Voluntary Genomic Data Submissions: One Year Later

41st Annual DIA Meeting

Washington, DC

June 28, 2005

Felix W. Frueh, PhD

Associate Director for Genomics

Office of Clinical Pharmacology and Biopharmaceutics

CDER/FDA

Agenda

- History/milestones of VGDS process development
- What the guidance does and does not do
- A word about biomarkers
- VGDS (and PGx) as a business strategy
- Role of VGDS in education and policy development
- VGDS goes global
- VGDS Best Practices
- Summary

VGDS Milestones

May 2002: First FDA-DIA PGx workshop – Introduction of "Safe Harbor" concept for PGx data submissions

November 2003: Release of draft Guidance for Industry: Pharmacogenomic Data Submissions

November 2003: Second FDA-DIA PGx workshop – Discussion around biomarkers, voluntary vs. required submissions, first public comments

February 2004: Docket for guidance "officially" closed – 35 sets of comments received

March 2004: First VGDS received

July 2004: First IPRG-sponsor meeting to discuss VGDS

VGDS Milestones, cont'd

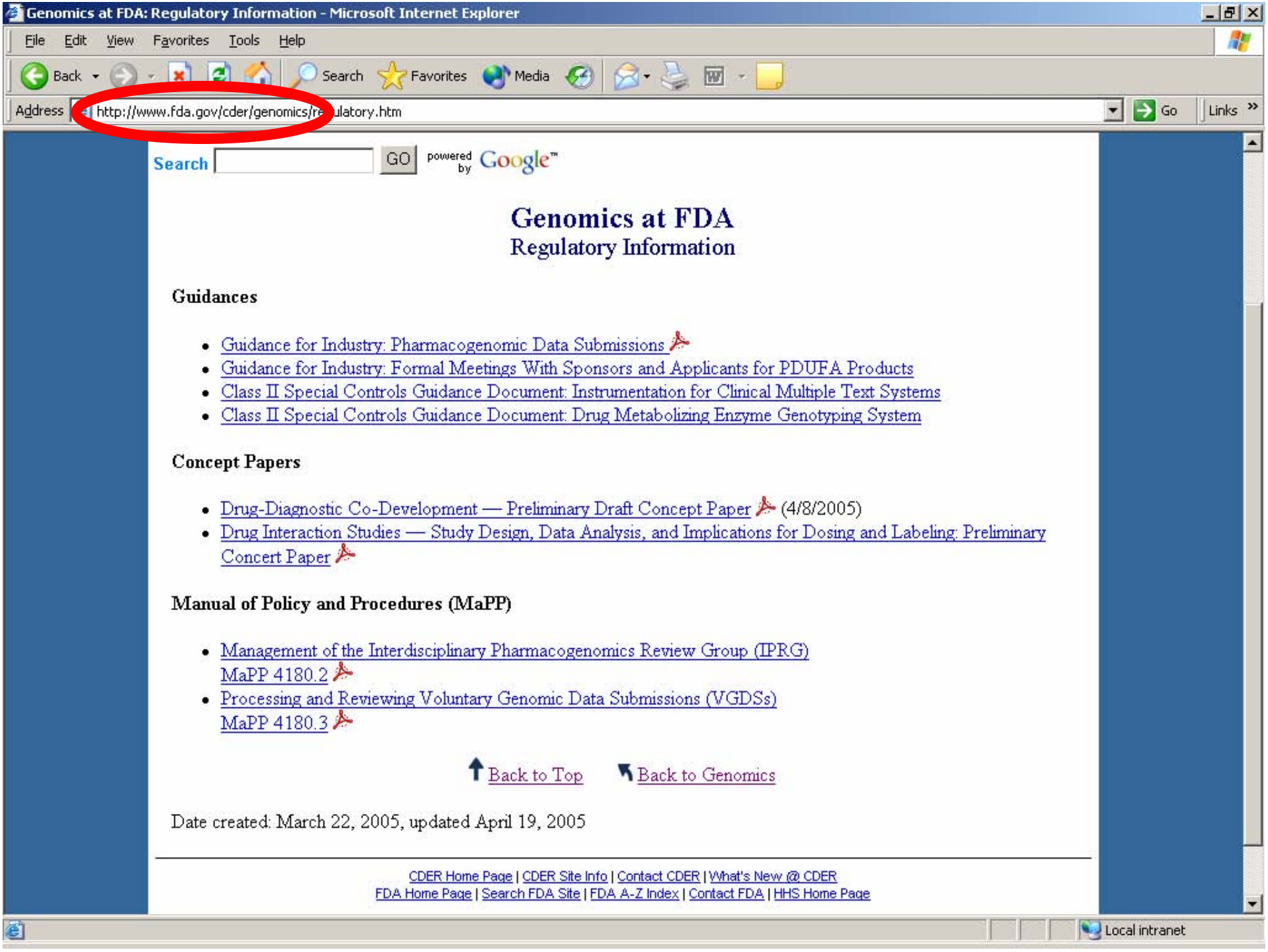
January/February 2005: IPRG formally created

March 2005: Final Guidance for Industry: Pharmacogenomic Data Submissions published, together with two companion documents detailing the VGDS process and the IPRG

