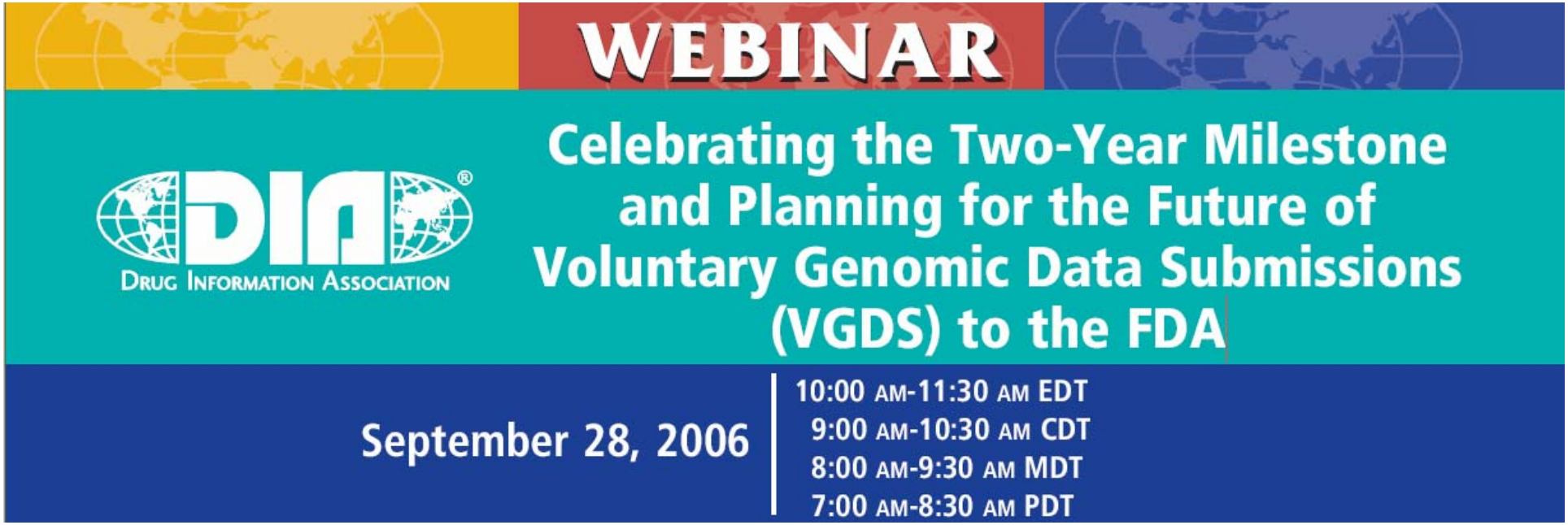
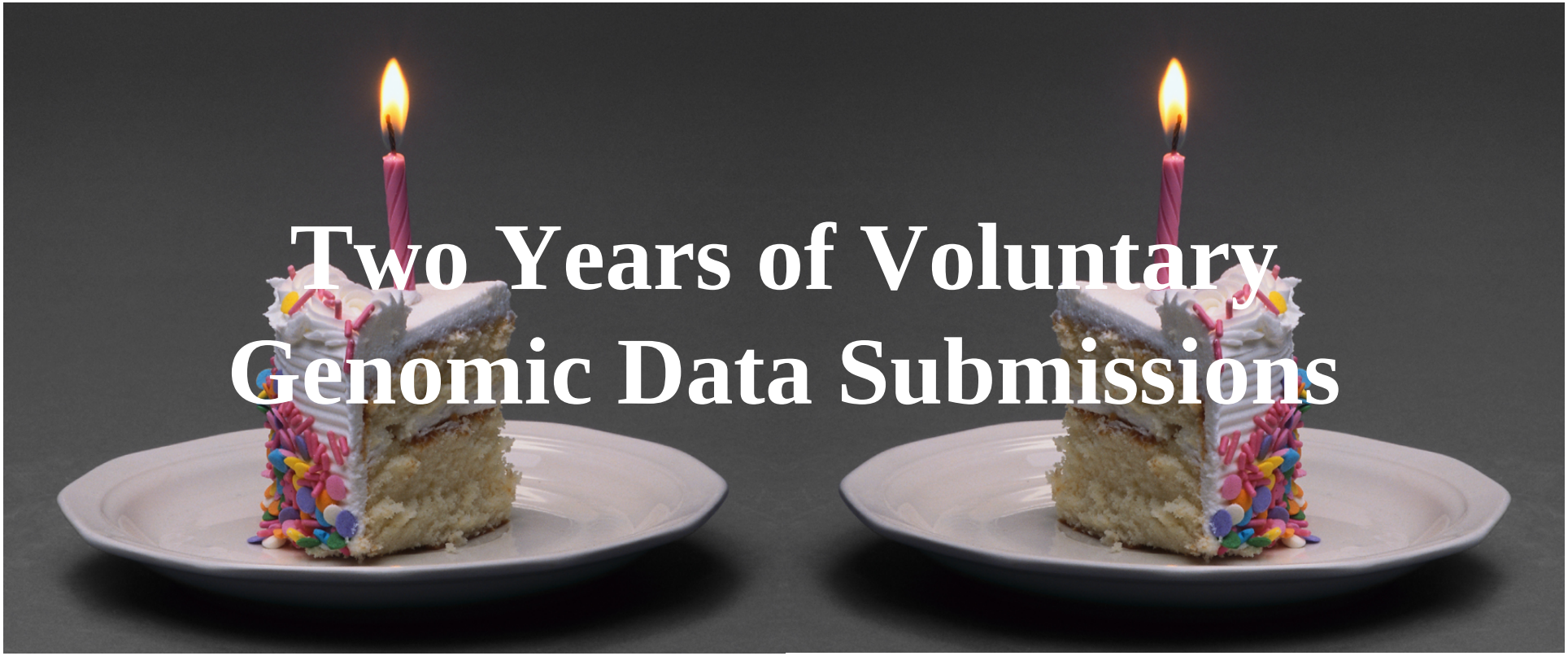


Federico Goodsaid, Ph.D., and Felix Frueh, Ph.D.
Genomics Group
OCP/OTS/CDER/FDA

Protecting and Promoting Public Health

Agenda

- **Two years of Voluntary Genomic Data Submissions**
- **Nonclinical Science in Voluntary Genomic Data Submissions**
- ***We hold these truths to be self-evident:* how do we know that a biomarker is valid?**
- **Best Practices in the Submission of Genomic Data**


