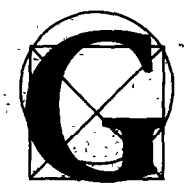

GENAISSANCE
PHARMACEUTICALS

March 28, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Dear Sir or Madam:

Subject: Federal Register Docket No. 02D-0018
Commentary on the FDA Guidance for Industry
"Collection of Race and Ethnicity Data in Clinical Trials"

Preamble

Genaissance Pharmaceuticals, Inc. is a biotechnology company whose business is based on the discovery and use of human gene variation for the development of personalized medicines. The Company markets its technology and clinical development skills to the pharmaceutical industry as a complete solution for improving the development, marketing and prescribing of drugs. Genaissance has agreements with eight major pharmaceutical, diagnostic and biotechnology companies: AstraZeneca, Bayer, BD (Becton, Dickinson and Company), Biogen, Johnson & Johnson PRD, Millennium, Pfizer and Pharmacia. Genaissance is located in Science Park in New Haven, Connecticut.

Genaissance is pleased to submit the following commentary based on the company's expertise in population genomics and pharmacogenomics.

Commentary

1. Definition of ethnicity. The categories that this guidance suggests for industry are based on racial and, to some degree, geographic characteristics of individuals. The classifications of "White," "Asian," "Black or African American," "American Indian or Alaska Native," "Hispanic or Latino," "Not Hispanic or Latino," and "Native Hawaiian or Other Pacific Islander" seem to be preferred and established by the U.S. Census Bureau. Although these categories may be useful for national demographics, they are substandard with regard to the state-of-the-art in genetic analysis of ancestry. In a population such as the United States that increasingly is mixed, the boundaries between these classifications are likely to be blurred further. For example, Genaissance has conducted genetic analysis of Hispanic populations from Florida and California. It is very clear that the label "Hispanic" encompasses individuals with African descent and Native American descent, as well as Caucasian descent.

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2. Relationships between race and metabolic profiles. There is medical precedence for the utilization of race in customizing treatments. The best known examples relate to blood pressure treatments and rates of alcohol metabolism. Although these criteria may be useful medically, they would represent severe shortchanging of clinical research for development of new drugs. The link between these clinical outcomes and race is anecdotal at best and discriminatory at worst. New genetic technologies offer much more precise relationships between the genotype of an individual and the clinical management of disease. For example, it is possible to conduct high-resolution analysis of metabolic enzymes with genetic markers and determine, based on genotype, the phenotype status of the patient as a fast or slow metabolizer. This information would be critical to prevent drug interactions as well as to optimize dosage.

3. Existing genetic technologies. There has been an explosion in knowledge of markers for variation in populations. At Genaissance, we have conducted gene haplotype analysis of various U.S. populations (Figure 1). The majority of haplotypes observed at a gene are copies of a cosmopolitan haplotype, that is, a haplotype observed in all four of our population samples (African American, Asian, Caucasian, and Hispanic Latino). Twenty-three percent of haplotypes observed were seen in a subset of these populations, with nearly 10% being population-specific. Haplotypes from the population-specific sector are ideal for population ancestry determination as described above. We have advanced genetic analysis to derive grouping of these individuals based on these gene haplotype markers. The outcome of this analysis is a quantitative means of

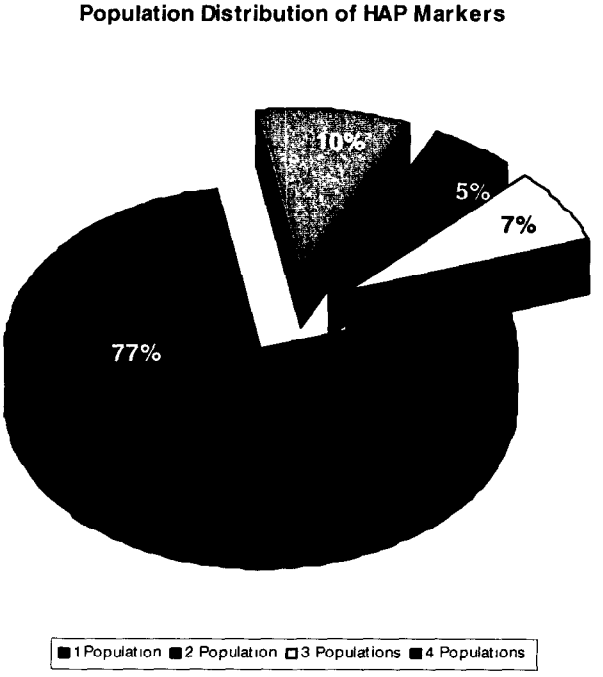


Figure 1. Gene haplotype distribution summary of all haplotypes observed for almost 4,000 genes

