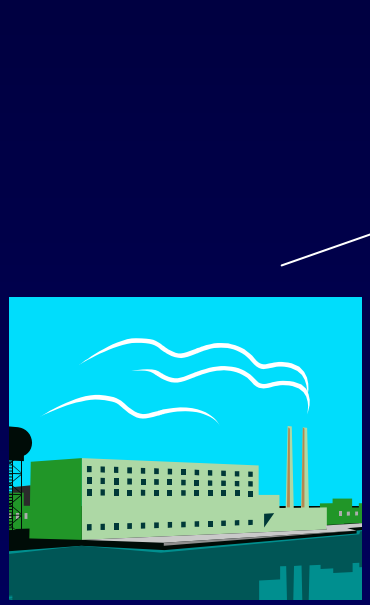
Regulatory Use of Genomic Data

- 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.

Process of Voluntary Genomic Data Submissions from Industry to FDA



VOLUNTARY
Genomic Data
Submission

FDA

Receiving
Tracking
Archiving

IPRG

Ext. Advisory
Committee

VGDS
Review

Feedback to Sponsor

Report

Conferences,
Workshops
with Industry

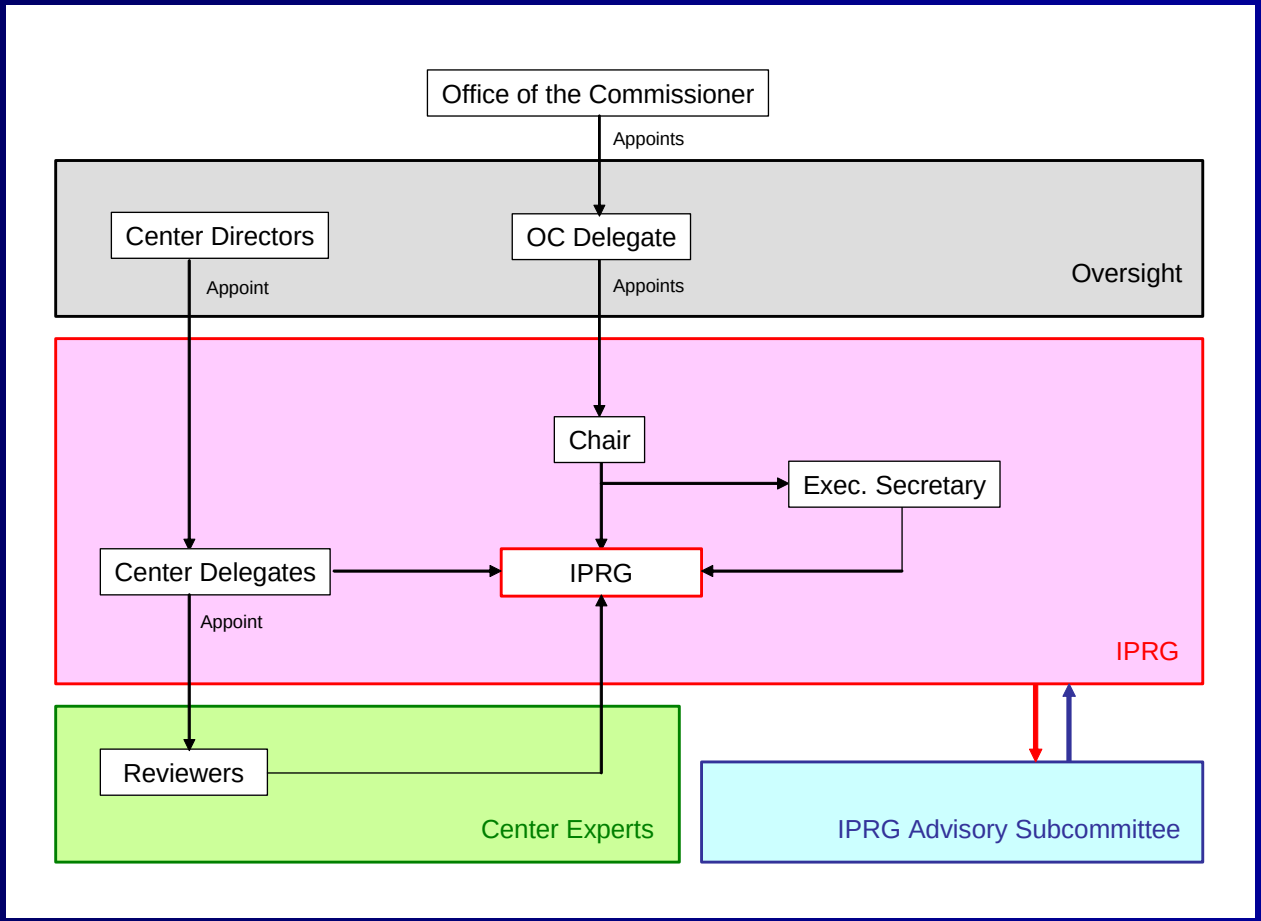
Knowledge
Management

Education

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-voluntary 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

IPRG – Organization



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."

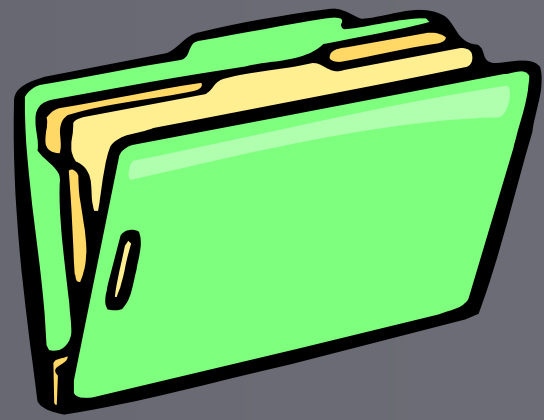
Best Practices for Effective and Productive VGDS Meetings

Once you decide to request a meeting …

- Determine the scope of the meeting prior to contacting IPRG
- Put request for meeting in writing and include:
  - Scope of meeting
  - List of sponsor attendees
  - List of FDA attendees, if available
  - Executive Summary
  - List of questions

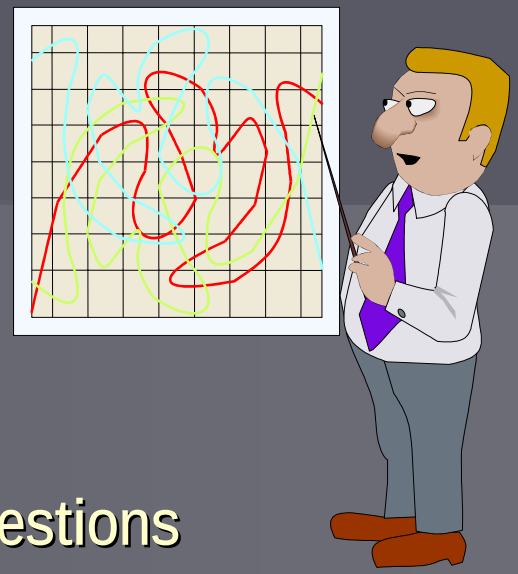
- Send background package with request or immediately after request is acknowledged
