Pharmacogenomic Data Submissions: Review of Guidances and Goals

Pharmacogenomics Working Group (PWG)

Teleconference

December 14, 2004

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FDA/CDER

Overview

- The bigger picture
- Pharmacogenomics related guidances
  - Pharmacogenomic Data Submission guidance
    - Public comments
    - Revision of Pharmacogenomics guidance
  - Drug/Test Combination Products guidance
- Voluntary Genomic Data Submission (VGDS) Process
- Interdisciplinary Pharmacogenomics Review Group (IPRG)
- Summary
- Look forward into 2005

Key Message

- We all worked hard to create a framework for voluntary submissions.
- We all agreed this was necessary.
- We now need the industry's support with submissions to produce value from this effort.

- Together, we can pave the way to translate PG from the bench to the bedside.

FDA's Critical Path Initiative

What's Wrong With Drug Development: *The Diagnosis*

"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
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

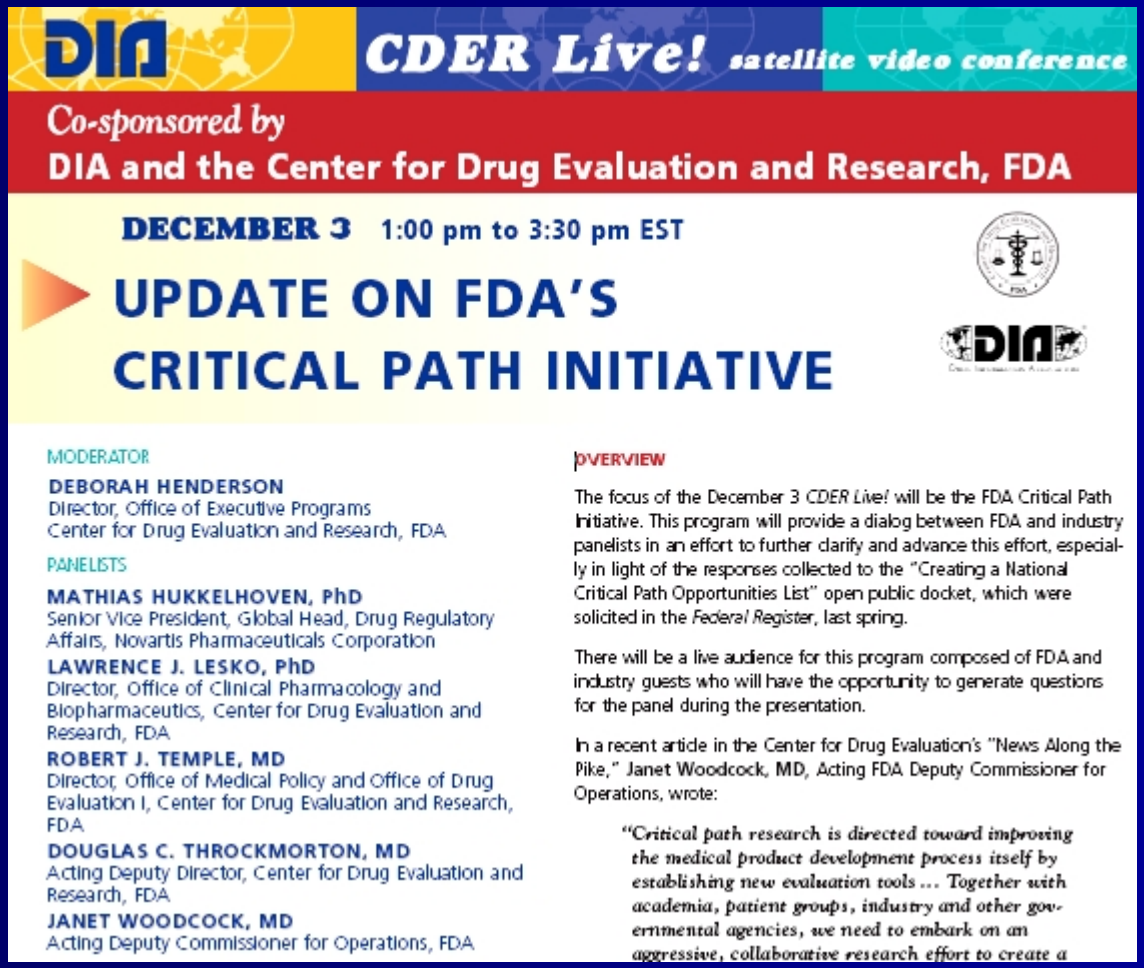
Stagnation

- Extremely high pre-IND failure rate of NMEs
- Less than 1 in 5 INDs for NMEs make it to NDAs
- 50% failure rate in phase III
- Time from IND to market is 8-10 years
- Multiple review cycles for most NME NDAs