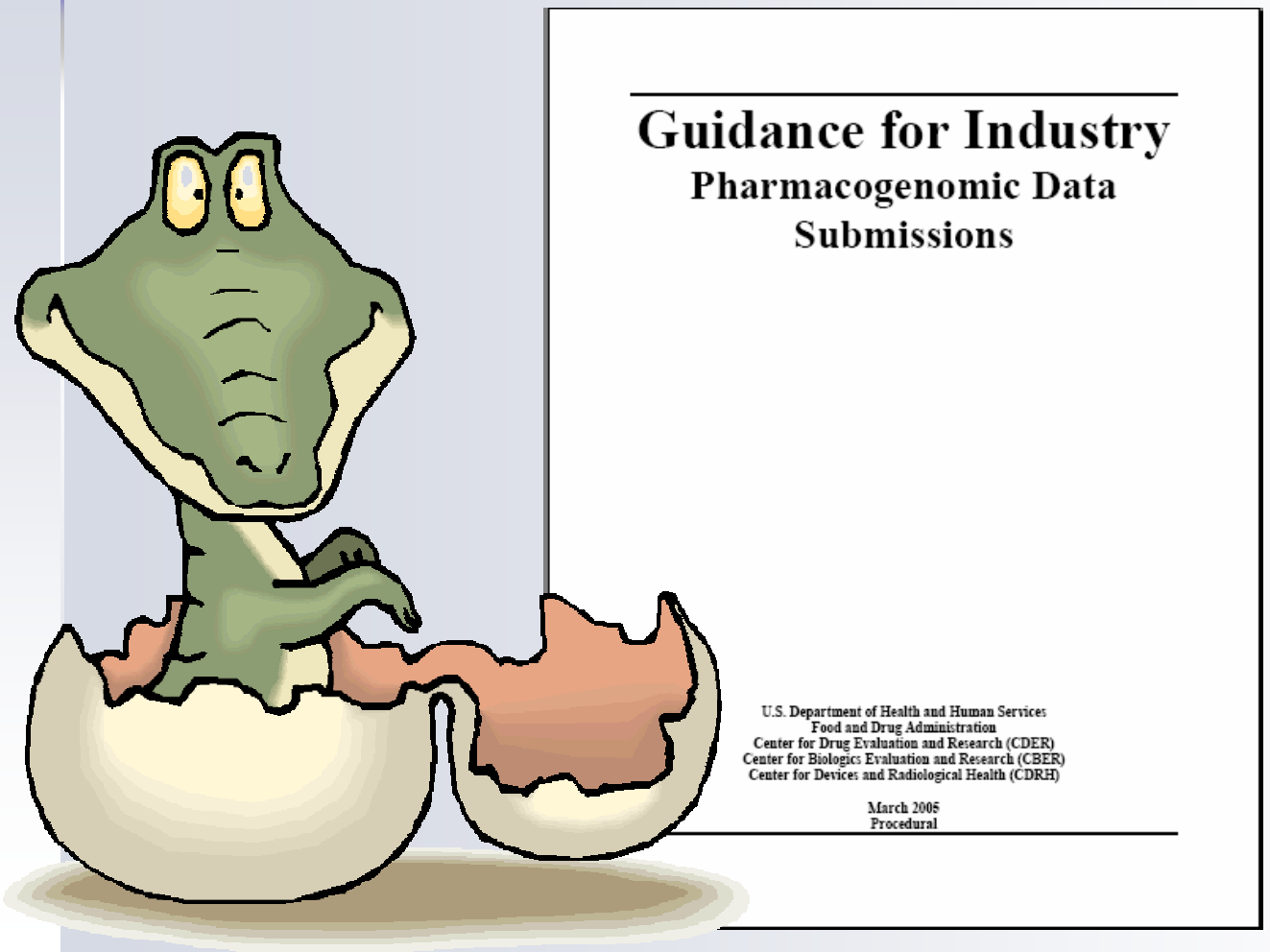
March 2005: Genomics at FDA website goes live

April 2005: Third FDA-DIA PGx workshop – Looking ahead: translating PGx into clinical trials and clinical practice

May 2005: First FDA/IPRG-EMEA/PGWP-sponsor meeting to discuss VGDS


Genomics at FDA: Regulatory Information - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites Media
Address http://www.fda.gov/cder/genomics/regulatory.htm
Go Links
Search GO powered by Google™
Genomics at FDA
Regulatory Information
Guidances
Guidance for Industry: Pharmacogenomic Data Submissions
Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products
Class II Special Controls Guidance Document: Instrumentation for Clinical Multiple Text Systems
Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System
Concept Papers
Drug-Diagnostic Co-Development — Preliminary Draft Concept Paper (4/8/2005)
Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling: Preliminary Concert Paper
Manual of Policy and Procedures (MaPP)
Management of the Interdisciplinary Pharmacogenomics Review Group (IPRG) MaPP 4180.2
Processing and Reviewing Voluntary Genomic Data Submissions (VGDSs) MaPP 4180.3
Back to Top
Back to Genomics
Date created: March 22, 2005, updated April 19, 2005
CDER Home Page | CDER Site Info | Contact CDER | What's New @ CDER
FDA Home Page | Search FDA Site | FDA A-Z Index | Contact FDA | HHS Home Page
Local intranet

Guidance for Industry: Pharmacogenomic Data Submissions



March 22, 2005

Why this Guidance Is Important

- **FDA Review**: Genomics can help to assess benefit/risk decisions – facilitates review decisions
- **Drug Development**: Guidance empowers FDA to make drug development more efficient (i.e. in IND meetings)
- **Targeted Therapy**: Genomic data submissions are an enabling step for medicines to become more precisely tailored to a patient's unique pathophysiology
- **Communication**: Encouragement of voluntary submissions, which will help to better understand variability in drug-response, foster use of new technologies, ...
- **Outreach**: Stakeholders (i.e. industry, patient advocacy groups, Personalized Medicine Coalition, ...) have expressed great interest and support

What Does the New PG Guidance Do?