Two Years of Voluntary
Genomic Data Submissions

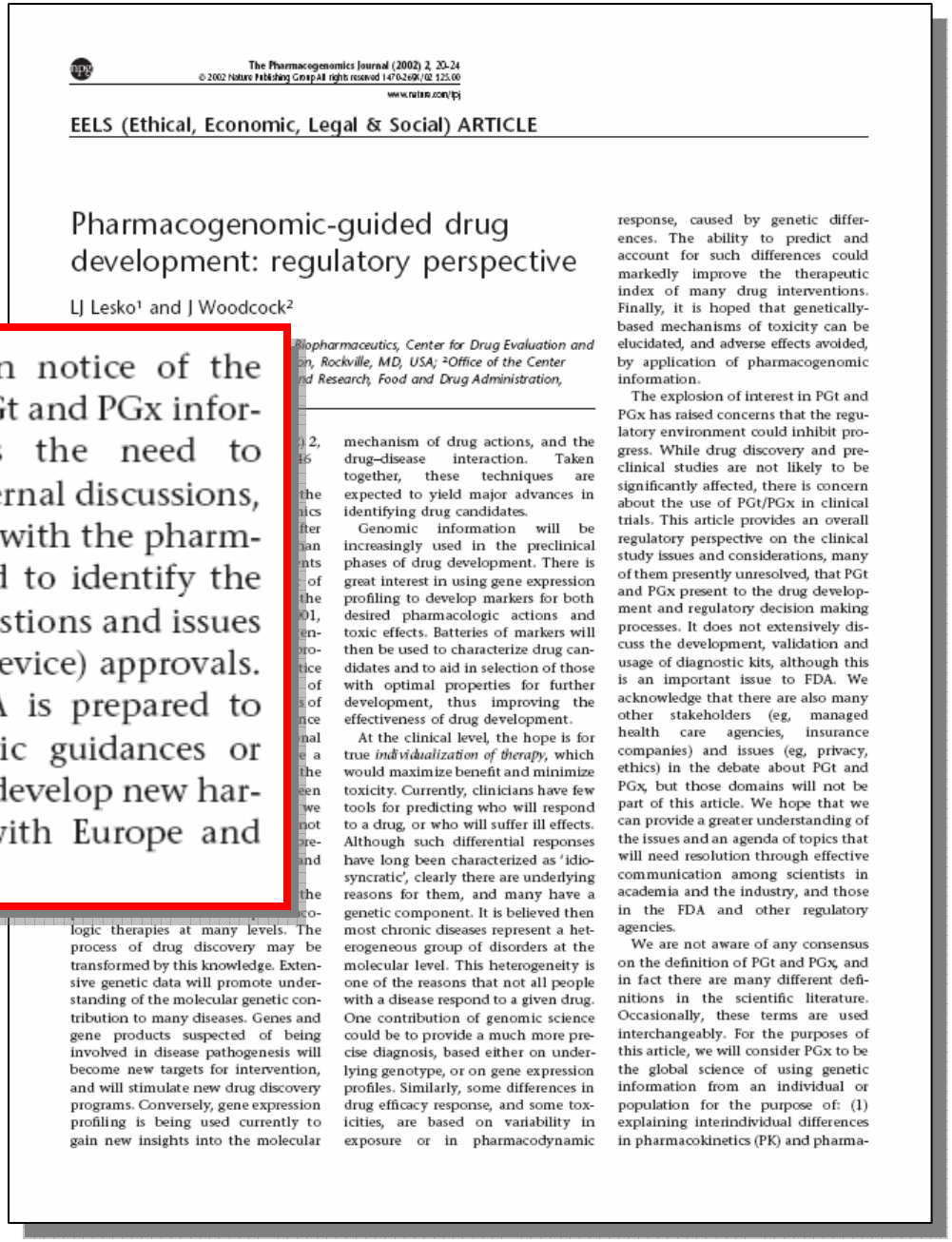
FDA has a mandate

- 21 CFR 201.57

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

2002 Vision

FDA has also taken notice of the recent explosion in PGt and PGx information and realizes the need to actively engage in internal discussions, and in open dialogue with the pharmaceutical industry and to identify the new implications, questions and issues related to drug (and device) approvals. If necessary, the FDA is prepared to develop new domestic guidances or work through ICH to develop new harmonized guidances with Europe and Japan.



The Pharmacogenomics Journal (2002) 2, 20–24

www.nature.com/tpj

EELS (Ethical, Economic, Legal & Social) ARTICLE

Pharmacogenomic-guided drug development: regulatory perspective

LJ Lesko[1] and J Woodcock[2]

...iopharmaceutics, Center for Drug Evaluation and ...n, Rockville, MD, USA; [2]Office of the Center ...d Research, Food and Drug Administration,

...2, ...is ...the ...ics ...fter ...an ...nts ...of ...the ...01, ...en- ...pro- ...tice ...of ...s of ...nce ...nal ...e a ...the ...een ...we ...not ...pre- ...and ...the ...co-

logic therapies at many levels. The process of drug discovery may be transformed by this knowledge. Extensive genetic data will promote understanding of the molecular genetic contribution to many diseases. Genes and gene products suspected of being involved in disease pathogenesis will become new targets for intervention, and will stimulate new drug discovery programs. Conversely, gene expression profiling is being used currently to gain new insights into the molecular mechanism of drug actions, and the drug–disease interaction. Taken together, these techniques are expected to yield major advances in identifying drug candidates.

Genomic information will be increasingly used in the preclinical phases of drug development. There is great interest in using gene expression profiling to develop markers for both desired pharmacologic actions and toxic effects. Batteries of markers will then be used to characterize drug candidates and to aid in selection of those with optimal properties for further development, thus improving the effectiveness of drug development.

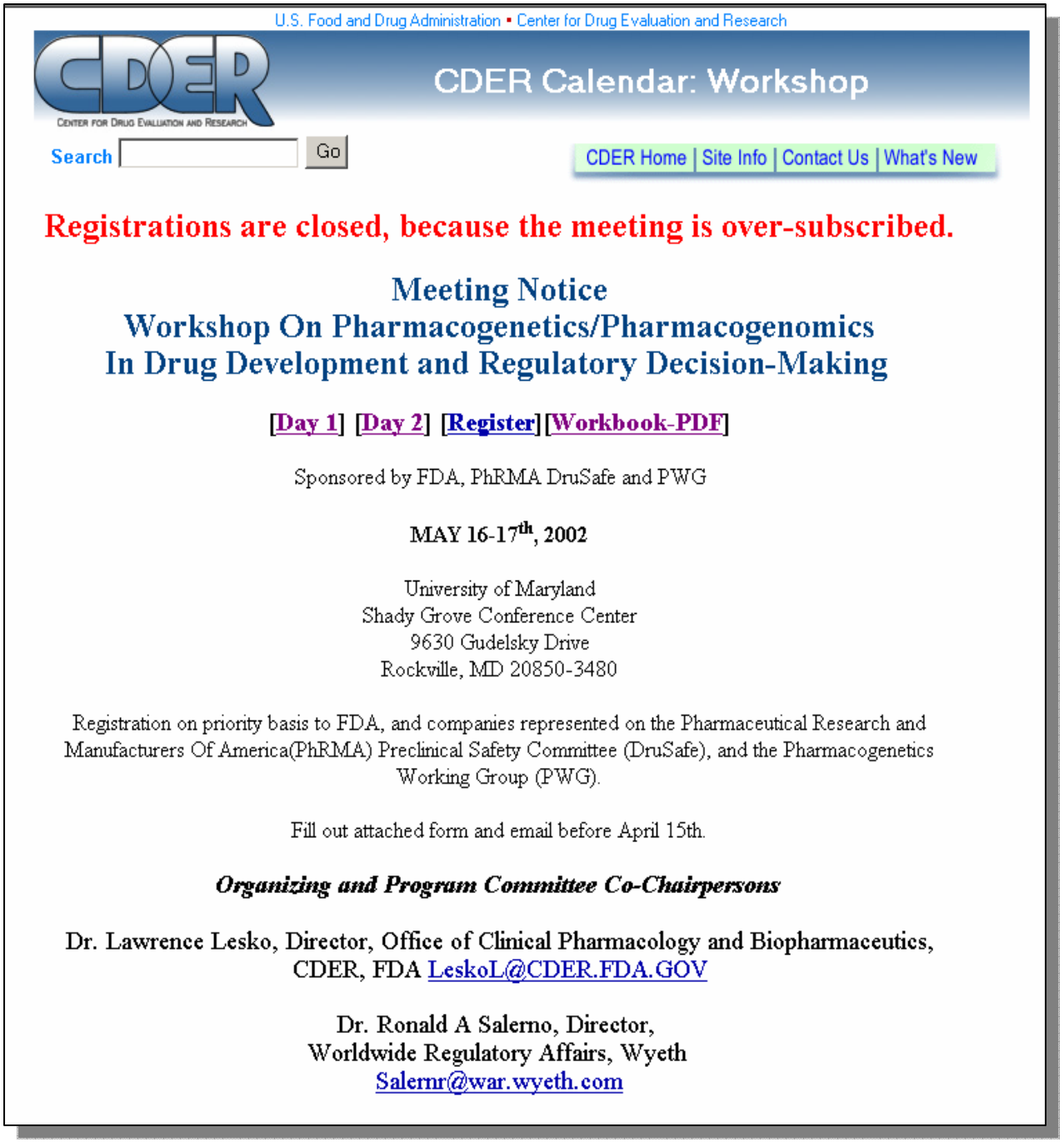
At the clinical level, the hope is for true *individualization of therapy*, which would maximize benefit and minimize toxicity. Currently, clinicians have few tools for predicting who will respond to a drug, or who will suffer ill effects. Although such differential responses have long been characterized as 'idiosyncratic', clearly there are underlying reasons for them, and many have a genetic component. It is believed then most chronic diseases represent a heterogeneous group of disorders at the molecular level. This heterogeneity is one of the reasons that not all people with a disease respond to a given drug. One contribution of genomic science could be to provide a much more precise diagnosis, based either on underlying genotype, or on gene expression profiles. Similarly, some differences in drug efficacy response, and some toxicities, are based on variability in exposure or in pharmacodynamic response, caused by genetic differences. The ability to predict and account for such differences could markedly improve the therapeutic index of many drug interventions. Finally, it is hoped that genetically-based mechanisms of toxicity can be elucidated, and adverse effects avoided, by application of pharmacogenomic information.

The explosion of interest in PGt and PGx has raised concerns that the regulatory environment could inhibit progress. While drug discovery and preclinical studies are not likely to be significantly affected, there is concern about the use of PGt/PGx in clinical trials. This article provides an overall regulatory perspective on the clinical study issues and considerations, many of them presently unresolved, that PGt and PGx present to the drug development and regulatory decision making processes. It does not extensively discuss the development, validation and usage of diagnostic kits, although this is an important issue to FDA. We acknowledge that there are also many other stakeholders (eg, managed health care agencies, insurance companies) and issues (eg, privacy, ethics) in the debate about PGt and PGx, but those domains will not be part of this article. We hope that we can provide a greater understanding of the issues and an agenda of topics that will need resolution through effective communication among scientists in academia and the industry, and those in the FDA and other regulatory agencies.

We are not aware of any consensus on the definition of PGt and PGx, and in fact there are many different definitions in the scientific literature. Occasionally, these terms are used interchangeably. For the purposes of this article, we will consider PGx to be the global science of using genetic information from an individual or population for the purpose of: (1) explaining interindividual differences in pharmacokinetics (PK) and pharma-

May 2002

"Safe Harbor" Concept



U.S. Food and Drug Administration ▪ Center for Drug Evaluation and Research

CDER Calendar: Workshop

Search Go

CDER Home | Site Info | Contact Us | What's New

Registrations are closed, because the meeting is over-subscribed.