Stagnation → Innovation

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

The Most Recent CP Update



DIA

CDER Live! satellite video conference

Co-sponsored by

DIA and the Center for Drug Evaluation and Research, FDA

DECEMBER 3 1:00 pm to 3:30 pm EST

UPDATE ON FDA'S CRITICAL PATH INITIATIVE

MODERATOR

DEBORAH HENDERSON
Director, Office of Executive Programs
Center for Drug Evaluation and Research, FDA

PANELISTS

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JANET WOODCOCK, MD
Acting Deputy Commissioner for Operations, FDA

OVERVIEW

The focus of the December 3 *CDER Live!* will be the FDA Critical Path Initiative. This program will provide a dialog between FDA and industry panelists in an effort to further clarify and advance this effort, especially in light of the responses collected to the "Creating a National Critical Path Opportunities List" open public docket, which were solicited in the *Federal Register*, last spring.

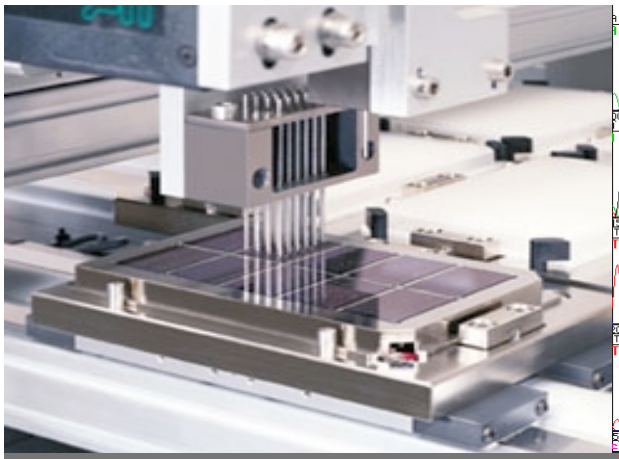
There will be a live audience for this program composed of FDA and industry guests who will have the opportunity to generate questions for the panel during the presentation.

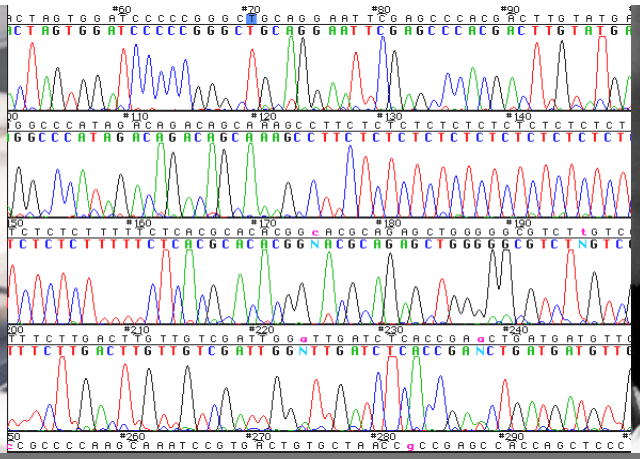
In a recent article in the Center for Drug Evaluation's "News Along the Pike," Janet Woodcock, MD, Acting FDA Deputy Commissioner for Operations, wrote:

> *"Critical path research is directed toward improving the medical product development process itself by establishing new evaluation tools ... Together with academia, patient groups, industry and other governmental agencies, we need to embark on an aggressive, collaborative research effort to create a*

Drug Labeling Regulations: 21 CFR 201.57

- "…if evidence is available to support the safety and effectiveness of the drug only in selected *subgroups of the larger population* with a disease, the ***labeling shall describe the evidence and identify specific tests needed for selection or monitoring of patients who need the drug***."





