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Commentary by the Biotechnology Industry Organization on the FDA Draft Guidance for Industry on the Collection of Race and Ethnicity Data in Clinical Trials for FDA Regulated Products

Preamble

On January 23, 2003, FDA put forth a "Draft Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials." In this draft guidance, FDA proposes that the sponsors of clinical trials collect race and ethnicity data on subjects of clinical trials, whether those trials are conducted in the United States or outside of the United States. The ethnic and race categories proposed in the Guidance reflect an FDA objective of standardization with OMB (Office of Management and Budget) and DHHS regarding OMB categories for race and ethnic information. FDA states that this is being proposed in an effort to ensure consistency in demographic subset analyses across studies used to support certain marketing applications to FDA and across data collected by other government agencies and for possible use in evaluating potential differences in the safety and efficacy of pharmaceutical products among population subgroups.

The Biotechnology Industry Organization (BIO) would like to provide the following commentary to improve the process described in the guidance based on current scientific understanding of the limited scientific value of the broad categories FDA proposes. Further, BIO will provide examples from novel technologies created and used by its member companies. BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products.

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Definitions

The categories that this guidance suggests for industry are based on an inconsistent set of criteria – some categories are racial, others are geographical, and one is neither racial nor geographical but rather is based on cultural or ethnic characteristics. 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" are suggested for use. Although these categories may be useful for national demographics, or for studying the impact of various health-related policies on minority communities, they are not suitable scientific analyses of ancestry – which might correlate more closely with any drug metabolism or other drug effect of interest or concern to the FDA. Moreover, in a population such as the United States where many people are of mixed ancestry, the boundaries between these categories are likely to be blurred further.

The categories used are from OMB and DHHS efforts that pre-date the work of the Human Genome Project, and reflect social, not scientific categories. Because the categories are not scientific, it would be inappropriate to impose such categories in the recruitment of patients for clinical research. Moreover, in the absence of a scientific basis for categorization of human diversity, any clinical data collection with racial labels and the subsequent FDA decisions based on that data collection are of uncertain value, and, thus, FDA should not compel the collection of data in this way.

Relationships between Race and Metabolic Profiles

We recognize that there is medical precedence for the use 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 in clinical management, they would represent severe shortchanging of clinical research for development of new drugs. The link between these clinical outcomes and racial, ethnic, and geographic groups is anecdotal at best and discriminatory at worst. The categories proposed are, simply, too crude to be used as an accurate measure of drug effect assessment. 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 drug metabolizer. This information would be critical to prevent drug interactions as well as to optimize dosage.

International Harmonization

The guidance document particulars also are difficult to implement anywhere other than the United States. Many foreign countries find the imposition of "American-centric" standards distasteful and resist them. Many EU countries will find these OMB categories improper. The only revision made to the OMB categories was to change "African American" to "Black, of African heritage." The guidance keeps categories of "Hispanic or Latino" and "Native Hawaiian or Other Pacific Islander." These race and nationality categorizations may be of some relevance for an American population but have very little relevance for a European, Asian, or Latin American populations (and other areas as well). Countries in these regions all have health

authorities as well who might not wish to have the demographic data skewed in such a way. It certainly would be very hard for a global project leader to implement this worldwide for multi-country trials.

Statistical Population Stratification

We are also concerned about the size of clinical trials that may have to be conducted if this guidance is finalized. The Guidance addresses the issue of the hypothesis generating aspect of sample size for the race/ethnic group representation. Basically, if prior studies suggest a basis for differential efficacy or safety response among populations, then the sample size must be adequate in each subgroup. "When prior studies neither support nor negate significant differences of clinical or public health importance, the phase 3 trial will be required to support the sufficient and appropriate accrual of participants by gender and race/ethnicity, so that a valid analysis of the intervention effects can be performed. However, the trial is not required to provide high statistical power for these comparisons. The term *valid analysis* refers generally to a reasonable descriptive approach to the data."

The content of the Guidance, as written, has empiric implications for the sample size within databases prepared for submission. The Agency has already requested that the population distribution of the databases submitted in the U.S. be representative of the target population. Depending on the particular study endpoint, there will generally be insufficient statistical power to demonstrate independent safety and efficacy in all representative subpopulations defined in the racial, geographic, and cultural matters set forth by FDA. For candidate drugs where there is no prior non-clinical or clinical data to suggest subpopulation differences in safety or efficacy parameters, general data collection parameters should be reserved for post-marketing studies, as appropriate.

In this regard, the FDA proposal seems to be inconsistent with the OIRM HHS Policy for Improving Race and Ethnicity Data, which is cited as a source for the FDA draft guidance. That guidance states in its Policy on the Collection and Reporting of Race and Ethnicity (II(E)):

> Data on race and ethnicity must be collected, analyzed, and reported in an objective, accurate, and useful manner… Such data will not be used by the Department in a way that would stigmatize certain populations or to suggest a biological or genetic connection based on nongenetic studies or when race and ethnicity are actually surrogates for other risk factors. Only those racial or ethnic groups with adequate sample sizes to provide statistically reliable data should be reported.

In the studies conducted by companies prior to FDA approval, the racial and ethnicity groupings would be surrogates for differences in drug metabolism or other drug effects, and, therefore, should not be used. Moreover, if FDA were to demand adequate sample sizes for statistically reliable data for each subgroup proposed, it will significantly impair research and the discovery of new therapeutics.