Meeting Notice
Workshop On Pharmacogenetics/Pharmacogenomics In Drug Development and Regulatory Decision-Making

[Day 1] [Day 2] [Register] [Workbook-PDF]

Sponsored by FDA, PhRMA DruSafe and PWG

MAY 16-17th, 2002

University of Maryland
Shady Grove Conference Center
9630 Gudelsky Drive
Rockville, MD 20850-3480

Registration on priority basis to FDA, and companies represented on the Pharmaceutical Research and Manufacturers Of America(PhRMA) Preclinical Safety Committee (DruSafe), and the Pharmacogenetics Working Group (PWG).

Fill out attached form and email before April 15th.

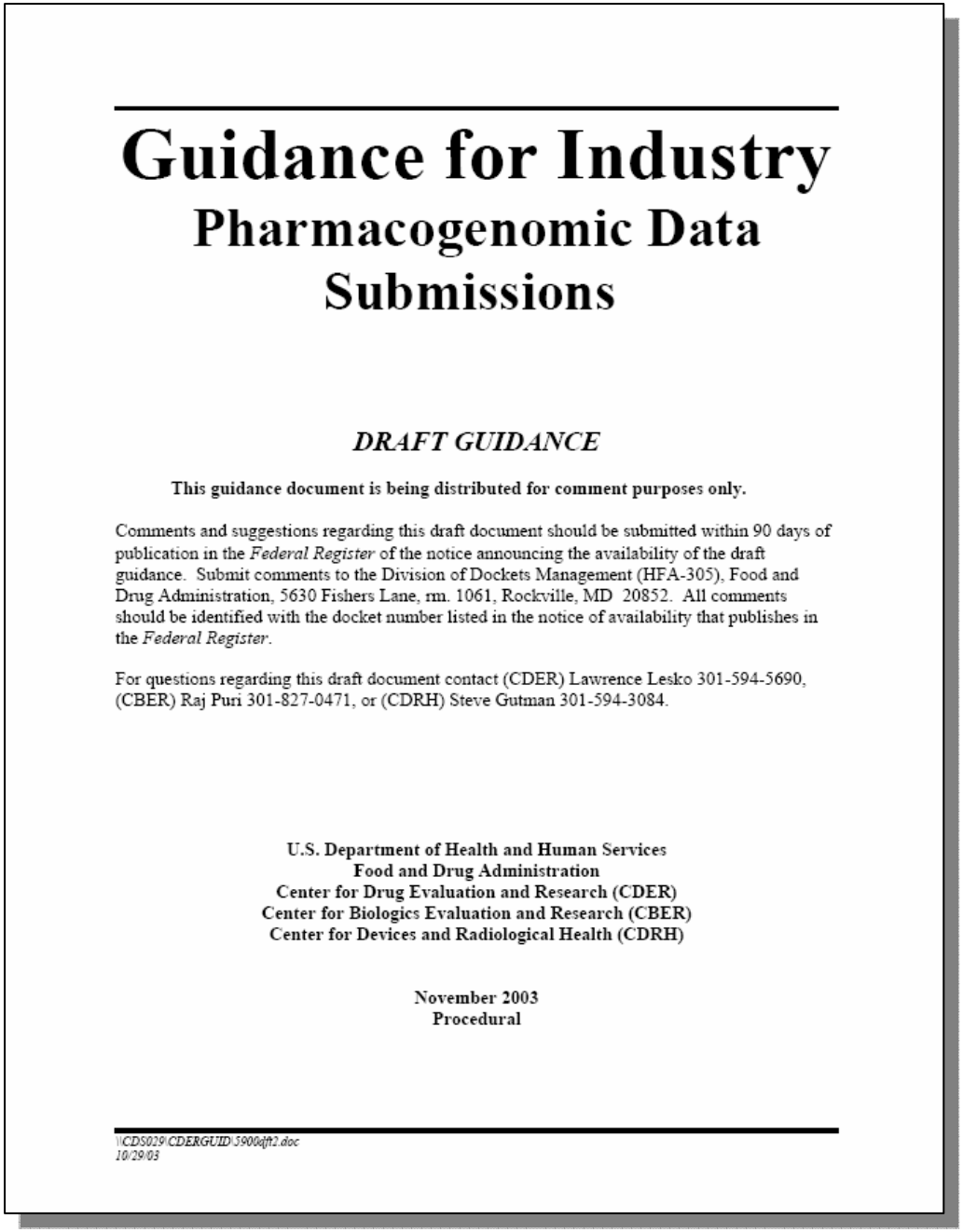
Organizing and Program Committee Co-Chairpersons

Dr. Lawrence Lesko, Director, Office of Clinical Pharmacology and Biopharmaceutics, CDER, FDA LeskoL@CDER.FDA.GOV

Dr. Ronald A Salerno, Director,
Worldwide Regulatory Affairs, Wyeth
Salernr@war.wyeth.com

November 2003

Voluntary
Genomic
Data
Submission



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

\\CDS029\CDERGUID\5900dft2.doc
10/29/03

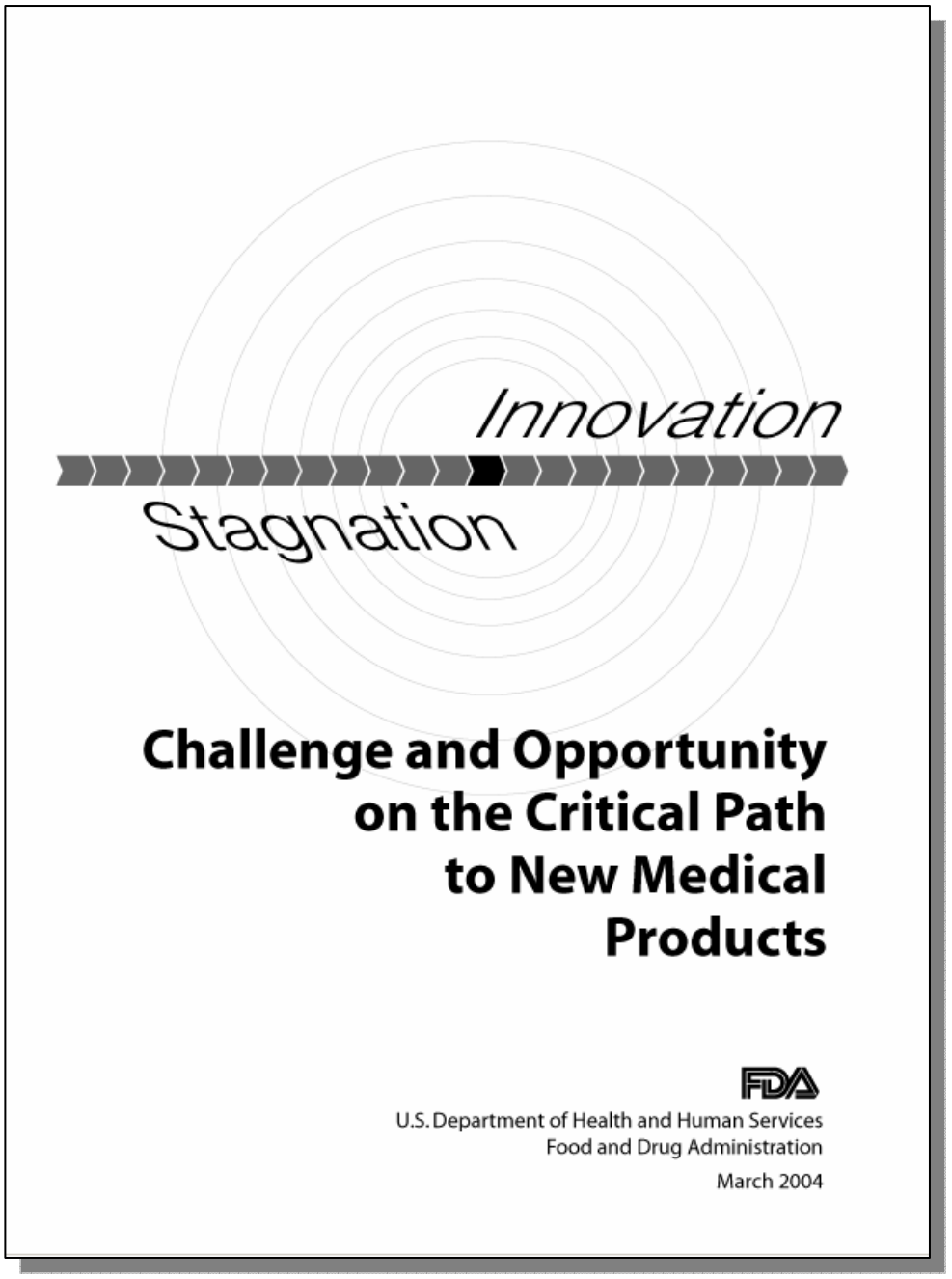
Draft Guidance: Comments to the Docket

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. ✓ ***General recommendations on content and format***
   - **How much data, what type, …**
4. ✗ ***Specific technical questions related to DNA-based assays***
   - **Data format, QC, analyzing microarray data, assay validation, marker validation**