VISION:

PG is part of biomedical research. PG will provide a toolkit to assess an individual's stage of disease, prognosis, and response to therapy.

PG testing will be used in the clinic as a tool to identify the best possible care for the patient.

PGx will improve health care.

Pharmacogenomics (PG)

- Addresses inter-individual differences in drug response
- Genomic (genetic) factors determine, next to environmental factors, how we react to drugs and other xenobiotics
- This science is not new, but has experienced a significant boost since the HGP has been completed and novel HT technologies became available
- **Several barriers block the translation of PG from the research laboratory to its clinical use**
- **One of the barriers HAS BEEN the lack of regulatory guidance**

The Need for a PG Guidance: Encourage Industry to Use PG and Remove Barriers

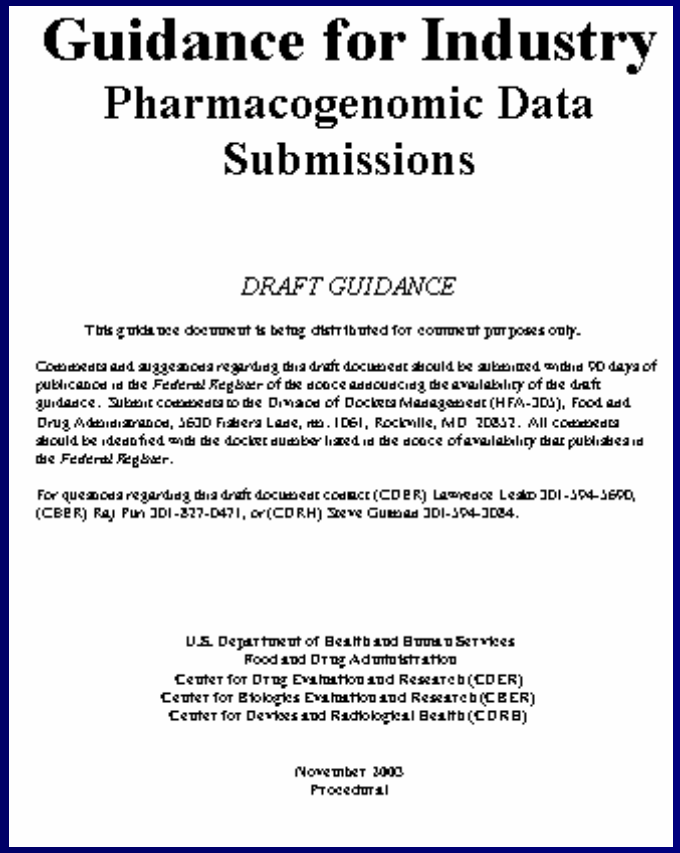
- Uncertainty and lack of clarity as to how FDA will treat PG data
- Fears that FDA would react prematurely or inappropriately to PG data
  - up-regulation of oncogenes in animal studies
  - additional clinical trials to study biomarkers
  - stop clinical development for safety reasons
- These fears were real and rational

PG-Related Guidances

Regulatory Context: Growing PG Guidance Family

- *FDA Critical Path (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

It will be out. Really.



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 301-594-5690, (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

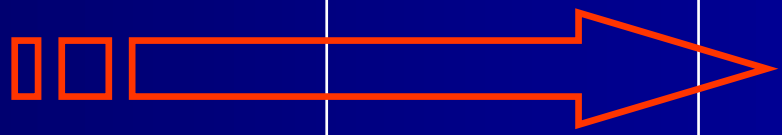
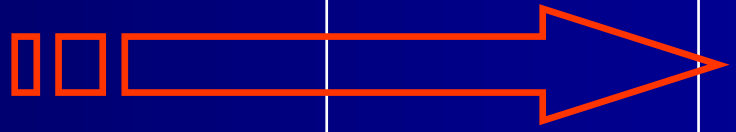
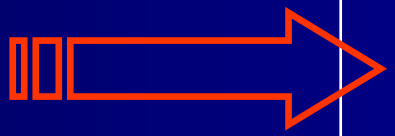
"....final guidance will be out in June 2004" (Lesko, March 2004)

"....final guidance will be out in September 2004" (Lesko, June 2004)