- Remember that a VGDS is a voluntary genomic DATA submission!

Background is extremely important…



- Package should include:
  - Scope of the meeting
  - Agenda
  - List of attendees
  - Specific questions IPRG should address
  - ! Avoid general questions like: “Is the protocol ok?”
- Provide package at least 4 weeks prior to meeting, or by date requested, in order for IPRG to fully prepare for meeting

Presentations Should ...



- Be short and to the point
- Leave time for discussion
- Focus on scope of meeting and your questions
- Focus on issues at hand (scientific, regulatory or administrative)
- Keep company history to a minimum and make relevant to agenda
- Indicate where you are in product timeline

Please Note: Have handouts and copies of presentation available for all attendees at the meeting

During Meeting …

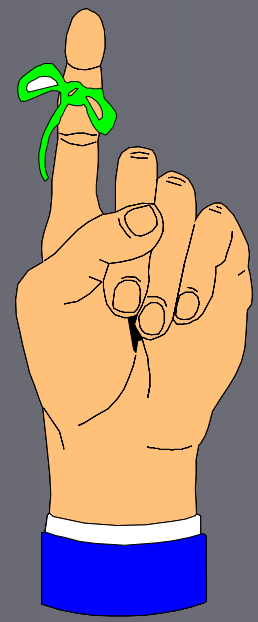
- Stick to the designated scope and questions
- Limit meeting to 1 hour for presentation, questions, responses, and action items
- Start and end on time
- Be open to advice from FDA
- Get action items reiterated or recapped at the end of the meeting

Avoid ...