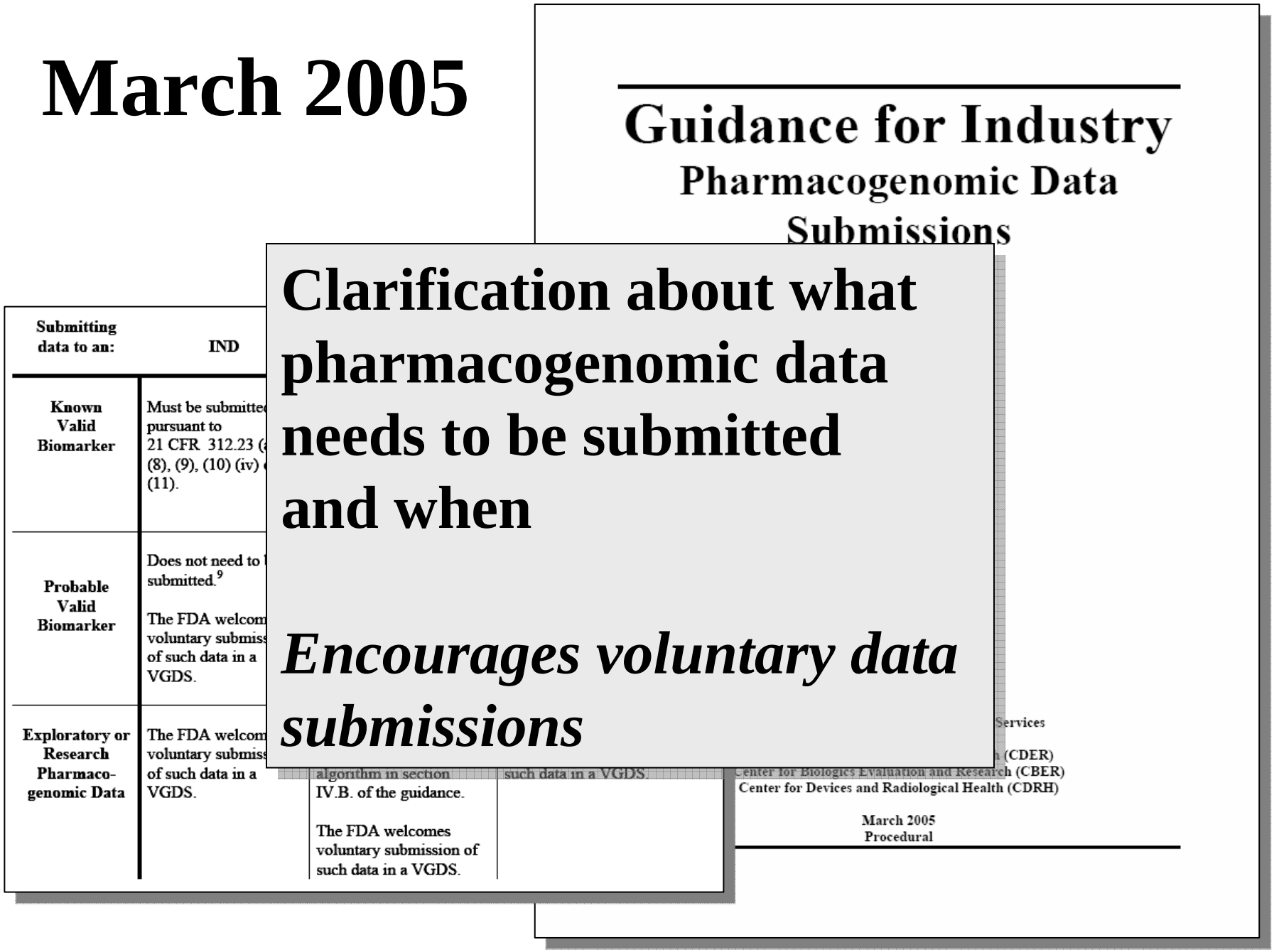
March 2004

Pharmacogenomics identified as a key opportunity

An initiative broadly welcomed by stakeholders



March 2005



Guidance for Industry

Pharmacogenomic Data Submissions

Submitting data to an:	IND
Known Valid Biomarker	Must be submitted pursuant to 21 CFR 312.23 ((8), (9), (10) (iv) ((11).
Probable Valid Biomarker	Does not need to submitted.[9] The FDA welcom voluntary submiss of such data in a VGDS.
Exploratory or Research Pharmaco-genomic Data	The FDA welcom voluntary submiss of such data in a VGDS.

algorithm in section IV.B. of the guidance.

The FDA welcomes voluntary submission of such data in a VGDS.

such data in a VGDS.

Services

(CDER)

Center for Biologics Evaluation and Research (CBER)

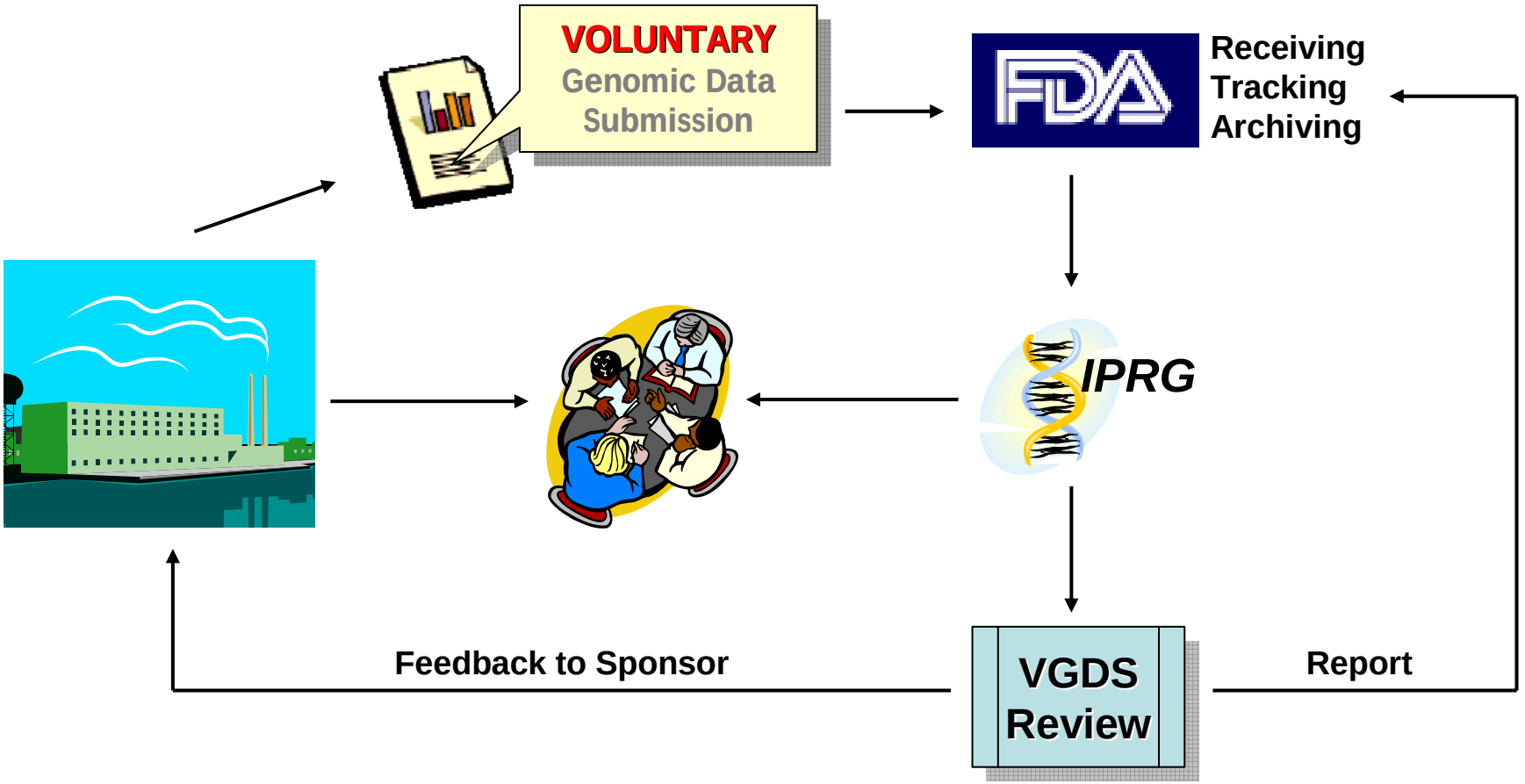
Center for Devices and Radiological Health (CDRH)