".....final guidance will be out in December 2004" (Lesko, August 2004)

"....final guidance will be out soon" (Lesko, November 2004)

Regulatory Guidances for Industry

Guidance	Draft	Public Comment Period	Final
Genomic Data Submission			Jan 2005
Multiplex Test			Q1 2005
Drug/Test Co-development		Feb 2005	

Guidance for Industry: Pharmacogenomic Data Submissions

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

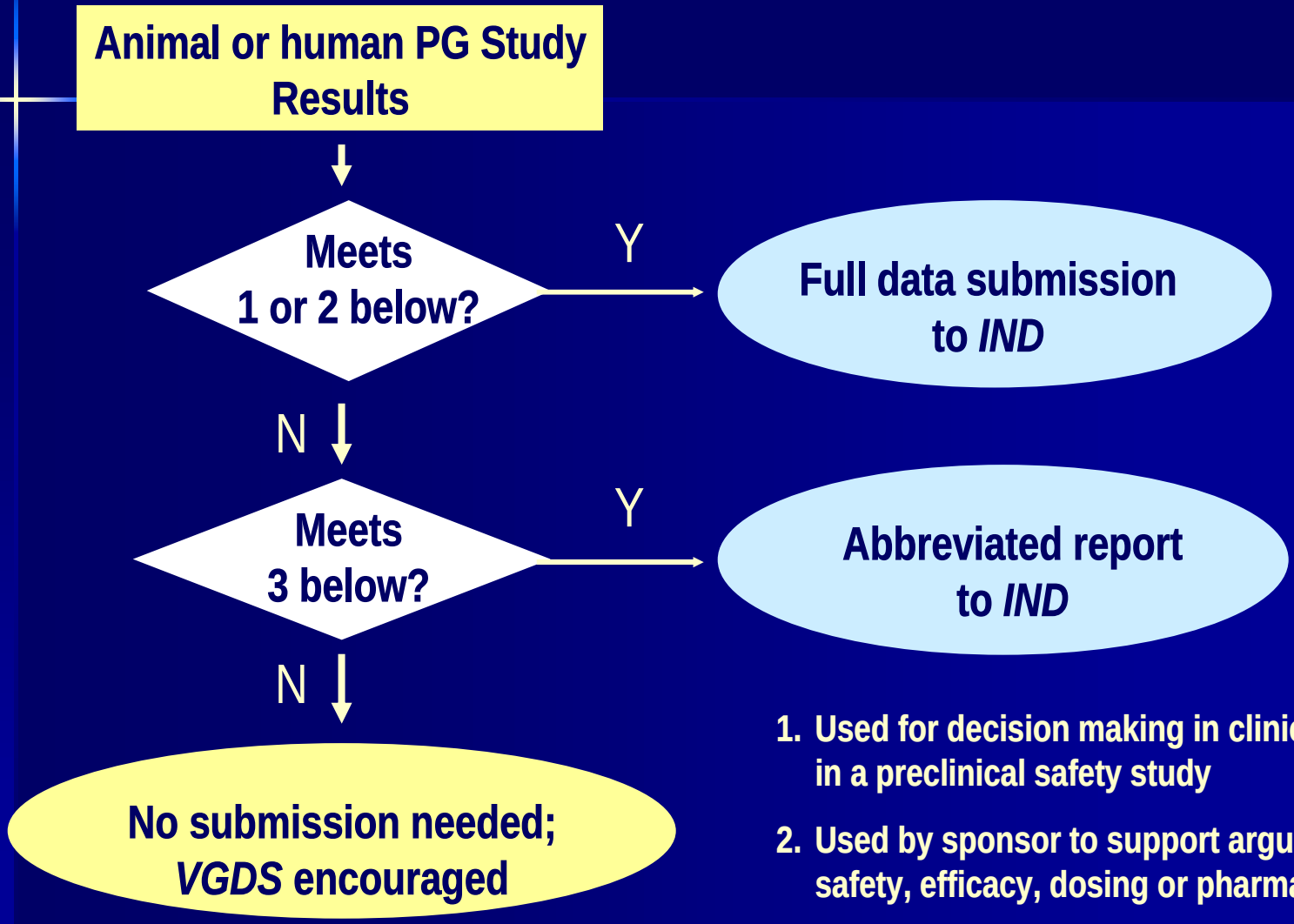
- The guidance is intended to facilitate scientific progress in the area of pharmacogenomics.