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

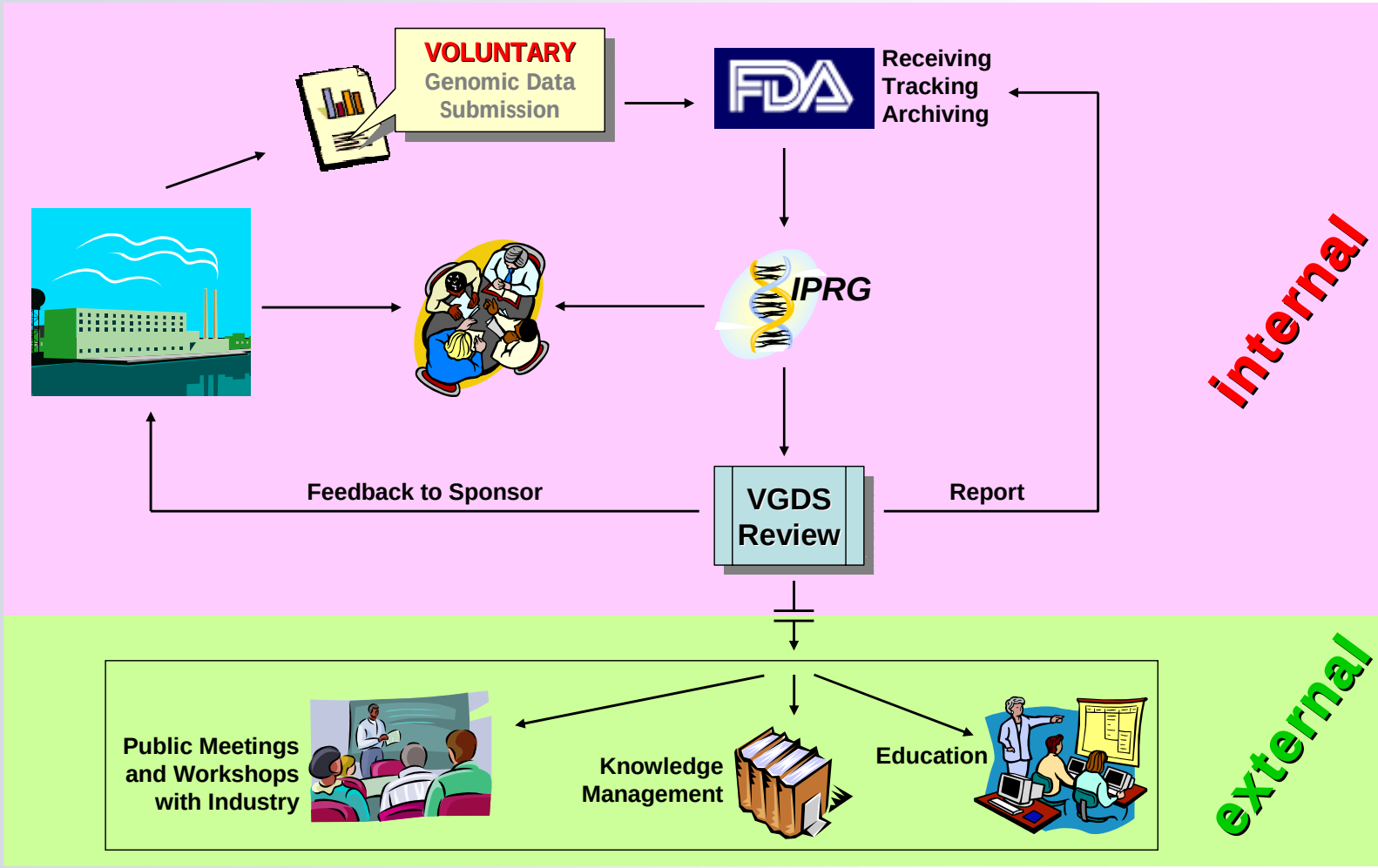
What Does the New PG Guidance *Not* Do?

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

VGDS:
A Novel Data Submission Path

- Submission of exploratory PG data submission regardless if subject of an active IND, NDA, or BLA
- Data may result from, e.g., DNA microarrays, single or limited gene expression profiles, genotyping or SNP profiling, or from other studies using evolving methodologies
- Intent to build expertise and foundation for developing scientifically sound regulatory policies
- VGDS creates a forum for scientific discussions with the FDA outside of regular review process
- Data not used for regulatory decisions

VGDS Review Process



IPRG: A New Interdisciplinary Agency-wide Review Group

- Representatives of CBER, CDER, CDRH, CVM, NCTR
- Reviews VGDS
- Consults for review divisions
- Provides advice to industry (VGDS and non-voluntary GDS)
- Ability to identify gaps in knowledge, e.g., validation, analytic methods, study design
- Presents educational/professional development courses within FDA and organizes public workshops