The FDA Draft Guidance Impermissibly Expands Beyond Current FDA Regulations

At present, anyone submitting an NDA is required to present the effectiveness and safety data from the clinical trials according to the "racial subgroup" of the subjects. See, 21 CFR 314.50(d)(5)(v): "The effectiveness data shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups." See also 21 CFR 314(d)(5)(vi)(a): "The safety data shall be presented by gender, age, and racial subgroups." The FDA can refuse to file an application if it does not contain the racial subgroup data. 21 CFR 314.101(d)(3), see page 2, footnote 5 to the Draft Guidance. And the FDA assesses whether the product is safe and effective for the different racial subgroups, and it can, and has, refused approval based on racial subgroup analyses. Even when it gives approval, the FDA can, and has, ordered companies to label their products based on the racial subgroup analyses required to be submitted.

In this "guidance" the FDA attempts to take the regulatory demands one step further – in addition to requiring companies to present data by "racial subgroups," the FDA seeks to have companies present the data by "ethnicity" as well. There is no statutory or regulatory authority to extend the categorization of clinical trial subjects by ethnicity. FDA should, at a minimum, withdraw that portion of its draft guidance. And even if FDA fails to change its draft guidance, it cannot lawfully compel companies to submit applications containing ethnicity data and it cannot refuse to file an application or refuse to approve an application based on ethnicity concerns.

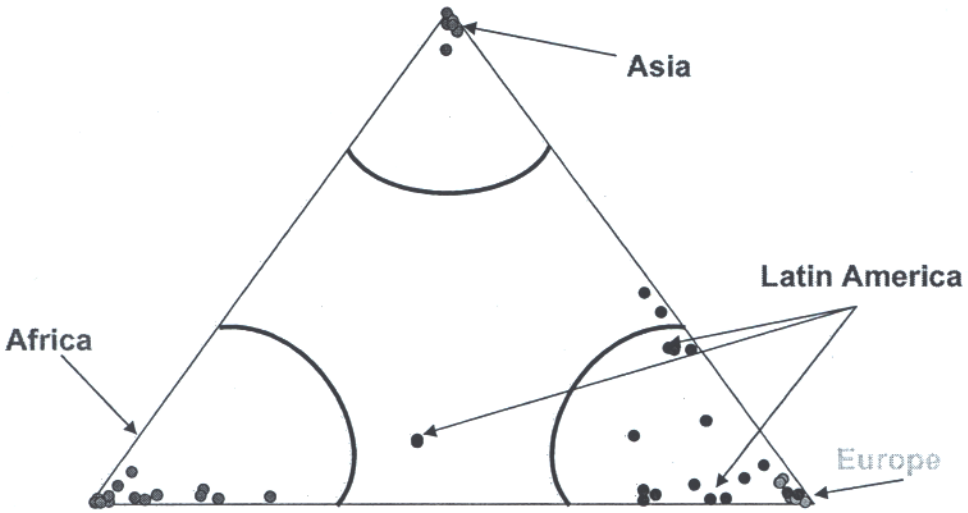
In addition to its legal shortcomings, the concept of "ethnicity" as a biological marker that would impact drug metabolism is not accepted scientifically. As FDA states in its draft document, its categorizations are "not scientifically based." Draft Guidance at page 3. One of the "ethnic" groups that FDA chooses to highlight in its document illustrates the non-scientific nature of an "ethnic" inquiry.

At least in the United States, persons who self-identify as "Hispanic or Latino" might be related genetically to persons from Spain and other parts of the Iberian Peninsula in Europe, to Native Americans from tribes either in the United States or Central or South America, or to persons whose ancestors came to the United States from Africa. Often, persons who self-identify might be related to persons from multiple racial groups.

Genaissance has provided a technical example of population diversity determination and how labeling persons as "Hispanic" means little scientifically. The company has conducted haplotype analysis of various U.S. populations, deriving groups of these individuals based on proprietary markers. The outcome of this analysis is a quantitative means of positioning individuals into consistent systems for ancestry determination. In this example, a genetic quantitative coordinate system is established and anchored by alleles demonstrating the greatest population specificity. In this manner, an Asian, European, and African American cluster can define the vertexes of a triangle (see figure attachment). 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.

A visual representation of the Genaissance assessment of the backgrounds of "Hispanic" persons is as follows:



Quantitative Ancestry Calculated with DNA Markers
(Provided by Genaissance Pharmaceuticals, Inc.)

Given this data, it is not reasonable for FDA to expect sponsors of clinical trials to label persons by their "ethnic" background when such a label will not provide meaningful scientific data upon which safety and effectiveness decisions could be based.

We note in this regard that several FDA employees are participating in the Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, entitled "Clinical Pharmacology in the Post-Genome Era: Advancing Towards Therapeutic Optimization, April 2-5, 2003. It is difficult to square the FDA's involvement in this post-genomic scientific forum with the agency's proposal to evaluate patients using centuries-old categories.

Thus, BIO concludes by respectfully requesting that the Guidance as written be withdrawn and the issues that it covers be carefully reconsidered based on sound science. The on-going progress in genomics should be optimally used to benefit patients of all races and ethnicities, and to

facilitate the development of new medicines, without unduly burdening their development with arcane and US centric requirements. We appreciate the opportunity to provide our comments and look forward to working with the agency further to facilitate such progress.

Sincerely yours,

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