Voluntary Genomic Data Submissions at the U.S. FDA

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Guidance for Industry: Pharmacogenomic Data Submissions

www.fda.gov/cder/genomics

www.fda.gov/cder/genomics/regulatory.htm

What Does the 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 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

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

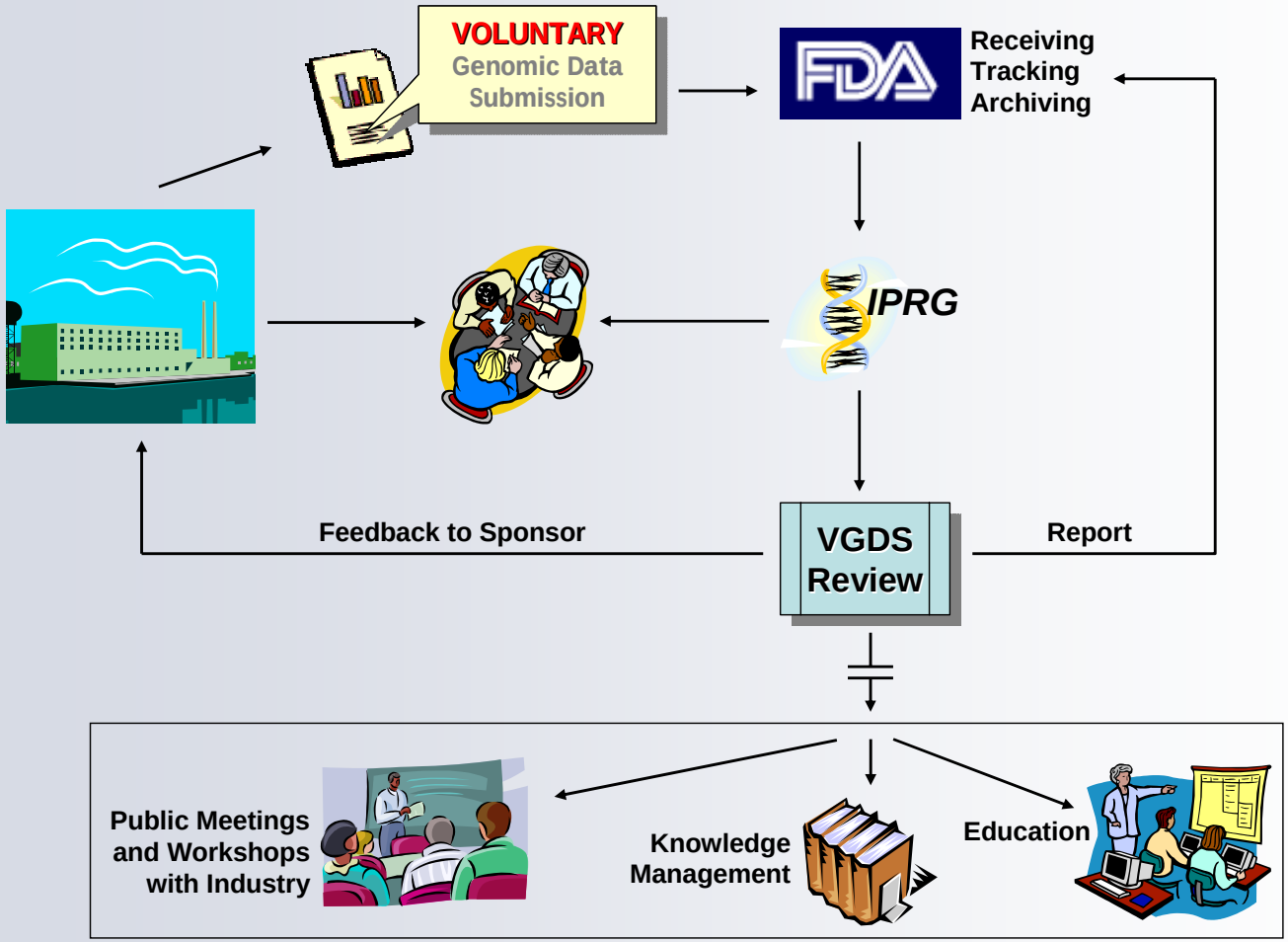
Classification of Biomarkers, cont'd

- **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

VGDS: A Unique 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

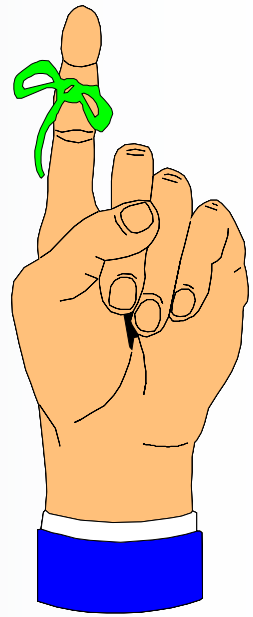


IPRG: An Interdisciplinary, FDA-wide Review Group

- 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

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.***



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

Drivers to Accept a VGDS

- Cover broad clinical areas to illustrate impact of genomics in all therapeutic fields
- Immediate impact, i.e. toxicogenomics
- Associated with active drug development programs
- Interesting designs for i.e. stratification/enrichment
- Challenging data analysis (tools, statistics, etc.)
- New technologies
- Follow-on submissions
- Biomarker discovery and qualification, i.e. use of repositories, biobanks

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

VGDS: Value and Benefits

- Sponsor:
  - Opportunity to have informal, scientific meeting with FDA PG experts
  - Eliminate uncertainty about PG data submissions and review at FDA
  - May assist in reaching strategic decisions
  - Receive and benefit from informal peer-review feedback on PG issues and/or questions
  - Gain insight into current FDA thinking about PG
  - May avoid future delays in review
- FDA:
  - Familiarize with PG experiments, data analysis and interpretation approaches
  - Education
  - Ensure data driven development of new policies and guidances
  - Build consensus around PG standards
- Both:
  - New strategies for using PG in drug development
  - Learn about benefits and limitations
  - Discuss analysis approaches

VGDS: Limitations

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

VGDS Lessons Learned

- Meeting Preparation:
  - Early communication