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.

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***

35 Sets of Public Comments to the Docket

- 25 from individual companies including biotechnology firms
- 4 from industry associations including PhRMA and BIO
- 4 from government agencies other than FDA
- 2 from private foundations focused on genomics

Rank Order of Comments: 4 Categories

1. Clarify the IPRG organization and roles
   - members, relationship to review division, nature of database, sharing data, communication of findings, process for industry meetings, confidentiality
2. Provide for detail on biomarker definitions
   - how to distinguish between probable and known valid biomarker
3. Specific technical questions related to DNA-based assays
   - GLP issues, submission format, QC, analyzing microarray data, assay validation
4. General recommendations on content and format
   - harmonization, clarify “decision-making”

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: Clarify Incentives to Sponsors to Submit VGDS

- Provides opportunity to have informal meeting with FDA PG experts
  - familiarize FDA with PG experiments, data analysis and interpretation approaches
  - 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
- Pave the way for potential time- and cost-savings by familiarizing FDA with PG and avoiding future delays in review
- Make a contribution to the VGDS repository so future policies and guidances are data-driven
- Impact FDA thinking and help build consensus around PG standards, policies and guidances

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)
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**

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)

GDS Guidance: Why the Delays?

- There is no issue with the process and/or the science.
- It simply took more time than we anticipated to move and clear a guidance through three centers:
  - CDER, CBER and CDRH sign-off
    - Associate Director of Medical Policy
    - Associate Directors of (Legal) Policy
    - Center Directors
  - Companion MAPPs (SOPs) development
    - Internal roadmap for VGDS process
    - Goals and responsibilities of IPGR
  - Web site (MAPPs, FAQ, links

Guidance for Industry: Drug/Test Combination Products

Towards More Robust Use of Diagnostics in Drug Development

- Biomarkers must be **used** to be accepted
- Barriers
  - Add-on costs to clinical drug trials
  - Limited interest
  - Commercialization of technology
  - FDA must clarify regulatory framework
- Greater emphasis on safety biomarkers
- Stimulus or incentive may be required

Drug/Test Combination Guidance

- Scope: Co-development of medicine and test to identify candidate patients
- Timeline: draft scheduled to complete in 2nd week of January 2005
- Public comment period of 90 days
- Topic in 3rd FDA-Industry workshop on April 13-15, 2005

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 (safety/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)*

Voluntary Genomic Data Submissions (VGDS)

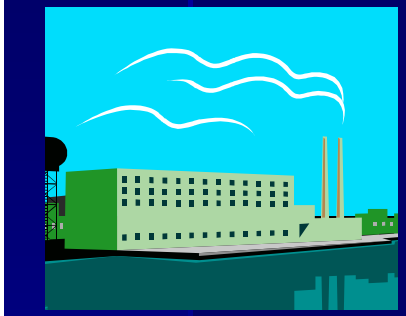
The Evolution of Voluntary Genomic Data Submissions

- May 2001 ~ Industry uncertain how FDA will treat PGx data
  - up-regulation of oncogenes in animal studies
  - additional clinical trials to study biomarkers
  - stop clinical development for safety reasons
- Series of FDA-Industry workshops
  - May 2002, November 2003, July 2004 and April 2005
  - Fostered dialogue, led to publications and finally to guidance for industry

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

- Submission of exploratory PGx 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

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

- Introduction: summary of studies, goals, data, analytic issues and questions
- Discussion: informal, free exchange of ideas, partial answers to questions
  - "validation" 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: "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 Wyeth 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."