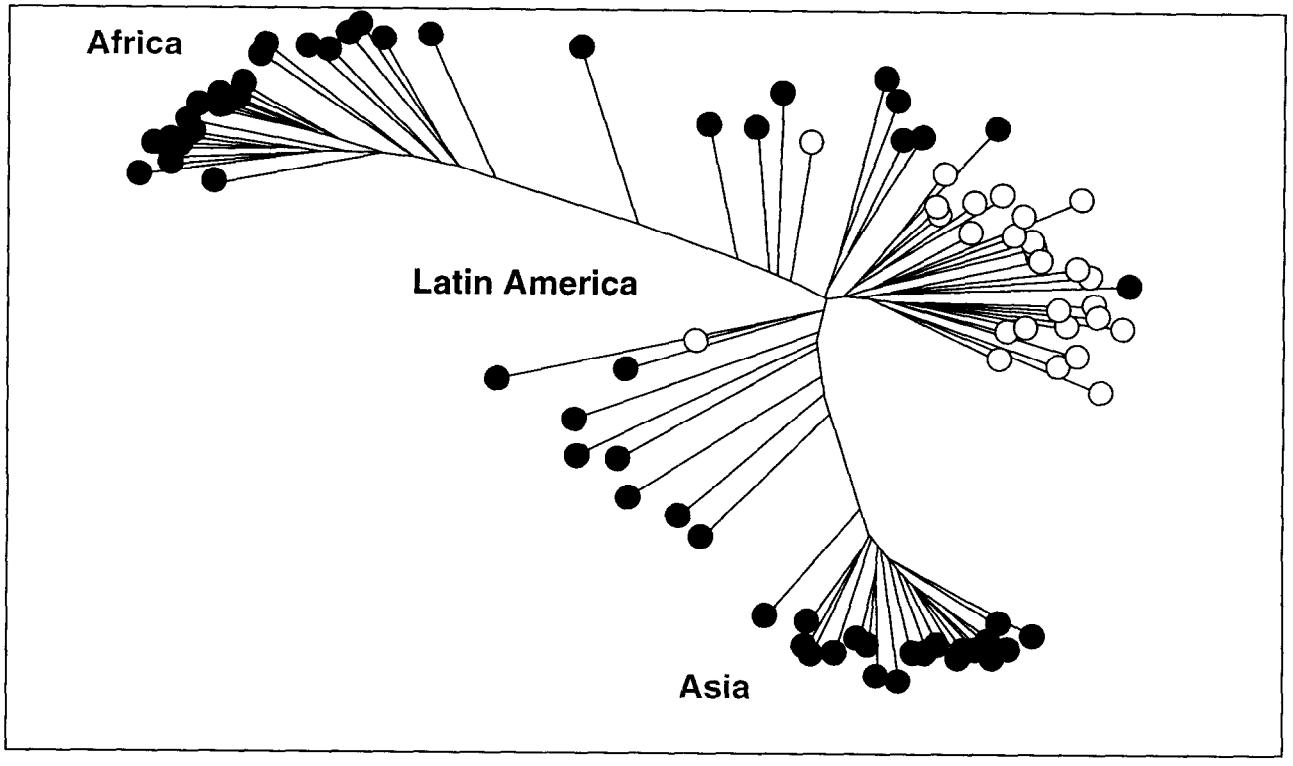


Figure 2. Grouping of individuals based on gene haplotype markers compared to ethnogeographic denominations.