Genomic Data Submissions: IPRG and Clinical Review Divisions

- Voluntary submissions are received by the IPRG and are handled confidentially – data and submission are kept separate from regular, required submissions
- Experience shows that most sponsors ask for review divisions to be present at meetings: mutually beneficial to have their expertise part of the discussion
- Contact to review division might already exist – if not, this is a good way to get them interested in sponsor's genomic data, reviewed and evaluated jointly with IPRG
- IPRG does not make regulatory decisions; however, sometimes scientific and regulatory aspects of questions asked in a VGDS are difficult to separate: presence of review division at IPRG meeting can facilitate the process

The New Role of Biomarkers: Current Conceptual Framework for Surrogate Development Is Limited

- Historically, successful surrogates have linked effects on markers for single effects in large populations (i.e. BP, HIV mRNA, etc.)
- This framework needs to be expanded because:
  - It is at odds with current goals for individualized therapy
  - Does not recognize multidimensional quality of clinical response
  - Does not include possibility of multiple biomarkers providing useful information in aggregate

Biomarker: Definition

- Characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacologic response to a drug
- Biomarkers are nothing new – genomic biomarkers complement traditional biomarkers
- A biomarker is valid if:
  - It can be measured in a test system with well established performance characteristics
  - Evidence for its clinical significance has been established

Classification of Biomarkers

- **Known valid**
  - Accepted by scientific community at-large to predict clinical outcome
- **Probable valid**
  - Appears to have predictive value but not yet replicated or widely accepted

- Classification leads to specifications for validation in the context of **intended use** for biomarker

Use of Probable or Known Valid Biomarkers in Clinical Setting

- Entry criteria for a clinical trial
- Patient stratification
- Indicator for disease status
- Drug response predictor test
- Monitor drug response
- Predict adverse events
- Guide dose selection

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
  - Biomarkers associated with clinical outcome

Biomarkers – the Holy Grail ?

- Genomic biomarkers provide:
  - "progressive reduction of uncertainty" about effects
  - "increasing level of confidence" about outcomes
- They are part of a bigger picture
  - Perhaps some will become surrogates for endpoints (i.e. toxicogenomics)
  - Most will remain a factor in a multidimensional set of information along the drug development process

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."

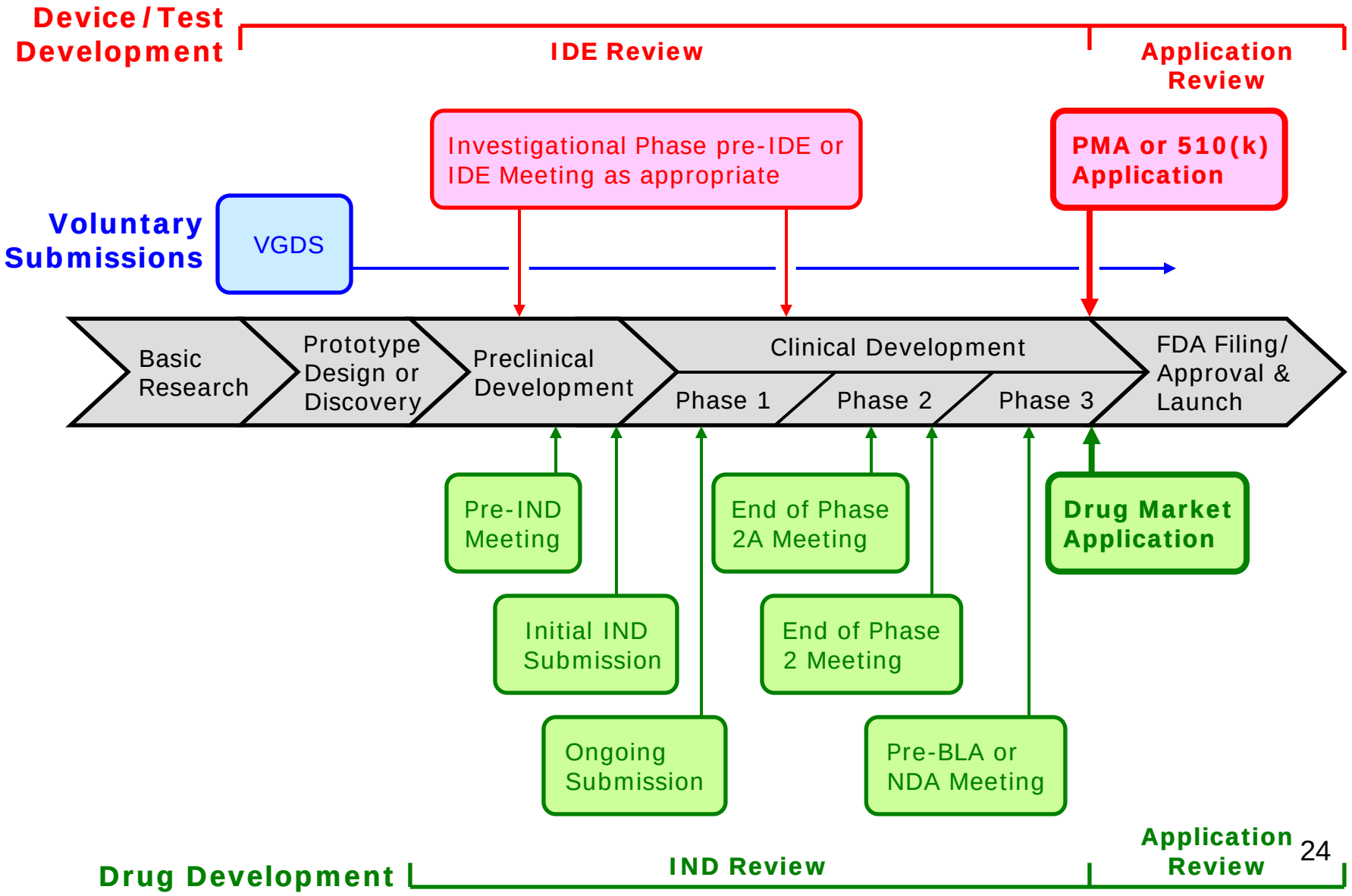
"Thanks for a very productive meeting - I got a lot of positive feedback, even from folks who were not there which means the attendees were indeed happy and felt both [company] and FDA scientists benefited. We need to work on the follow up and use this a case example for our workshop."

