

PERLEGEN

SCIENCES

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
rm. 1061
Rockville, MD 20852

Docket No. 2003D-0497

To Whom It May Concern:

The guidance entitled "Pharmacogenomic Data Submissions" is clear and helpful in delineating the process by which pharmacogenomic data will be evaluated and how the data can be submitted as a VGDS to establish a history and context. The document was especially helpful in addressing GLP issues in collecting pharmacogenomic data. Perlegen Sciences, Inc. would like to make the following comments on the draft guidance:

Comment 1

It is important that a clear distinction be made between genotyping data and expression data derived from microarrays. This distinction is clearly delineated except on page 11 of the draft guidance, which specifically addresses the format and content of a VGDS. The document discusses the use of MAIME standard for submission of microarray expression data. It then continues (beginning on line 438) "An analogous approach could be used for formatting a VGDS containing genotyping or other genomic data derived from technology platforms **other than** nucleic acid hybridization arrays" [emphasis added]. At Perlegen, we use high density oligonucleotide arrays as a technology platform to derive genotype data. These arrays are distinct from expression microarrays in their design and use, and in the data analysis algorithms used in their interpretation (Hinds et al, in press). As genotypes are derived from these arrays, these data ultimately can be validated and evaluated in a platform-independent manner. We would hope that the more specific guidance about data submission that the Agency is developing (lines 469 and 670) also will take into account this distinction.

Comment 2

The algorithm for submission draws a distinction for "general exploratory or research information" (item 4, page 9), where "submission of a synopsis of the study" (lines 373 and 374) is sufficient to satisfy requirements. However, voluntary submission of all data in a VGDS is encouraged. Perlegen is interested to learn the extent to which exploratory information is regarded as germane to the Agency. Our process generally involves the evaluation of over a million SNPs in pooled samples of several hundred cases and controls. This process is used as a screen to enrich for a subset of the SNPs that have an implied large allele frequency difference between cases and controls (Frazer et al, 2003). This SNP subset (generally about 30,000 SNPs) is then genotyped individually in each case and control subject, and the allele frequency differences for each SNP is derived. Those SNPs with potentially significant association with the phenotype of interest, be it drug efficacy or adverse reaction, are then subjected to confirmation in additional samples (replication). This entire process is somewhat analogous to the drug screening process where several thousands or millions of compounds are screened to identify lead compounds which are further refined in subsequent tests. The subset of SNPs (several 10's to 100's) would be

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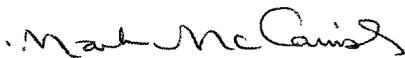
confirmed by replication and validated by a different platform. These 'lead SNPs' would be considered the SNPs significantly associated with the phenotype of interest. It is not clear from the draft guidance document what data would be most useful to include in a VGDS. We suggest that all of the data on the > 1 million SNPs screened in selecting the 'lead SNPs' should not be included in a VGDS as this would be analogous to supplying all data on screening a compound library. Data on the lead SNPs themselves would be sufficient and should be submitted. In addition, these 'lead SNPs' would be used to select or stratify patients in prospective clinical trials. Data from any prospective trial using the 'lead SNPs' to select or stratify patients would require submission of a complete report to the IND, BLA, or NDA. We suggest outlining such an example in the guidance document to further elucidate this process.

Comment 3

Pertinent to the example above, we noticed that although the draft guidance clearly states the need for informed consent regardless of the purpose for the genetic sample collection (lines 307 to 309), no mention of the appropriate use of anonymized or anonymous genetic samples is provided. Lesko and colleagues (2003), summarizing the FDA May 16-17 Pharmacogenomics Workshop, provide important points delineating the appropriate use of anonymized or anonymous samples. For example, they note anonymized or anonymous data and samples can be useful for research purposes and hypothesis generation. We submit that this includes establishing the pharmacogenomic association as outlined above (ie, selection of 'lead SNPs'). Therefore, the data submitted as a VGDS establishing a pharmacogenomic association could be completed with anonymized samples. In contrast, clinical trials using the 'lead SNPs' for patient selection or stratification should use linked samples as the data derived from these studies could be used for regulatory decision making. We believe these important points should be addressed in the draft guidance and that an algorithm describing the appropriate use of anonymized or anonymous samples should be included. Also the glossary should provide definitions of linked versus anonymized or anonymous samples.

Overall Perlegen Sciences is very pleased with the draft guidance. We look forward to the opportunity of participating with the FDA in the development of future guidance documents.

Sincerely,



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References Cited

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Hinds, DA, Stokowski RP, Patil N, et al. Matching Strategies for Genetic Association Studies in Structured Populations. *Am J Human Genetics*. 2003; in press.

Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. *J Clin Pharmacol* 2003;43:342-358.