

Division of Dockets Management (HFA-305)
United States Food & Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852
USA

Stockholm January 30, 2004

Dear Sirs:

**Subject: Comments to Draft Guidance on Pharmacogenomic Data Submissions -
DOCKET NO. 2003D-0497, CDER 2003163**

Global Genomics AB would like to submit comments on the October 29, 2003 Draft Guidance: Guidance for Industry, Pharmacogenomic Data Submissions. Global Genomics is an emerging biotechnology company that develops innovative tools used in functional genomics and has recently launched a novel technology called tangerine gene expression profiling. New technologies that challenge old paradigms with potentially large impact on drug discovery and development must be presented to and evaluated by industry and government to promote better-informed science. One of the Company's goals is to promote better science and regulatory processes by participating in the FDA-sponsored workshops.

There are many guiding principles that should be adhered to when creating industry guidance, a few which include:

1. Creating policies that provide the most cost-effective benefit to human health.
2. Promoting research and development with the best tools and analysis that science has to offer.
3. Minimizing burden of review and analysis by regulatory agencies.

From this standpoint, Global Genomics would like to confirm the need for the highest quality pharmacogenomic information in IND, BLA, and NDA submissions to the FDA, and to promote the creation of policies that encourage the use of the best technologies that help define biomarkers, stratify patients in clinical trials, identify patients at higher risk for an adverse response (ADR), etc.

Driving Force: High quality pharmacogenomic information is paramount to protecting public health

There are an estimated 2 million cases of ADRs in US hospitals annually, of which 100,000 result in death¹. The cost to the US economy in drug-related morbidity and mortality is estimated at \$177 billion². Lower toxicology, more effective drug candidates, and higher quality IND and NDA submissions, means marketed drugs with fewer ADRs. In short, better pharmacogenomic tools will help the process of reducing healthcare costs.

¹ Miller et al, Am. J. Hosp. Pharm 30, 584, 1973

² Ernst et al, J. Am. Pharm. Assoc., 41, 192, 2001

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Policies On Best Science: State-of-the-Art (SOTA) performance standards should be established

In the view of Global Genomics, before scientists and regulators can agree on what constitutes a biomarker and accept a specific biomarker in disease identification, the scientific and regulatory community must set performance benchmarks to promote the best science by reviewing abilities of underlying technologies that provide relevant pharmacogenomic information.

The Draft released on October 29, 2003 supports this view (lines 82-84): *It is important for the FDA to have a role in the evaluation of pharmacogenomic tests, both to ensure that evolving FDA policies are based on the best science and to provide public confidence in the field.*

Furthermore, lines 128-131 state: *For the purposes of this guidance, a pharmacogenomic test result may be considered a valid biomarker if (1) it is measured in an analytical test system with well established performance characteristics and (2) there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results.*

Global Genomics encourages the FDA to:

- Continue fostering review of tools in research and development within industry and government forums.
- Establish state-of-the-art performance standards for technologies used to generate pharmacogenomic information. This does not imply that the FDA should validate technologies themselves and/or approve technologies used to support information in regulatory submissions – rather, that the agency, with assistance from academia and industry, should establish standards that promote new and better technology development.

Mutually agreed upon performance standards can eliminate ambiguity in IND, BLA, and NDA review by qualifying data from different technologies.

Example: SOTA standards in Voluntary Genomic Data Submissions (VGDS) used to establish valid biomarkers

The draft guidance discusses the potential use of pharmacogenomic data to support drug development and/or to guide drug therapy (lines 163-166): *“For example, a sponsor may wish to provide supportive data demonstrating that changes in drug-induced gene expression differ between species that have different toxicologic responses to a drug, thus correlating changes in certain gene expression patterns with a specific toxicity”* - a common toxicological approach.

In light of technologies that generate data of questionable quality, the FDA should adopt policies to ensure submission of high quality pharmacogenomic information. The case of microarrays (chips) highlights this need, where revolutionary upon introduction, chips have reached a performance plateau due to technological limitations. Microarrays are questionable in detecting all genes that are truly expressed, and at detecting low-expressed genes, as well as genes with subtle changes in regulation.

To elevate the quality of gene expression analysis, *understand the tests systems and techniques being employed* (lines 226 – 231), and promote the best science, Global Genomics proposes that key gene expression technology SOTA standards be established:

- Coverage – a gene expression technology should be able to detect ALL genes that are expressed in a given sample. Closed systems, such as microarrays, limit analysis only to those genes represented by oligos or cDNAs fixed on them.
- Sensitivity in detection – technologies need low detection thresholds in order to see all expressed genes (i.e. detect at least one part in 3 million corresponding to < 0.1 transcript per cell).
- Sensitivity to detect small changes – where subtle changes in expression can represent lethal toxicological effects, technologies should have high statistical power to detect these changes.
- Sensitivity in sample size – where small samples are available for study (i.e. nanogram range), such as in adipose or brain tissue, this criterion becomes a prerequisite.
- Reproducibility – technologies should demonstrate small run-to-run variability.

There are applications where specific technologies are better suited due to performance ability. As in the case of biomarkers, their development demands a higher performance technology to ensure proper definition. However, once a biomarker has been established, the case can be made for the use of less rigorous, validated technologies in diagnosis, such as microarrays.

By bringing to light, discussing and agreeing to the performance abilities of technologies and setting SOTA standards, the FDA and industry can ensure the highest level of information quality, accurately define biomarkers (lines 121 – 145) and improve chances of NDA approval. Better medicines mean fewer adverse drug reactions and an improvement in public health.

Global Genomics is grateful for the opportunity to help shape guidance for the use of pharmacogenomic information and looks forward to participating in this and other initiatives by the FDA. At your request, we would be willing to help the FDA incorporate these policy suggestions.

Sincerely yours,

Ulf Boberg, Ph.D.
Chief Executive Officer



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