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

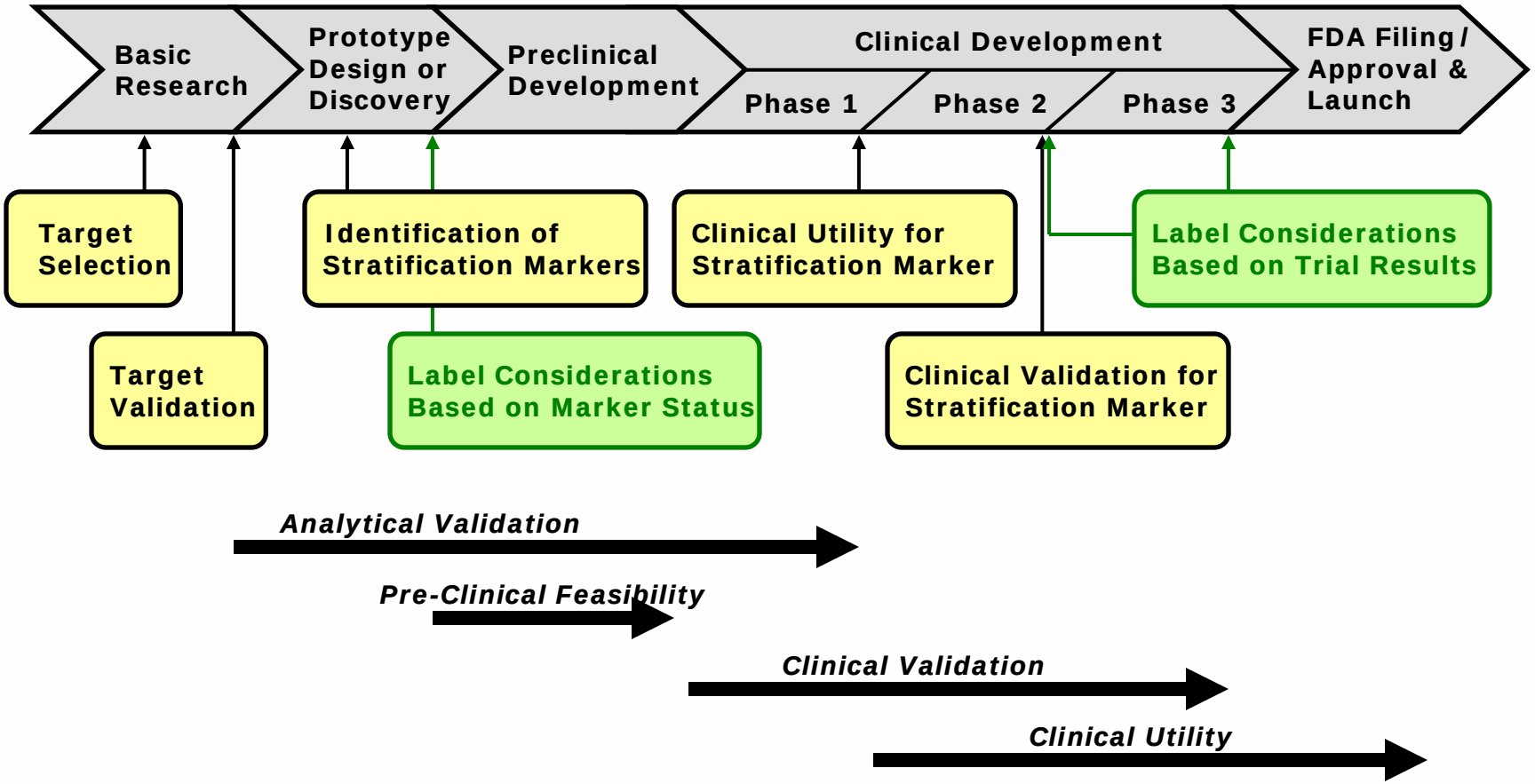
Why You Need to Submit a VGDS:

- A VGDS provides an opportunity to have informal, scientific meeting with FDA PGx experts
  - may assist in reaching strategic decisions
  - receive and benefit from informal peer-review feedback on PGx issues and/or questions
  - gain insight into current FDA thinking about PGx
  - familiarize FDA with PGx experiments, data analysis and interpretation approaches
- Pave the way for potential time- and cost-savings by familiarizing FDA with PGx 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 PGx standards, policies and guidances