Interdisciplinary PG Review Group (IPRG)

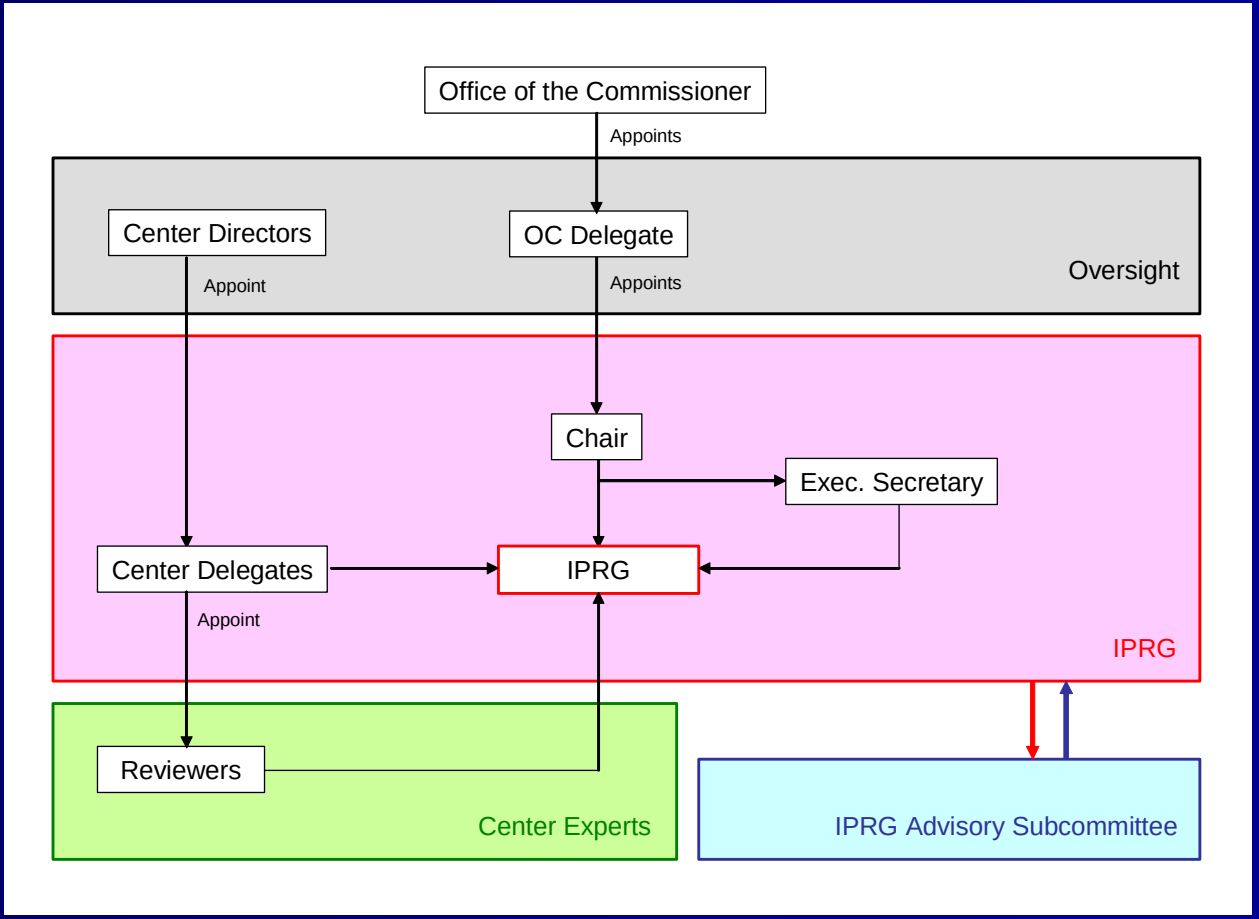
A New Review Group: Interdisciplinary PGx Review Group (IPRG)

- Reviews all VGDS for questions and issues related to science, standards, policies and providing general guidance
- Provides competent PG experience for advice to industry, e.g., in industry meetings
- Consults for review divisions in genomic related questions
- 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

Organizational Infrastructure: The IPRG

- Oversight
  - OC, CDER, CBER, CDRH, NCTR
- Full-time members
  - Chair, Executive Secretary, Center Delegates, Genomics Group
- Ad hoc members
  - Center Experts, Reviewers
- Advisory Committee (to be formed)

IPRG – Organization



Summary: Specific Points

- FDA identifies pharmacogenomics as a key opportunity on the Critical Path to new medical products
- Three guidance documents are being developed
- The draft of the Pharmacogenomics Data Submission guidance has not undergone extensive revisions in its final form
  - Changes made primarily to clarify certain principles of guidance
  - Companion documents address many of the comments to the docket
- New voluntary data submission path (VGDS) has been created
- New interdisciplinary review group (IPRG) has been established
- Draft of Drug/Test Co-development guidance expected Q1 2005