- Requesting meeting before you have adequate information and data ready to discuss
- Surprising IPRG at meeting with new information not included in background package, or sending new information just before meeting. Re-schedule instead.
- Having side discussions before, during or after meeting – stick to agenda and timeframe

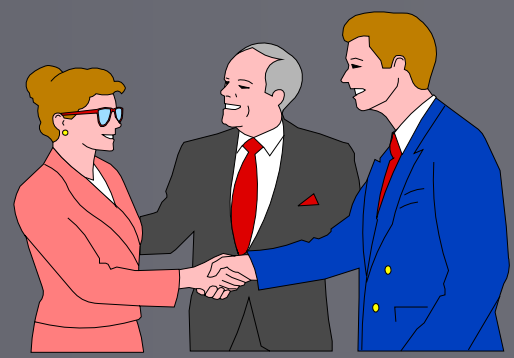
IPRG Disclaimer

PLEASE NOTE: *The views expressed in this document are the opinion of the members of the Interdisciplinary Pharmacogenomics Review Group (IPRG) and may not reflect the opinion of a review division. Therefore, the provided answers should not be interpreted as regulatory guidance, but as a scientific assessment of the issues raised. Should aspects of the subject matter discussed herein become part of a non-voluntary data submission, application, or supplement, it is at the full discretion of the appropriate review division to completely and independently assess the product(s) in question.*



General Advice

- Keep meeting informal
- Provide several options for dates when scheduling – be flexible
- Begin meeting with an introduction of attendees
- If you have to cancel a meeting, do so at least 48 hours ahead
- (Bring your own laser pointer)



Drug/Test Combination Products: FDA Guidance Development

- Analytical performance
  - Describes analytical data standards; content similar to CDRH draft guidance on multiplex test.
- Clinical performance
  - Describes sensitivity and specificity, and other performance attributes of testing biological samples.
- Clinical validation
  - Describes prospective and retrospective approaches to validating the clinical utility of a test, including pertinent statistical considerations.
- Labeling
  - Describes drug and device labeling respectively.

Drug/Test Combination Products: Benefits

- Co-development of drug/test combination products
  - Patient stratification (safety/efficacy)
  - Enrichment in clinical trials (efficacy)
- Product label and/or marketing
  - Should a patient be treated (safety/efficacy)?
  - What is the best dose (efficacy)?
- Can be critical for bringing product to market
- Can save drugs from withdrawal
- Can rescue candidate drugs

Drug/Test Combination Products: Issues

- Strategy (use during drug development only)
- Competitive advantage (i.e. ID responders)
- Timing (development, approval)
- Cost (development, reimbursement)
- Availability of alternative therapy (what if none?)
- Platform (platform change)
- Complexity (point-of-care vs. service laboratories)
- *Clinical usefulness* (i.e. therapeutic area, marketability)

Drug/Test Combination Products: Clinical Usefulness

- Predictive value of test (positive vs. negative)
  - Example:
    - Treatment is effective in 10% of population, severe AE exist
    - Test has 95% negative predictive value (meaning that risk for AE is low in test positives) and 50% positive predictive value (likelihood to respond to treatment)

  → *Useful ? (might depend on therapeutic area)*
- Limited scientific information
  - Test is 100% accurate but covers only small percentage of phenotype: predictive value hard to assess due to limited scientific knowledge
  - Example: HERG genotyping test to predict drug-induced QT prolongation

  → *Useful ? (could be useful, but who will pay for it)*

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.*"