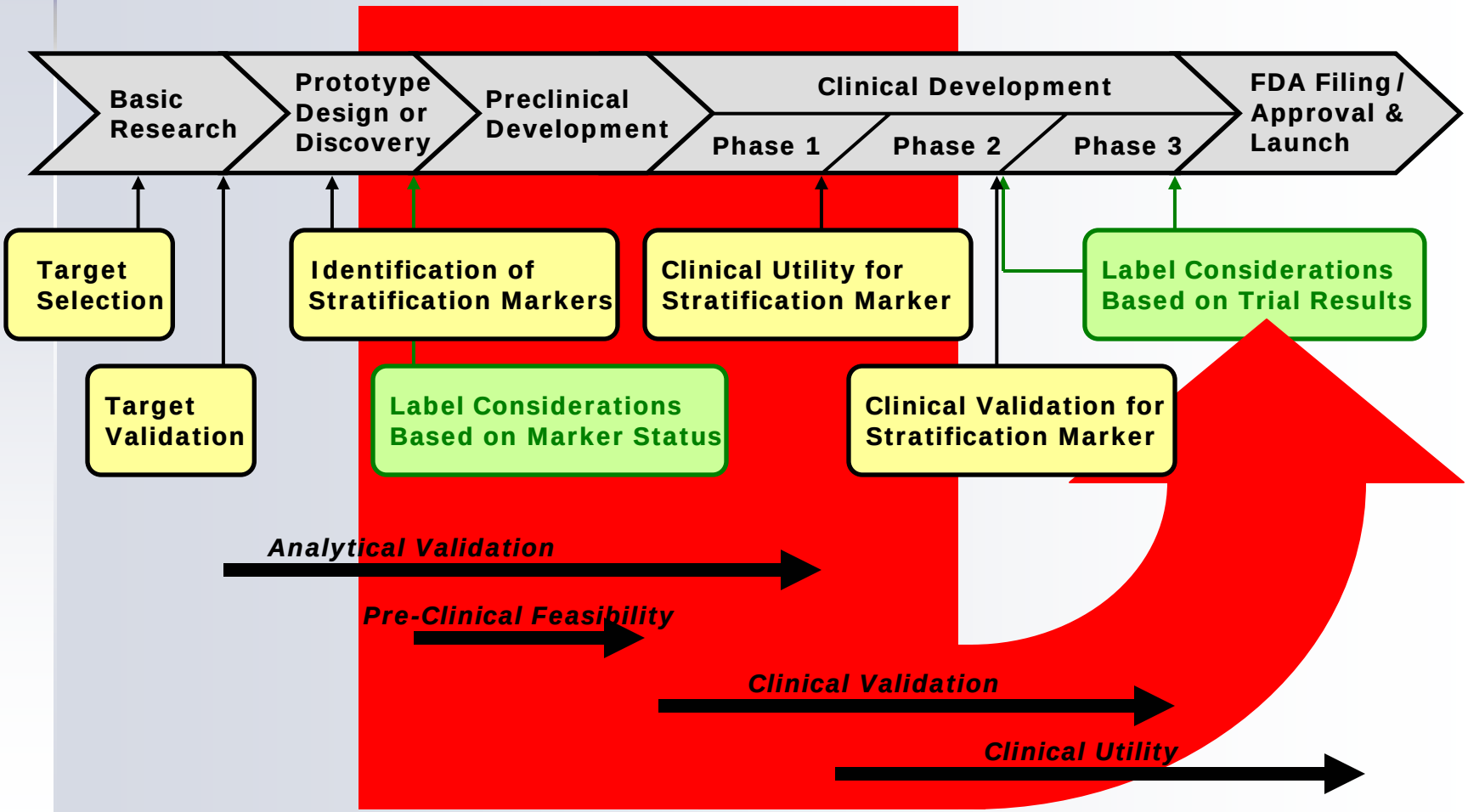
Drug(-Test) Co-Development Process:



Drug Development Timeline: Use of Biomarkers



Strategic Thinking: How a VGDS Can Help



Strategic Use of Genomic Biomarkers

- Use Genomic Biomarker for:
  - Stratification to separate responders from non-responders
  - Stratification to exclude patients at risk for AE
  - Enrichment of responder population
- Get:
  - Increased chance of winning,
  - In a shorter period of time,
  - At less cost (decreased size of trial).

Making the Business Case: FDA's Regulatory and Exclusivity Incentives

- Orphan Drug Act
  - Facilitate development of medicines for treating diseases affecting <200,000 patients
    - PGx diagnostic may define orphan indication
    - New or old drugs (may have additional indications)
  - 7 yr of market exclusivity for indication
  - Grants and tax credits to subsidize development costs
  - Expedited review

http://www.fda.gov/orphan.htm

Regulatory and Exclusivity Incentives

- 3 year exclusivity
  - Facilitate development of new claims for medicines supported by new clinical trails
  - PGx diagnostic may define target population
  - Effect larger than previously demonstrated or a superiority showing = new claim

http://www.fda.gov/cder/about/smallbiz/exclusivity.htm

VGDS, PGx, and Education

- A successful FDA internal education program for pharmacogenomics has been setup
- VGDS data (with permission from the sponsor) is used to illustrate the use and analysis of DNA microarray data in drug development
- Goal is to understand how data is evaluated and interpreted by the sponsor, not to conduct complete and new data analysis (re-interpretation)
- Meetings with sponsors are planned in “dual-mode”: i.e. both parties will present their findings and discuss the parameters that are critical for analysis

