Challenges and Issues for Pharmacogenomics Data Review in the FDA’s VGDS Program

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A Novel Data Submission Path
- Voluntary Genomics Data Submission (VGDS)

- Defined in Guidance for Industry on Pharmacogenomics (PGx) Data Submission (draft document released in 2003; final publication, 2005)
  - To encourage the sponsor to interact with FDA through submission of PGx data on a voluntary basis
  - To provide a forum for scientific discussions with the FDA outside of the application review process
  - To establish a regulatory environment (both the tools and expertise) within the FDA for receiving, analyzing and interpreting PGx data
VGDS Status

- Total of ~40 submissions have been received
- The submissions contain PGx data from:
  - DNA Microarrays
  - Proteomics
  - Metabonomics
  - Genetic data (e.g. genome wide association studies (GWAS))
  - Other biomarker methodologies
- 2007: From VGDS to VXDS
VGDS Objectives

• Goals
  – Data repository
  – Reproduce the sponsor’s results
  – Conduct alternative analysis

• Need a bioinformatics infrastructure in the FDA to accomplish these goals
ArrayTrack: An FDA Bioinformatics Tool for VGDS

Clinical and non-clinical data

Microarray data

Proteomics data

Metabolomics data

Chemical data

Public data
MicroArray Quality Control (MAQC) - Address the Challenges and Issues Identified in VGDS

• QC issue – How good is good enough?
  – Assessing the best achievable technical performance of microarray platforms (QC metrics and thresholds)

• Analysis issue – Can we reach a consensus on analysis methods?
  – Assessing the advantages and disadvantages of various data analysis methods

• Cross-platform issue – Do different platforms generate different results?
  – Assessing cross-platform consistency
<table>
<thead>
<tr>
<th>Projects</th>
<th>Scientists (orgs)</th>
<th>Duration or status</th>
<th>Focused on</th>
<th>Outcomes (peer reviewed publications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAQC-I</td>
<td>137 (51)</td>
<td>02/2005 – 09/2006</td>
<td>Reliability of microarray technology</td>
<td>6 manuscripts</td>
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<tr>
<td>MAQC-II</td>
<td>194 (86)</td>
<td>09/2006 – 03/2009</td>
<td>Clinical application using Microarrays and GWAS</td>
<td>Manuscripts under review</td>
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<td>MAQC-III</td>
<td>---</td>
<td>On-going</td>
<td>Next generation sequencing</td>
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<td>MAQC-IV</td>
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<td>Planning stage</td>
<td>Personalized medicine</td>
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Gate to the Future
- Integrating Research and Bioinformatics into Regulation
Companion Guidance

Lessons Learned from VGDS and MAQC have led to development of “Companion to Guidance for Industry on Pharmacogenomic Data Submission (Docket No. 2007D-0310)”

– Over 10 pharmas have provided comments

Guidance for Industry
Pharmacogenomic Data Submissions — Companion Guidance

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, 5600 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) Federico Goodman, 301-796-1515 or (CDER) Raj Puri, 301-827-6471.

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Procedural
Recommendations Related to Data Submission

• The companion guidance encourages the electronic data submission (e-submission) for VGDS

• E-submission for microarray gene expression data
  – Tab-delimited table to summarize the gene expression experiment
  – Raw and/or normalized data need to be submitted for VGDS
  – The submission of gene lists with statistical analysis protocol is required

• E-Submission for clinical and non-clinical data
  – Follow the guidance and format of CDISC/SEND

The document is evolving!
Issues and Challenges

• Due to lack of specific instruction for submission, we observed
  – The majority of submission are summarized in the pdf documents, including study data and statistical results and findings (e.g., gene lists, p-value, FC)
  – E-format of raw and digested data is usually available after communication

• The major challenge is related to statistical analysis
  – Description is not clear in detail so that the results are difficult to be reproduced
  – Various methods (some are customized approaches) are reported; no clear criteria to assess the validity of the methods

• Needs in VGDS as well as for regulatory submission
  – Standard(s) for data submission, including both PGx and study data
  – Standard(s) for reporting analysis methods and procedure