  - Manage expectations
  - Data vs. no data submissions
  - Evaluation of sponsor questions
  - “VGDS Best Practices”

- Data Submission:
  - Need for standards (e.g. HL7, CDISC, others)
  - Dedicated server, access rights for IPRG (intranet)

VGDS Lessons Learned, cont'd

- Regulatory and Policy Impact:
  - Need for more clarity: e.g. studying "off"-groups
  - Statistical considerations
  - Innovative trial designs (e.g. enrichment strategies)
  - Involvement of Clinical Review Divisions
  - Drug-Test Co-development

VGDS Lessons Learned, cont'd

- Education:
  - Creation of FDA/CDER course on pharmacogenomics
  - Rotations in Genomics Group to expose reviewers to genomic data sets (new candidates always welcome!)

- Other:
  - Sponsors appreciate opportunity for open, informal data exchange and discussion
  - Biomarker validation critical
  - Sponsors (in formal feedback) rank VGDS meetings a 4 out of 5, with regulatory aspect being viewed more important/helpful than scientific impact.

VGDS Lessons Learned, cont'd

- Data Review:
  - Complexity of data
  - Much data/information is VERY exploratory
  - Whole genome scans (SNPs and gene expression)
  - Statistical considerations
  - Biological interpretation, e.g. pathway analysis
  - Need for customized software and analysis tools
  - More thorough data analysis is valued by sponsors: sponsor and FDA present results

Globalization of VGDS – Aspects of Joint Meetings

- 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 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!

The Future of VGDS

- VGDS will ...
  - ... become an integral part of drug development programs – used for, i.e. strategic decision making
  - ... be used to finesse clinical study designs
  - ... serve to develop benchmarks for genomic biomarker qualification
  - ... become VXDS for the submission of other eXploratory data (i.e. proteomics, metabolomics, etc.)
  - ... continue to be a critical part of reviewer training on PG issues

  ... have demonstrated when and how to use PG data in drug development and how to review it.

  → PG data will be used in required submissions and staff has gained experience and expertise for adept review of such data.

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