VGDS, PGx, and the Development of new Policy

- Many of the submissions raised interesting questions that are being discussed by IPRG more broadly than just in the context of the submissions themselves: i.e.:
  - Statistical issues surrounding clinical trial design
  - Retro- vs. prospective clinical trials
- These discussions lead to new guidance and policy development that are critical to the use of pharmacogenomics in drug development
- Sponsor contributions are critical

VGDS Goes Global

- May 17, 2005: first joint FDA/IPRG – EMEA/PGWP – sponsor meeting
- Videoconference, two screens: one for presenter, one for slides
- Preparation is key:
  - Interaction before meeting included in depth scientific evaluation of sponsor questions
  - This pre-meeting dialogue between FDA and EMEA resulted in a better product
  - Sponsor provided excellent presentation for interactive discussion via videoconference: presenters were present at EMEA (London, UK) and FDA (Rockville, MD)

VGDS Goes Global, cont'd

- Meeting minutes are jointly prepared by FDA and EMEA and are shared with sponsor
- What we learned, next steps:
  - FDA and EMEA evaluated, with only minor differences, the submission similarly, no dispute over science
  - Both agencies adjusted their usual format to accommodate the requirements necessary for a joint event
  - Communication is critical: clear definitions are a must
- Positive experience: next meeting planned for Q3 2005
- First step to "harmonizing"? This could provide a new paradigm for this process: learning while doing!

VGDS and Use of Genomic Data: What Are the Obstacles ?

- Why some companies decide NOT to submit a VGDS:
  - It's not a "safe harbor"
  - It's "voluntary", why bother?
  - Fear of inappropriate data interpretation
  - FDA will ask for MORE information if genomic data is part of submission
- Genomic data and its use in drug development:
  - Business incentives
  - Clinical trial designs: how far can we go
  - Impediments: statistics and economics, what can we do?
  - Should FDA simply REQUIRE genomic data to be submitted?

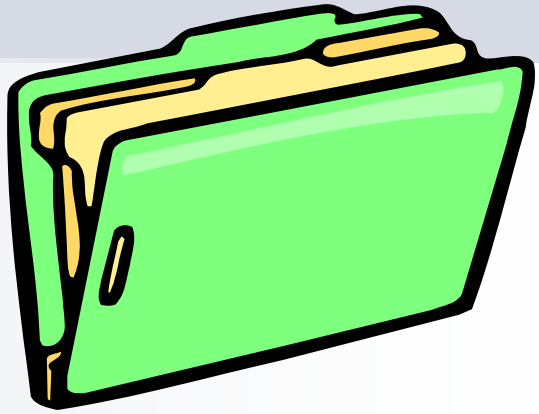
OK, you're forward thinking and you decided to submit a VGDS

How to do it – Best Practices

First Steps:

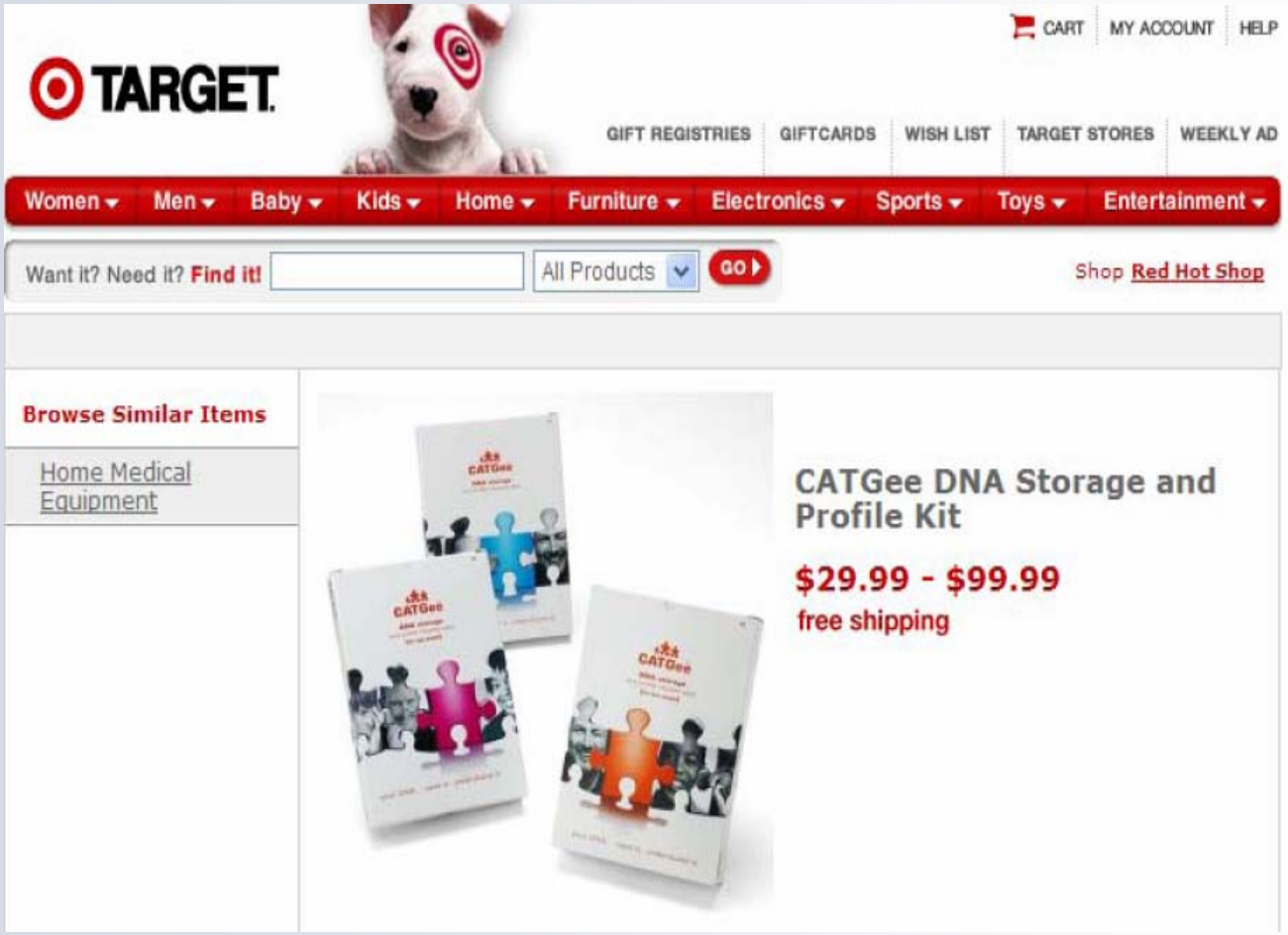
- It might be a good idea to simply contact the Executive Secretary or IPRG Chair to discuss...
- Determine the scope of the meeting
- Put request for meeting in writing and include:
  - Scope of meeting
  - List of sponsor attendees
  - List of FDA attendees, if available
  - Executive Summary
  - List of questions
- Send background package with request or immediately after request is acknowledged