Summary: General Considerations

- FDA has used PG technology for improving drug development and therapeutics under its critical path initiative
- Further development of PG biomarkers as diagnostics is needed to increase usefulness of the technology
- Clinical outcomes will need to be better correlated with PG biomarkers
- New business model and regulatory path needs clarification for PG biomarkers/drug combinations

Look forward into 2005

Submission of PGx Information to FDA

- Continue to see marked increase in PGx in IND protocols and completed studies
  - Numbers ramped up between 2001 and 2003 and we stopped counting
- Will see increasing amount of PGx data in NDAs especially in oncology and for known valid biomarkers of CYP enzyme activity
  - EGFR inhibitor drug class is model
- Optimistic that more voluntary submissions will be presented to the IPRG
  - Catalyzed by final guidance and word-of-mouth

To Do List

- Finish “Suite of PG Guidances”
- Prepare and publicize a national Critical Path Opportunity list
- New standard format for submitting clinical trial data including PGx data
- Collaboration with National Academy of Clinical Biochemistry
  - Guidelines for use of PGx in lab medicine practice
  - Completion in June 2006
- Prioritize most pressing drug development problems that provide greatest opportunity
  - Concrete projects with deliverables
- Re-focus internal research
  - FDA-sponsored research project on warfarin to address questions related to CYP2C9

Continuing Challenge: Clear Framework of Biomarker Classification and Use

- Classification ~ exploratory, probable valid and known valid (not entirely clear)
  - Valid = degree of certainty (disease-specific, treatment-specific and context-specific) based on scope of evidence
  - But, can't tell in advance so study results determine category and…..
- Use ~ function drives voluntary submission vs. required submission (IND, NDA) and …..
- Submission Format ~ classification + use
  - full report < abbreviated < synopsis

Re-labeling of Previously Approved Drugs to Include PGx Information

- Conceptual framework to identify candidate drugs and evaluate evidence
  - Develop the appropriate questions
  - Capture the relevant evidence
  - Abstract and summarize the evidence
  - Evaluate the quality of studies
  - Assess the overall strength of evidence
  - Determine test performance characteristics
  - Consider other factors in relabeling decision
  - Prepare specific language for label