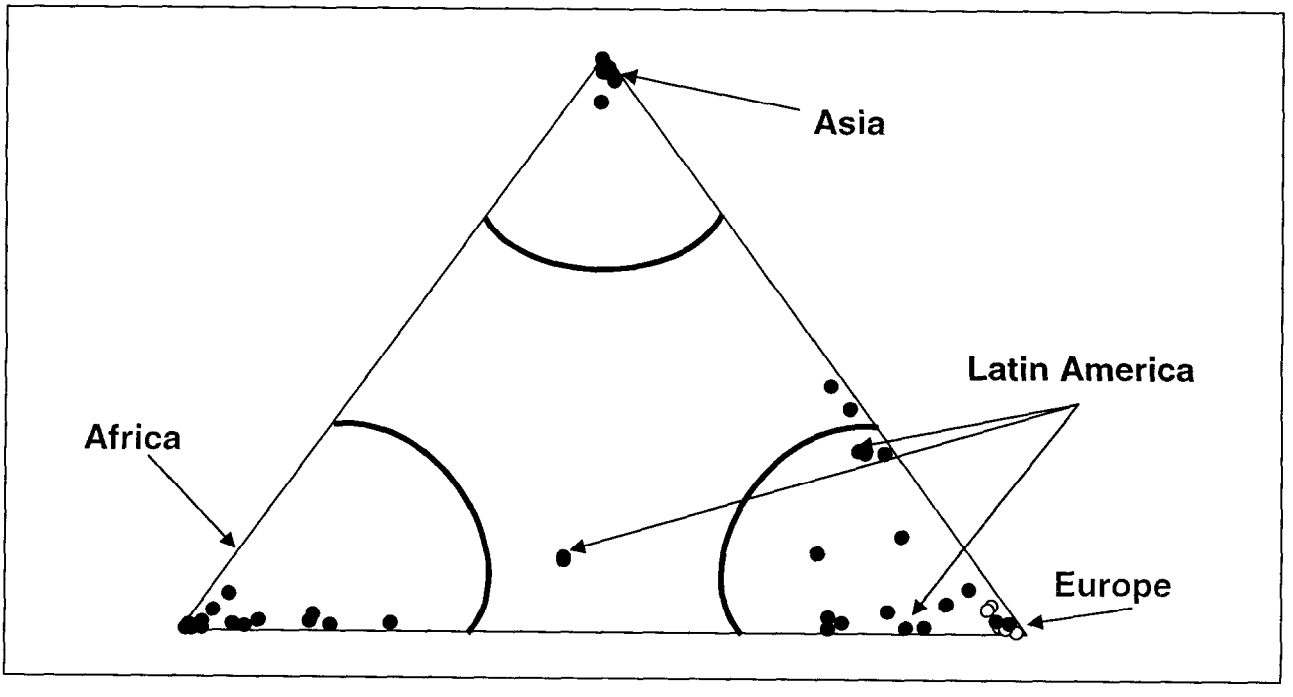


Figure 3. Quantitative Ancestry

positioning individuals into consistent systems for ancestry determination. At some point it should be possible to include the coordinates of location for any individual with regard to a map, derived from a standard set of genetic markers. Such a system would afford high-resolution genetic identification of ancestry, consistent analysis of ethno-geographic backgrounds, and possible use directly to diagnostics for improvement of drug therapy.

In addition to the Genaissance markers, there is considerable public domain data stemming from the human genome program. Therefore, either from commercial sources or from public domain databases, genomics technology and state-of-the-art genotyping allow the standard of care concerning race to be based on genetic markers.

4. Technical Example. Genaissance has developed a quantitative approach to DNA-based determination of an individual's ancestry. The company has conducted haplotype analysis of various U.S. populations, deriving groups of individuals based on proprietary markers. The outcome of this analysis is a quantitative means of positioning individuals into consistent systems for ancestry determination and relatedness. In this example, a quantitative coordinate system based on genetics is established and anchored by alleles demonstrating the greatest population specificity (Figure 2). In this manner, Asian, European, and African American clusters define the vertexes of a triangle (Figure 3). Note that the African American vertex is the least clustered, consistent with population admixture.

   As a test case, Genaissance has conducted genetic analysis of Hispanic populations from Florida and California. It is very clear that the label "Hispanic" encompasses individuals with African descent and Native American descent, as well as Caucasian descent, as shown by the spread of this population over the triangle. Each individual in this diverse population can then be assigned a quantitative position in the triangle.

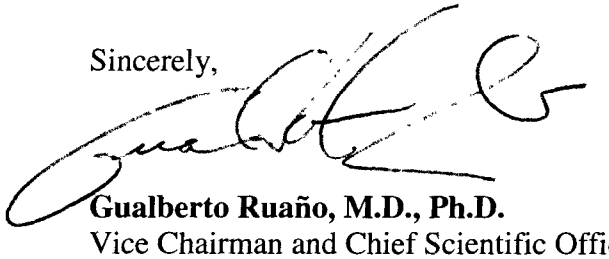
   The system could be expanded and refined with more population sampling and clustering to create other polygons in two-dimensional space or multiple dimensions. For implementation, such a system would require a "turn key" modus operandi where the input is DNA and the output is a genetically defined score assigning the individual to a particular region of the coordinate system.

   This technical example demonstrates that at some point it should be possible to include the coordinates of location for any individual with regard to a standard set of genetic markers. Such a system would afford high-resolution genetic identification of ancestry, consistent analysis of ethno-geographic backgrounds, and possible use directly to diagnostics for improvement of drug therapy.

Recommendations:

1. It behooves the FDA to stimulate the adoption of new genetic systems for ancestry determination rather than antiquated and potentially inaccurate racial denominations.
2. In certain situations, as recommended in OMB Directive 15, when more detailed "race" and "ethnicity" information may be desired, it is scientifically feasible and medically advisable to proceed to genetic systems of ancestry determination.

Sincerely,



Gualberto Ruaño, M.D., Ph.D.
Vice Chairman and Chief Scientific Officer

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By Federal Express

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