Background is extremely important…

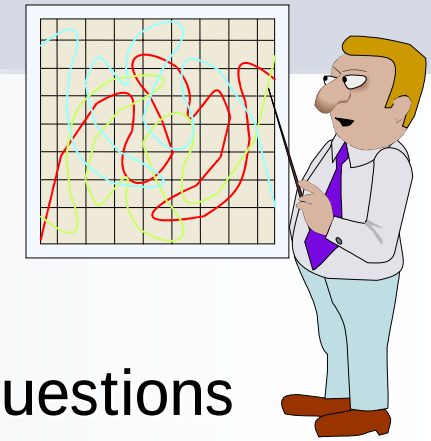


- Package should include:
  - Scope of the meeting
  - Agenda
  - List of attendees
  - Specific questions IPRG should address
  - ! Avoid general questions like: “Is the protocol ok?”
- Provide package at least 4 weeks prior to meeting, or by date requested, in order for IPRG to fully prepare for meeting

It's a voluntary genomic DATA submission !



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 …

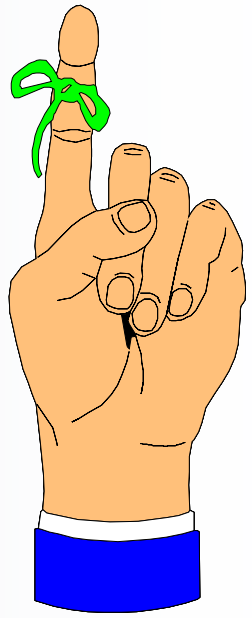
- Stick to the designated scope and questions
- Limit meeting to 1 hour or less for presentation, questions, responses, and action items
- Start and end on time
- Be open to advice from FDA
- Get action items reiterated or recapped at the end of the meeting
- Take meeting minutes

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

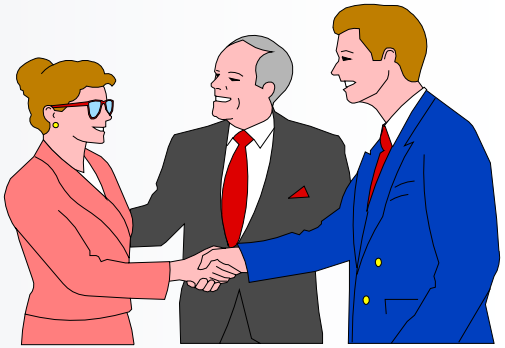
IPRG Disclaimer

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)



In Conclusion

- First VGD submission a little over one year ago, approx. 15 since
- Diversity in submission quality led to the development of best practices; since, the quality has been consistently high.
- Despite it being a critical point in comments to the draft guidance, most sponsors would like to have Clinical Review Divisions participate in IPRG – sponsor meetings
- Informal feedback has been very positive – more formal feedback will be collected (questionnaire)
- The two first sponsors have submitted a second, follow-up VGDS
- VGDS can be part of drug (and device) development strategy
- There are good business reasons to use PGx in drug development
- The VGDS process has taken on an international spin
- Discussions around expanding VGDS into VXDS have started...

Acknowledgements

- Larry Lesko, PhD
- Janet Woodcock, MD
- Allen Rudman, PhD
- Shiew-Mei Huang, PhD
- Federico Goodsaid, PhD
- All of IPRG
- Colleagues at EMEA
- Colleagues at Industry

www.fda.gov/cder/genomics

Felix.Frueh@FDA.gov
Office of Clinical Pharmacology and Biopharmaceutics
FDA/CDER