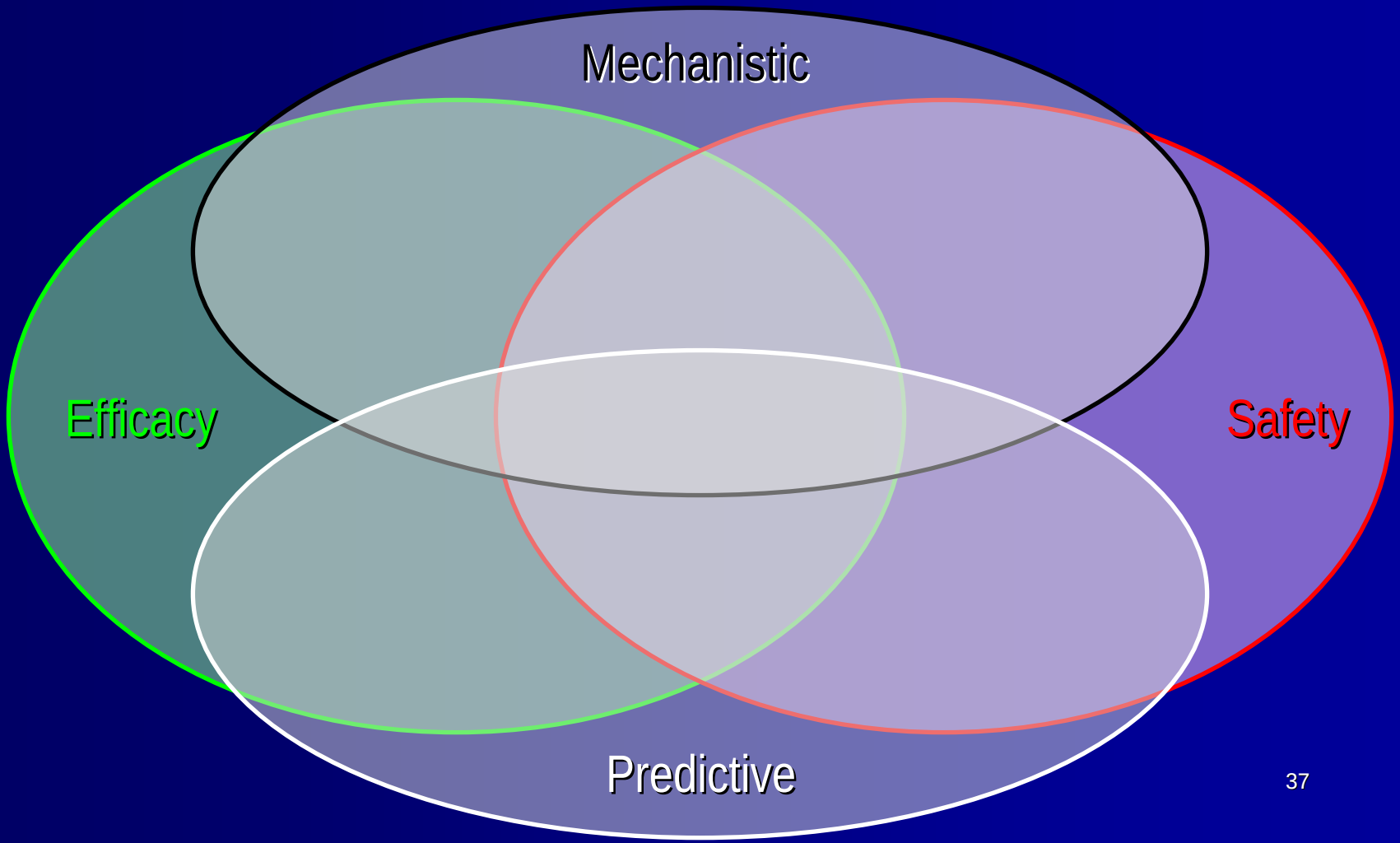
- Probable valid biomarker: "*[…] scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.*"
  - The data elucidating its significance may have been generated within a single company and may not be available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