March 2005

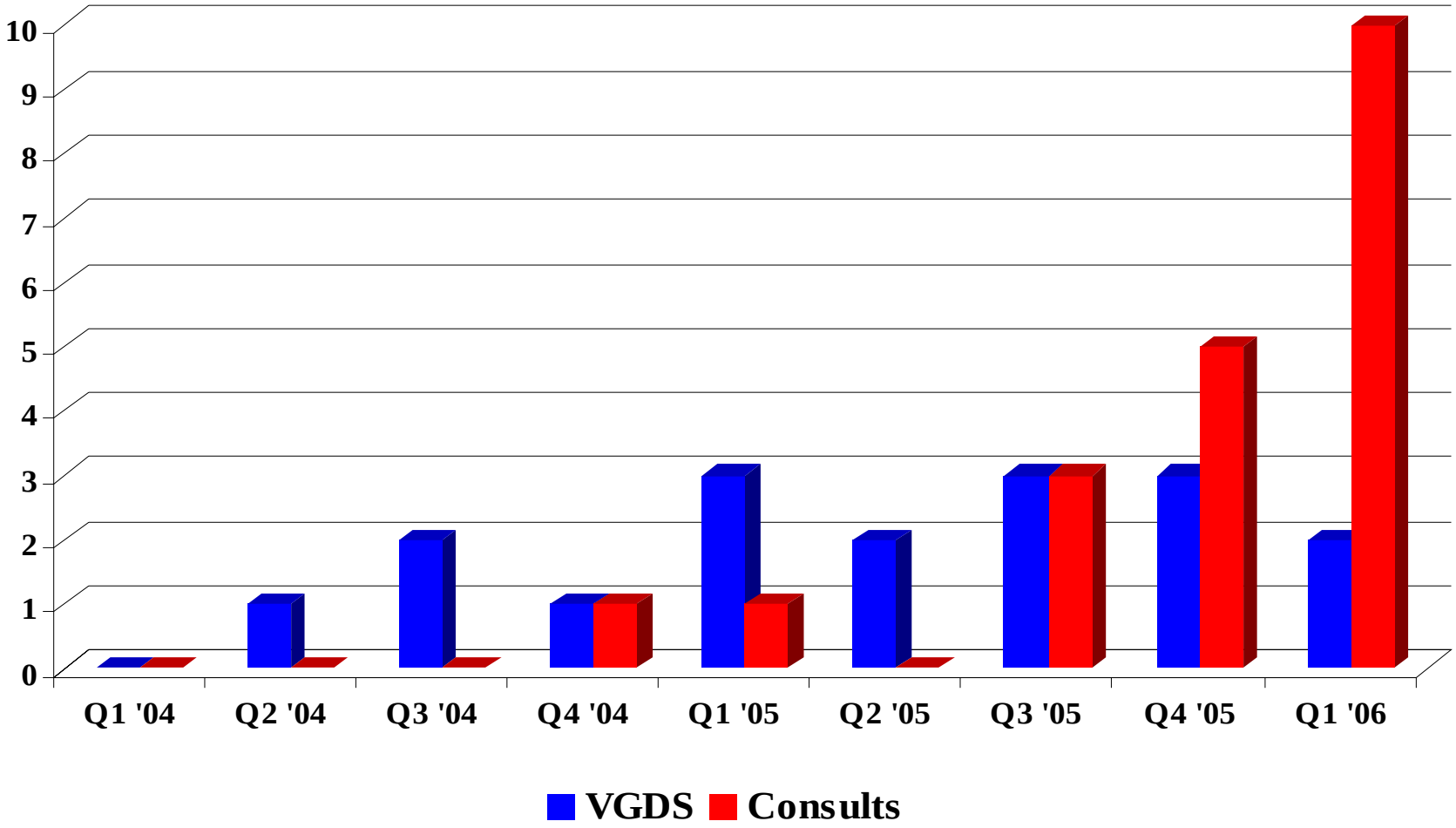
Procedural

Clarification about what pharmacogenomic data needs to be submitted and when

Encourages voluntary data submissions


VOLUNTARY
Genomic Data
Submission
FDA
Receiving
Tracking
Archiving
IPRG
Feedback to Sponsor
VGDS
Review
Report

If you build it, they will come…



Genomic Data Submitted to the FDA – General Observations

- **No pivotal genomic data submitted, but many submissions with genomic data supporting one or more hypotheses**
- **Simple approaches (e.g. single SNP or gene expression measurement) used today in clinical trials**
- **Testing the waters – what is FDA doing with genomic data?**
- **Complex data sets submitted as VGDS – not sure how or when to use data**
- **Strategic use of VGDS and IPRG meetings**

VGDS – Program at FDA so far

- ***VGDS statistics:***
  - **25 submissions received**
  - **15 sponsor meetings held**
- ***Impact:***
  - **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**

Data based on 25 submissions

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

VGDS – Limitations

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

May 2005

First FDA/EMEA bilateral joint VGDS meeting

U.S. Food and Drug Administration

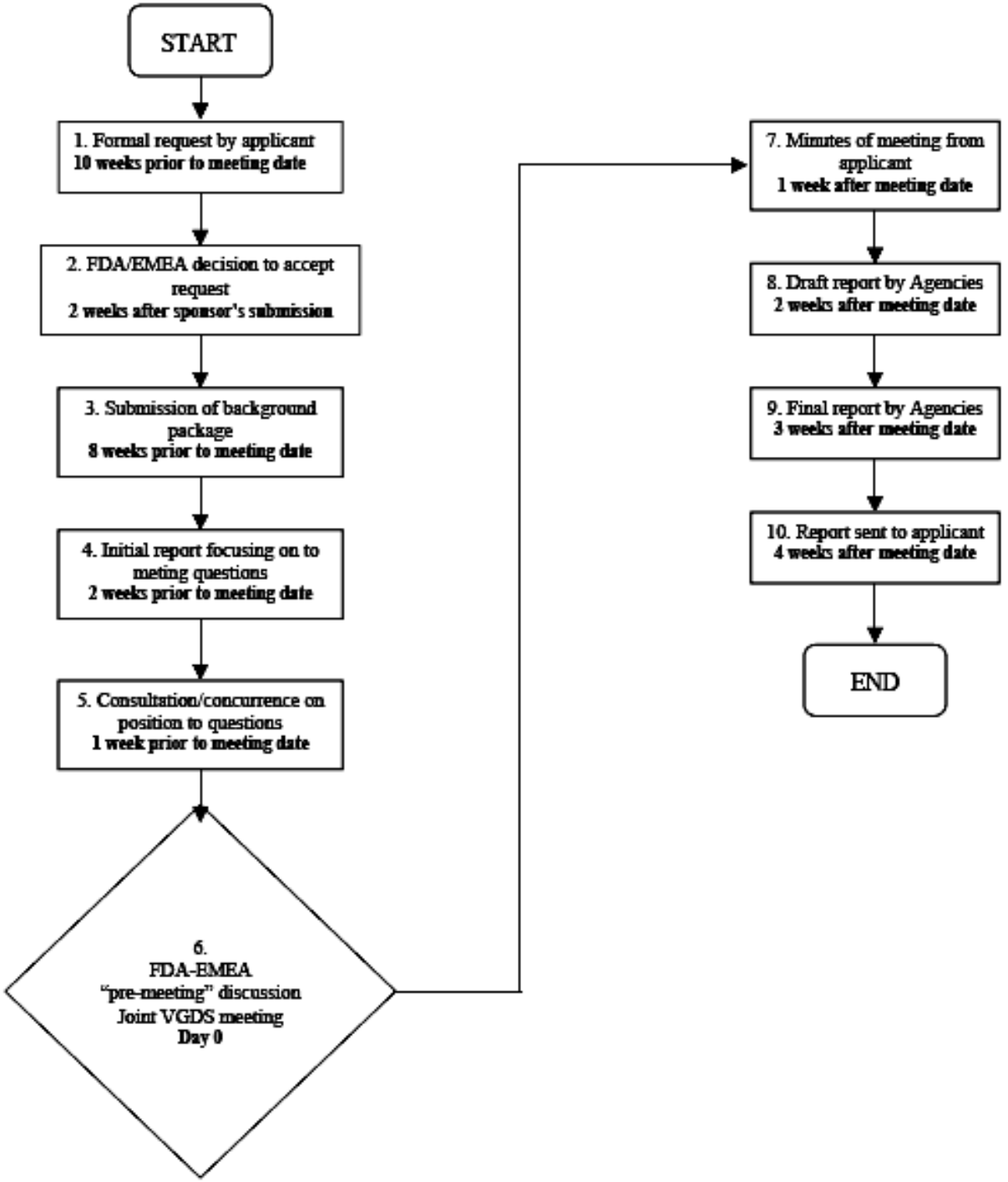
European Commission

European Medicines Agency

Guiding principles
Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs)
within the framework of the Confidentiality Arrangement

Joint FDA-EMEA VGDS Briefing Meetings

- **Voluntary Submission of Genomic Data**
  - **FDA**
    - ***Guidance for Industry*- Pharmacogenomic Data Submissions**
  - **EMEA**
    - **Guideline on Pharmacogenetics Briefing Meetings**


START
1. Formal request by applicant
10 weeks prior to meeting date
2. FDA/EMEA decision to accept request
2 weeks after sponsor's submission
3. Submission of background package
8 weeks prior to meeting date
4. Initial report focusing on to meting questions
2 weeks prior to meeting date
5. Consultation/concurrence on position to questions
1 week prior to meeting date
6.
FDA-EMEA
"pre-meeting" discussion
Joint VGDS meeting
Day 0
7. Minutes of meeting from applicant
1 week after meeting date
8. Draft report by Agencies
2 weeks after meeting date
9. Final report by Agencies
3 weeks after meeting date
10. Report sent to applicant
4 weeks after meeting date
END