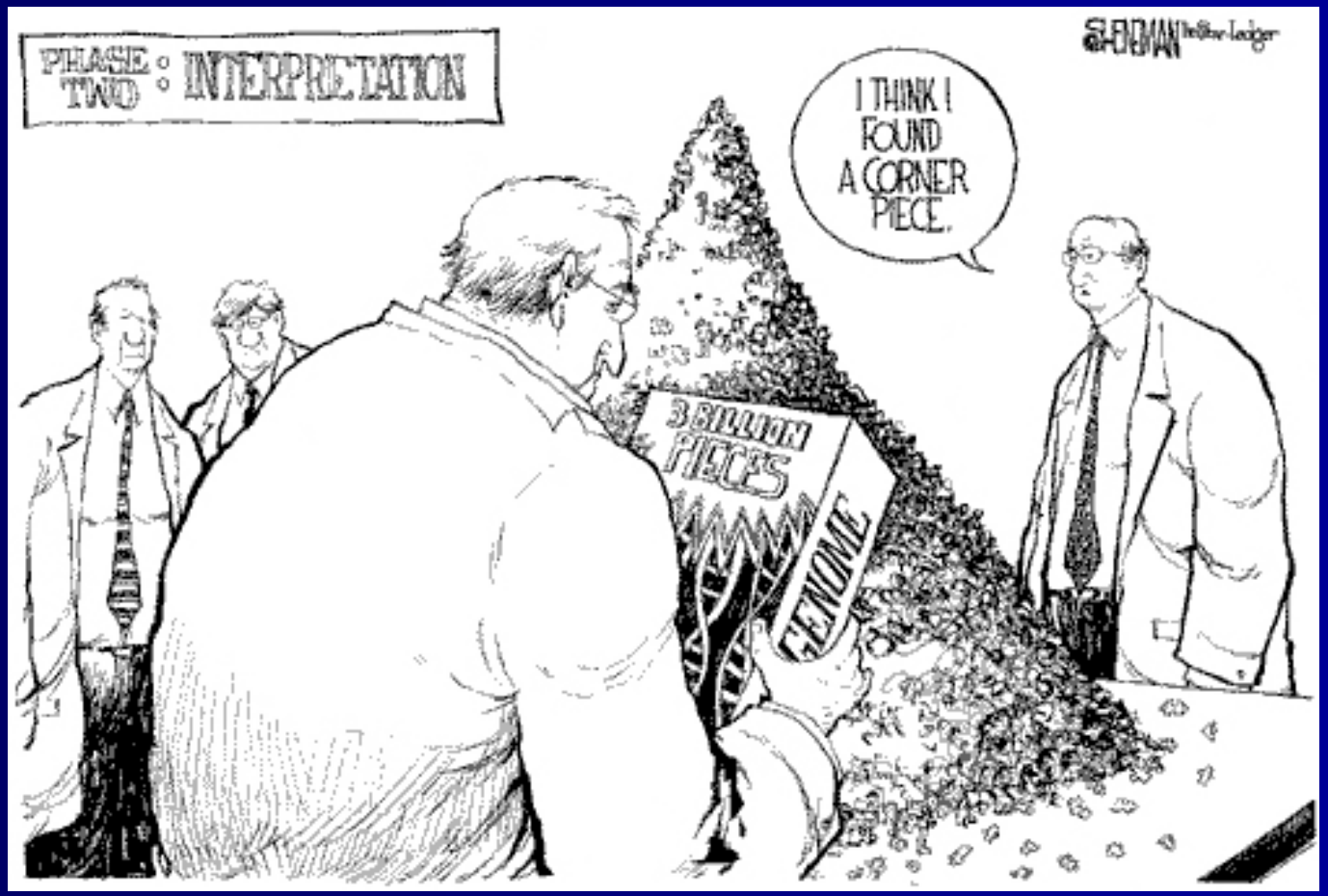
Example: Irinotecan and UGT Polymorphism

- Labeling – absence of PGx information in label discussed at CPSC on November 4, 2004
  - Sufficient scientific and clinical evidence linking UGT1A1*28 with 9-fold greater risk of toxicity (12 vs. 0)
  - Analytical measurement is robust enough to be used as response predictor test (9 vs. 0 ~ 3 abstain)
  - Insufficient evidence to recommend exact dosing for genotype-defined subsets
- New labeling – sponsor agreed, in consultation with FDA, to include data on increased risk of neutropenia in UGT activity-deficient genotypes

Institute for Global Pharmaceutical Development

- Founding partners ~ FDA, University of Arizona and SRI International
  - Nonprofit institute focused on noncompetitive ways to expedite drug development
  - Precompetitive research and educational programs
- In 3 month planning process to be operational by January 2005
  - Governance/management structure
  - Business plan
  - Research and educational agenda

WE NEED TO DO THIS TOGETHER !



Questions for Industry

- Are there additional barriers to the use of PG in drug discovery and development?
- We have been asked to consider PG in the ICH setting. Do you think we are ready for harmonization?
- Do you envision the process of voluntarily submitting data as generally applicable for other areas than genomics (proteomics, metabolomics, other biomarkers)?
- At recent meetings, the notion that PhRMA is going around diagnostic companies has come up. A direct path to clinical labs with homebrews seems to be preferred. Is this true? What are the barriers to submitting a Dx for FDA approval?

Acknowledgements

- Dr. Janet Woodcock, Acting Deputy Commissioner for Operations
- Dr. Lawrence Lesko, Director, OCPB
- Dr. Steve Gutman, Director, OIVD
- Dr. Shiew-Mei Huang, Deputy Director for Science, OCPB
- Dr. Federico Goodsaid, Senior Staff Scientist, Genomics
- Dr. Allen Rudman, Senior Policy Advisor, Genomics and Exec. Secretary, IPRG
- All members of the PG Guidance WG
- All members of the D/T Guidance WG
- Cross-Center FDA Genomics WG and OCPB PGx WG
- Many industry and academic colleagues who have collaborated to thoughtfully advance the use of PGx