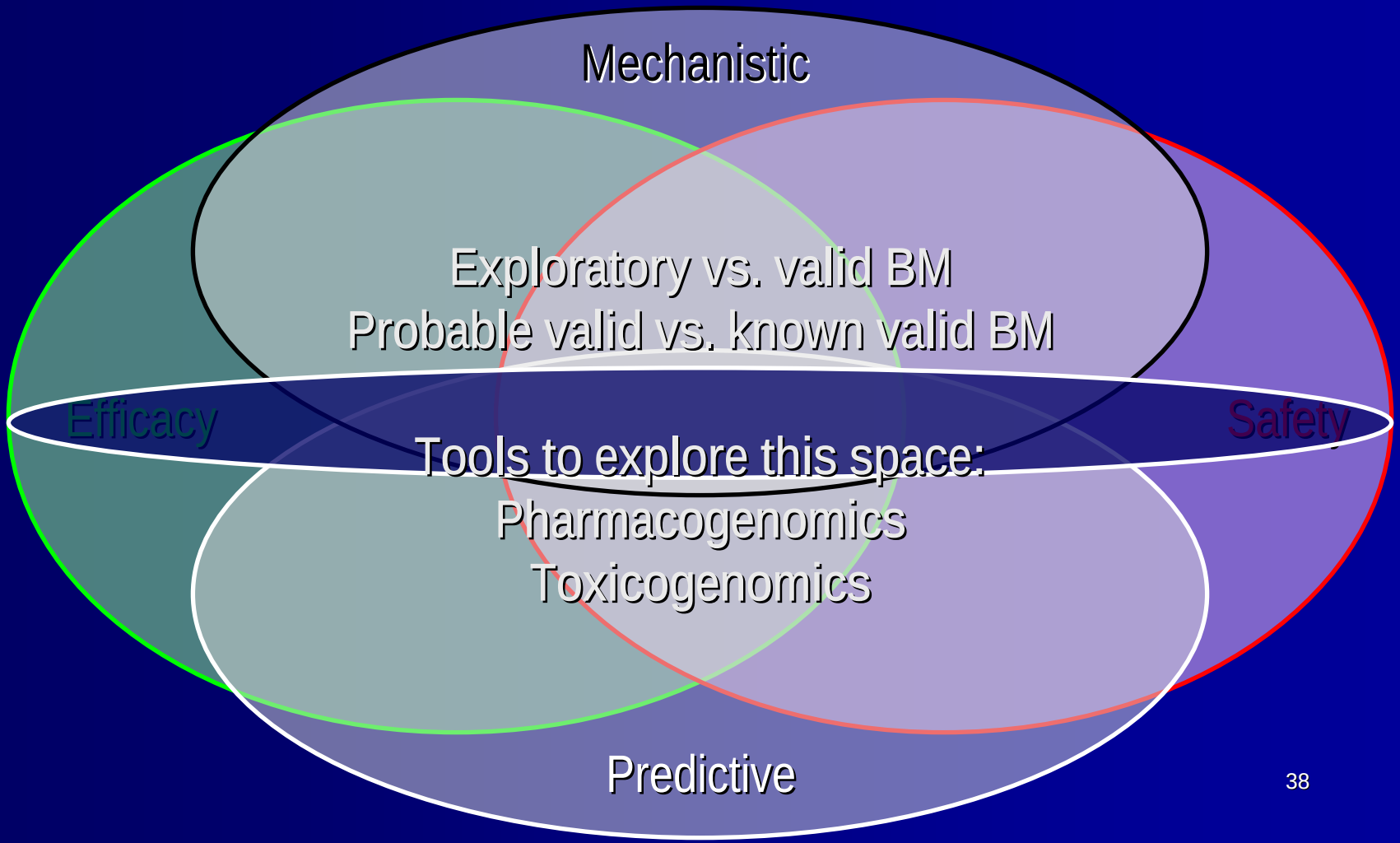
- Change: Expanded definition with the following addition

"<u>The classification of biomarkers is context-specific.</u> 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: Standardization and Acceptance

- 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)

FDA's Involvement in Pharmacogenomics

1. Critical Path initiative
2. Regulatory guidance development
3. Non-regulatory guidance development
4. Infrastructure VGDS and IPRG
5. Workshop, conferences, publications
6. Labeling, re-labeling
7. CPath
8. Research Projects

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

FDA Funded Projects Include, e.g.:

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
5. Database Development

Conclusions

- FDA recognizes pharmacogenomics as a key opportunity on the Critical Path to develop new medical products
- Guidance documents are being developed
- Review infrastructure has been set up
- Early experience with VGDS extremely positive (MORE IS NEEDED!)
- FDA actively engages in pharmacogenomics research

- Qualification protocols for genomic biomarkers are needed
- Technological issues need to be addressed
- Data standardization is critical
- Databases are needed

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- Members of the Interdisciplinary Pharmacogenomics Review Group
- Many more colleagues at the FDA

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