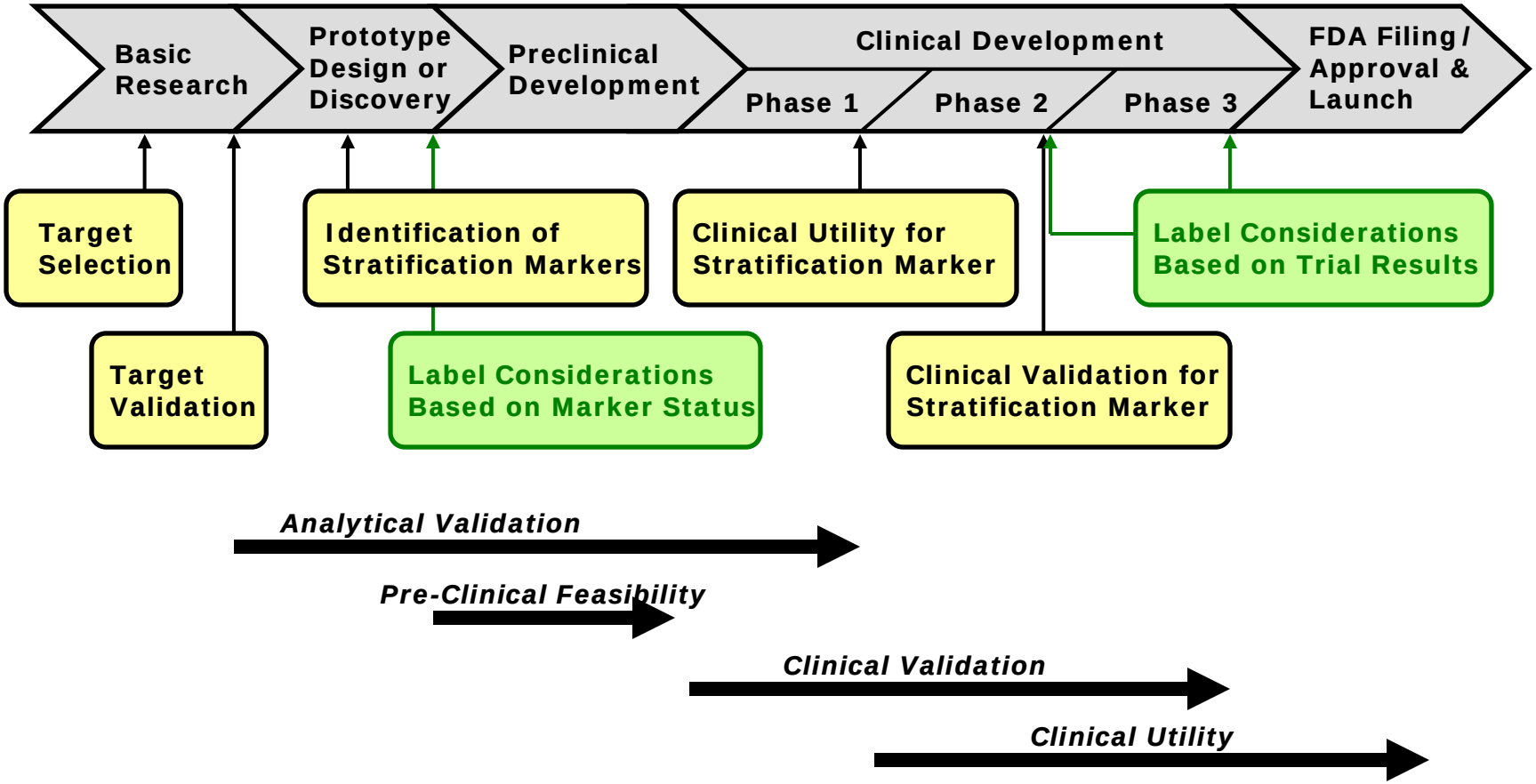
VGDS – *Joint Meetings FDA/EMEA*

- **2 meetings held, 2 more in planning**
- **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”**

VGDS – *What's next in the program?*

- **Pharmacogenomics Grand Rounds (started)**
- **Expansion into other exploratory areas: VXDS**
- **Benefit from cross-center interaction in other collaborative ways**
- **New responsibilities for IPRG**
- **Best Practices for genomic data submissions**
- **Electronic genomic data submission standards**
- **Website update: Q&A, lessons learned, other**
- **Outside experts (invited by sponsor)**

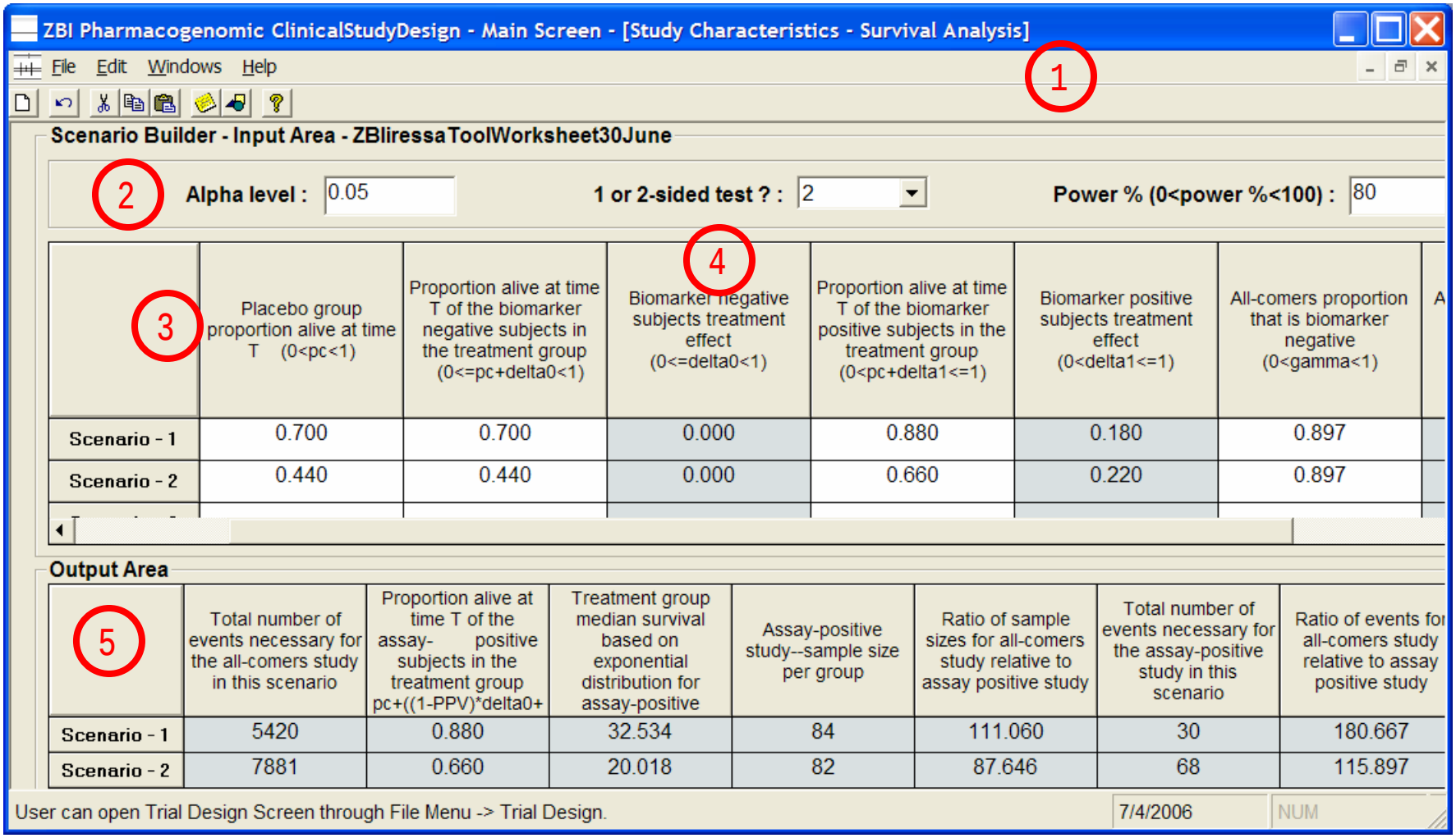
Drug and Biomarker Development Process



Clinical Science in Voluntary Genomic Data Submissions

- **What is the clinical impact of a pharmacogenomic marker?**
- **Clinical study design in drug-test codevelopment.**
  - **How many groups?**
  - **How many patients per group?**

FDA / ZBI PG tool spreadsheet: platform for using PG info in clinical study design



Nonclinical Science in Voluntary Genomic Data Submissions

- **PPARs**
- **Hepatotoxicity**
- **Vasculitis**
- **Muscle toxicity**
- **Cardiotoxicity**

Lessons Learned in Voluntary Genomic Data Submissions

- **Exploratory Biomarkers: *General Observations***
  - **Time-dependence of gene expression changes vs. histopathology**
    - **gene expression changes may precede histopathological or clinical chemistry findings**
    - **lack of temporal association does not necessarily correspond with negative findings if the ultimate goal of defining a biomarker or a gene-set is to utilize it to flag the potential for damage during treatment with a drug**
  - **Diagnostic applications of biomarkers require a temporal correspondence with the pathological measurement that these are developed for.**
  - **Microarray data with no associated physiological changes are very useful from a basic scientific perspective.**
    - **pathway analysis and comparison to reference databases are helpful in inferring hypotheses on mechanism of action for drugs**
    - **potential safety issues can be extrapolated by an accurate pathway analysis of the gene activation pattern**
    - **these conclusions will have to be experimentally verified, but would certainly add valuable knowledge and contribute to the process of defining biomarkers**

Lessons Learned in Voluntary Genomic Data Submissions

- **Exploratory Biomarkers: *Goals of the VGDS process***
  - **for certain types of VGDS data submissions, the primary interest of the sponsor would be to discuss a particularly circumscribed or strictly methodological aspect of microarray data**
    - **submission of the microarray data with 'less' ancillary data might be appropriate (although basic experimental information should always be provided).**
  - **experience reviewing VGDS data reveals, however, that the quality of interaction with sponsors often directly correlates with the breadth and detail of submitted data**
  - **VGDS is a forum for scientists from the Review Divisions**
    - **nonclinical (pharmacology/toxicology)**
    - **clinical (medical officer)**
    - **for such a discussion, ancillary data such as histopathological findings would be considered invaluable by FDA, as a means of integrating pharmacogenomic data with current regulatory science**

Lessons Learned in Voluntary Genomic Data Submissions

- **Qualified Biomarkers**
  - **independent cause-and-effect**
  - **may or may not be surrogates for histopathology**
  - **conclusions from measurements with qualified biomarkers would be acceptable in the context in which these biomarkers were qualified**
- **Specific Claims**
  - **data required depends on the nature of the claim made by the sponsor**
    - **safety issue**
    - **regulatory decision**

Lessons Learned in Voluntary Genomic Data Submissions

- **How should we consider toxicogenomic data such as those on PPARs?**
  - **These are Exploratory Biomarkers that should be qualified in the mechanistic context they are to be applied.**
  - **Conclusions from measurements with these qualified biomarkers would be acceptable in the context in which these biomarkers were qualified.**

We hold these truths to be self-evident: **how do we know that a biomarker is valid?**

We hold these truths to be self-evident: myths in biomarker validation

- **The validity of preclinical and clinical biomarkers has been traditionally settled over the course of time, debate and consensus.**

- **The acceptance of biomarker validity is limited by fear of:**
  - **added test burden**
  - **replacement of well-established biomarkers**
  - **exceptions in the sensitivity and specificity of exploratory biomarkers**
  - **incorrect context**

- **These fears have also restricted the application of novel biomarkers in drug development and regulatory review.**

We hold these truths to be self-evident: how do we know that a biomarker is valid?

- **What is a valid biomarker?**
  - ***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.***
    - **http://www.fda.gov/cder/guidance/6400fnl.pdf**

Guidance for Industry
Pharmacogenomic Data Submissions

The ones we know from 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.**
- **The Genomics Group in OCP has assembled a web-based *Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels*.**
- **This web-based table sets precedents in the definition of clinical biomarkers in specific contexts and in the "valid" classification justified within the label context.**
- **This table sets a paradigm for public communication of biomarker validity.**

Genomics at FDA

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 list of these markers and links to pharmacogenomic data, taking into account multiple regulatory contexts in which these biomarkers were approved. Most drug labels in this table provide pharmacogenomic information with no immediate recommendation for a specific action (i.e. genetic testing); however a few labels re... mend or require genetic testing thereby specifying the use of these markers for reaching a therapeutic decision.

The table includes:

1) context-specific biomarker (column 1)
2) reference drug label information about the l... ntext within which the drug was approved (column 2 subsection 1)
3) test criteria (column 2 subsection 2)
4) prototypic drug associated with the l... the biomarker context (column 2 subsecti... n 3)
5) other drugs in a similar context (c...
6) pertinent references (column 4)

Drugs sharing ...e context o... labels have had their pharmacogenomic informa... s information can be accessed ...acing t... ...der the right side of the drug name. All approved d... labels at Drugs@FD... ...pts/cder/drugsatfda/) which can be accessed by clicki... eft side of the drug name. The t... ...asis.

Search for Genomic Biomarker

Search for Drug

Biomarker	Label Context			Other Drugs Associated with this Biomarker	References
	...abel	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	**3**	Imatinib mesylate		PMID: 12851888; PMID: 16226710 PMID: 16294026

5) other drugs in a similar context (column 3)
6) pertinent references (column 4).

Drugs sharing the context 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 the symbol under the right side of the drug name. All approved drugs in this table are linked to labels at Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/) 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.

Biomarker	Label Context			Other Drugs Associated with this Biomarker	References
	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		PMID: 12851888; PMID: 16226710 PMID: 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 averag fold higher voriconazole exposure (AUCτ) than their hom extensive metabolizer counterparts. Subjects who are extensive metabolizers have, on average, 2-fold hi voriconazole exposure than their homozygous e metabolizer counterparts."	3	Voriconazole	Omeprazole[m1] toprazole [m2] meprazole[m3] zepam[m4] lfinavir[m5] beprazol[m6]	PMID: 12867215 PMID: 11866669
CYP2C19 Variants with alternate Context	**CYP2C19 Variants, drug exposure in metabolism**- Lansoprazole is metabo P450 system, specifically through th isozymes. Studies have shown that lan clinically significant interactions with othe cytochrome P450 system. Because of the s direction of the effect on theophylline clear unlikely to be of clinical concern. Nonetheless, may require additional titration of their theophylli lansoprazole is started or stopped to ensure clinical blood levels.			illin,Clarithromycin, razole;[m7] razole and Naproxen anil and Atovaquone [m9] Delavirdine [m10]	PMID: 12680476 PMID: 12495367 PMID: 12809821; PMID: 16413249; PMID: 16413245 PMID: 15871633; PMID: 15496214 PMID: 14664653

Direct link t

Popup provides PGx label information

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 biomarker qualification.**

Biomarker Qualification Process Map

Classification of Biomarkers

- ***Known valid***
  - **Accepted by scientific community at-large to predict clinical or pre-clinical outcomes.**
- ***Probable valid***
  - **Appear 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

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

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

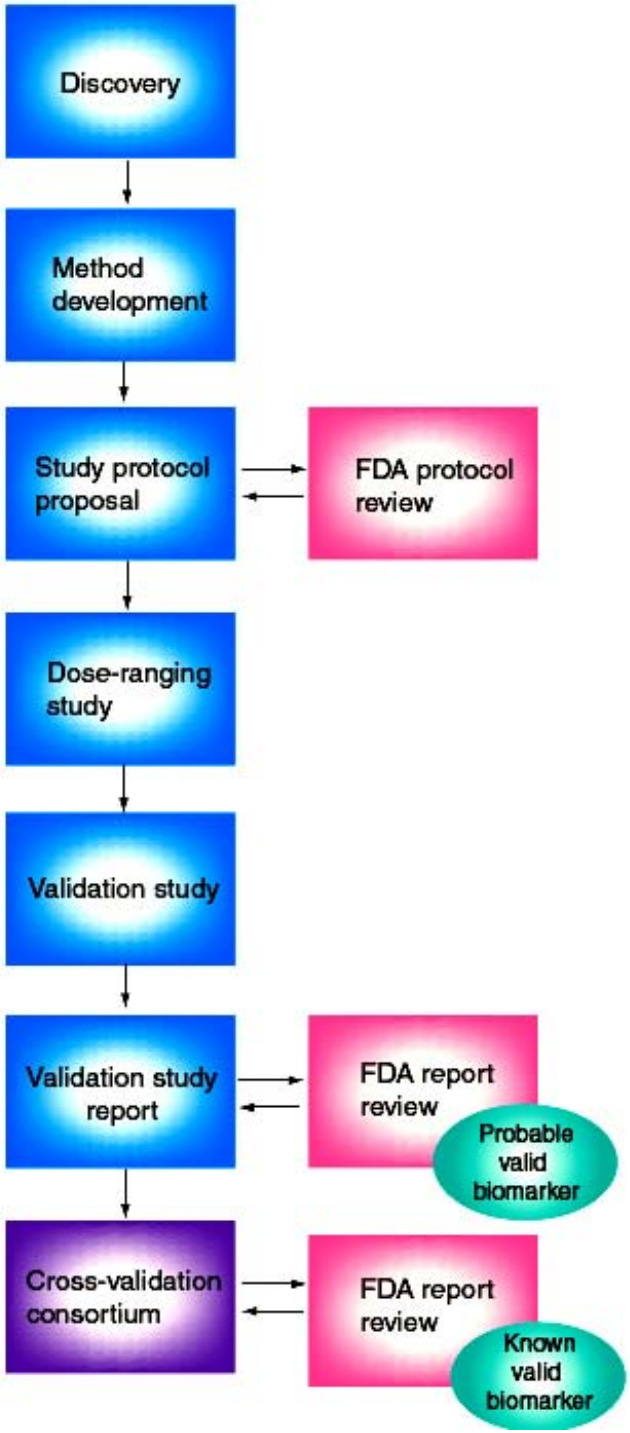
- **Examples from drugs labeled in U.S.**
  - ***Safety***
    - **TPMT (6-MP, azathioprine)**
    - **UGT1A1 (irinotecan)**
    - **CYP2C9/VKORC1 (warfarin)**
    - **CYP2D6 (Strattera)**
  - ***Efficacy***
    - **EGFR status (Erbitux, Tarceva)**
    - **Her2/neu status (Herceptin)**
    - **Philadelphia chromosome ~ Bcr-abl (Gleevec)**
    - **C-kit (Gleevec)**

Preclinical Biomarker Qualification Process Map

Anticipated Submissions

CRADA

PSTC



Process map proposal for the validation of genomic biomarkers. **(Goodsaid F, Frueh F (2006).** ***Pharmacogenomics*****, 7, 773-782)**

Pilot Structure for Biomarker Qualification at the FDA

- **New responsibilities of IPRG in this pilot structure**
  - **creation of a specific review function for the assessment of biomarker qualification data sets**
  - **evaluate study protocols and review study results for the qualification of novel biomarkers of drug safety**
    - **appropriate preclinical, clinical and statistical considerations**
    - **this function will also lead to a development of best practices and guidance for the submission of biomarker data.**
- **Pilot structure will interact with other FDA review bodies to draft a recommendation on the qualification of these biomarkers for regulatory approval by the appropriate FDA review Division.**

IPRG Biomarker Qualification Review Team

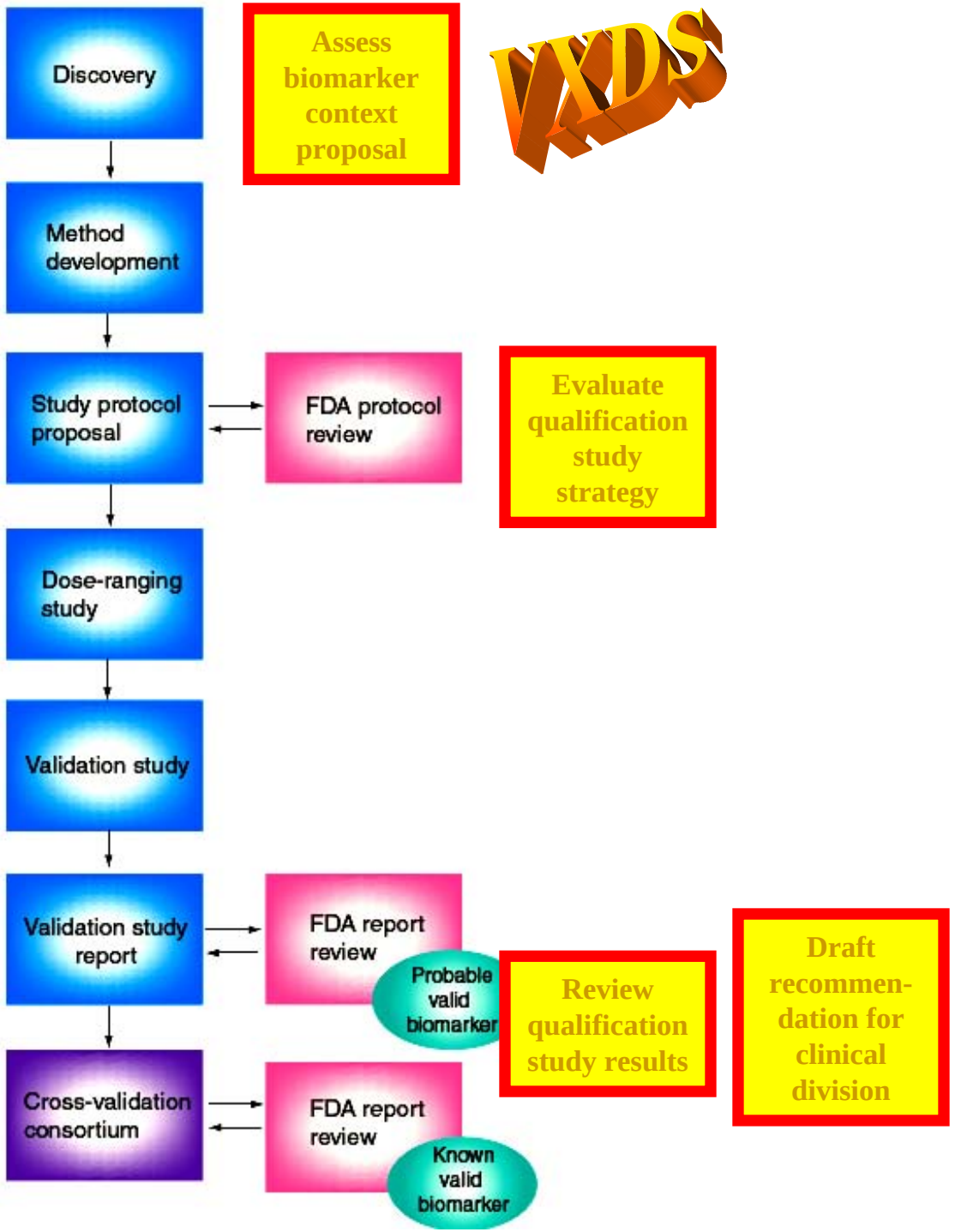
- ***Structure***
  - **Chair**
  - **IPRG members**
  - **Additional experts as needed and appropriate.**

- ***Goal***
  - **Create a specific review function for the assessment of biomarker qualification data sets.**

- ***Responsibilities***
  - **Assess biomarker context proposal**
  - **Evaluate qualification study protocol**
  - **Review qualification study results**
  - **Draft recommendation for clinical division**

Preclinical Biomarker Qualification Process Map

IPRG *Biomarker Qualification Review Team Responsibilities*



How to do it.

Case Study: *Nephrotoxicity Biomarkers*

- ***VXDS Meeting on Exploratory Biomarker Data.*** **Cover the scientific basis and experimental data supporting the context for qualification of a specific set of biomarkers.**
  - **INPUT: Exploratory biomarker data and proposed applications. Possible applications: mechanistic, diagnostic or predictive. Nephrotoxicity biomarkers under qualification at this time are likely to be mostly diagnostic, correlating with histopathology. The key question here will be whether the proposed biomarker is likely to have a long-term impact on the safety and/or cost of new drugs.**
  - **PROCESS: Review of scientific data and proposed applications supporting the biomarker. A meeting will be held with the sponsor to share this information before a decision by the IPRG Biomarker Qualification Review Team will be made.**
  - **OUTPUT: Recommendation on whether to proceed with qualification of exploratory biomarker.**

Case Study: *Nephrotoxicity Biomarkers*

- ***Qualification Study Strategy*. A first draft for a qualification protocol proposal will be reviewed by the Biomarker Qualification Review Team so that a consensus may be reached with the sponsor concerning data needed in a qualification package.**
  - **INPUT: Proposed qualification study proposal from sponsor.**
  - **PROCESS: Review by the IPRG Biomarker Qualification Review Team of qualification study proposal presented by sponsor in a face-to-face meeting. The qualification study proposal may be reviewed in the context of the number and type of nephrotoxicants and control compounds included in it, as well as the extensive use of current metrics to measure the effect of these compounds in the model animal. This reflects an iterative process to reach a consensus between the sponsor and the IPRG Biomarker Qualification Review Team regarding the qualification study.**
  - **OUTPUT: Consensus qualification study protocol.**

Case Study: *Nephrotoxicity Biomarkers*

- ***Qualification Data Report.*** **The Qualification Data Report will be reviewed by the IPRG Biomarker Qualification Review Team and the results of this review will be communicated to the appropriate division regarding the qualification of biomarkers submitted for approval.**
  - **INPUT: Qualification study report from sponsor.**
  - **PROCESS: Review by the IPRG Biomarker Qualification Review Team of the qualification study report. The review includes an assessment of data or analysis gaps. Sponsor is required to fill those gaps for a successful biomarker qualification. A final decision to accept, reject or amend the Qualification Data Report will be made by the review team and a recommendation will be drafted to classify the exploratory marker as a probable or known valid biomarker.**
  - **OUTPUT:** ***Decision to recommend or reject qualification communicated as appropriate to PTCC and cardio renal division.***

Best Practices in the Submission of Genomic Data

Why do we need to write a document on *best practices for VGDS submissions*?

- **To summarize experience gained from the analysis of Voluntary Genomic Data Submissions.**
- **To provide a reference document for future voluntary submissions and analyses.**
- **To provide a reference document for discussion at the FDA regarding best practices for submission of genomic data.**

Best Practices and Development of Standards for the Submission of Genomic Data to the FDA

Workshop Co-sponsored by

FDA | DIA Drug Information Association | PhRMA | Bio BIOTECHNOLOGY INDUSTRY ORGANIZATION

November 27-28, 2006 | Washington Marriott Hotel, Washington, DC, USA

Study Design

Clinical Study Design and Data
Angela Men, PhD
Pharmacologist, CDER, FDA

Minimum Standards for Nonclinical Toxicology Data
Lilliam Rosario, PhD
Pharmacologist, CDER, FDA

Genotyping

Methods
Shiew-Mei Huang, PhD, FCP
Deputy Director for Science, Office of Clinical Pharmacology, CDER, FDA

Reports
Maria Chan, PhD
CDRH, FDA

Proficiency Testing

Proficiency Testing
Laura Reid, PhD
Director of R&D, Expression Analysis

Gene Expression

RNA Isolation, Handling and Characterization
Shashi Amur, PhD
Senior Staff Scientist, Genomics Group, Office of Clinical Pharmacology, Office of Translational Science, CDER, FDA

Labeling Reactions
Michael Orr, PhD
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Hybridizations and Fluorescence Reader Settings
James Fuscoe, PhD
Director, Center for Functional Genomics, NCTR, FDA

Normalization and Analysis of Hybridization Data
Leming Shi, PhD
Computational Chemist, NCTR, FDA

Biological Interpretation of Differentially Expressed Genes
Emanuela Lacana, PhD
Visiting Associate, CDER, FDA

Data Submission Formatting
Weida Tong, PhD
Director, Center for Toxicoinformatics, NCTR, FDA