Biotechnology Industry Organization

May 16, 2014

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

**Re: Docket No. FDA–2013–N–0745: Action Plan for the Collection, Analysis, and Availability of Demographic Subgroup Data in Applications for Approval of Food and Drug Administration-Regulated Medical Products; Notice of Public Hearing; Request for Comments**

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Action Plan for the Collection, Analysis, and Availability of Demographic Subgroup Data in Applications for Approval of Food and Drug Administration-Regulated Medical Products; Notice of Public Hearing; Request for Comments." BIO shares the Agency's commitment to better engage populations traditionally under-represented in clinical studies, while maintaining a focus on speeding safe and effective medicines to patients in need.

BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

## GENERAL COMMENTS:

BIO member companies strive to conduct efficient, informative clinical trials to define the safety and efficacy of investigational therapies for all relevant populations. Sponsors are prioritizing the enrollment and analysis of relevant subpopulations in their clinical development programs and take seriously their obligations outlined in the Code of Federal Regulations to present safety and effectiveness data "by gender, age, and racial subgroups," as well as for "other subgroups of the population of patients treated."[1] In addition to these regulatory requirements, BIO member companies have developed and employed proactive strategies to promote enrollment from relevant subpopulations that are traditionally under-represented in clinical trials. Examples include:

[1] 21 CFR 314.50 (d)(5)(v) and (vi)(a)

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

- employing strategies for site selection to maximize enrollment of relevant subpopulations;
- minimizing and more thoughtfully administering protocol exclusions;
- ensuring early involvement of clinicians, community consultants, and activists;
- leveraging study branding to build familiarity in under-represented communities; and
- addressing practical barriers to participation (*e.g.*, subsidizing child care and transportation).

To support these and other proactive efforts by industry to engage relevant patient subpopulations, BIO encourages FDA to conduct complementary outreach to key stakeholders (*e.g.,* patients, health care providers, community leaders, *etc.*) from traditionally under-represented subpopulations. BIO believes that stakeholder education by FDA on the role of clinical research in promoting public health, opportunities to become involved in clinical research, and the appropriate considerations and expectations for individuals who elect to participate in clinical research would promote greater enrollment from these populations.

As stated, BIO supports the enrollment of representative proportions of subgroup participants in clinical trials consistent with disease prevalence, however, BIO strongly believes that an approval for a larger population should not be delayed if the Sponsor has made a good faith attempt to include specific subpopulations in the trial, which can be monitored and discussed with FDA (*e.g.,* sharing the site selection process) during development. Rather than imposing absolute requirements that could delay access to essential medicines, BIO encourages FDA to support the good faith efforts made by companies to enroll relevant but historically under-represented subpopulations in clinical trials of investigational medicines. FDA's efforts to support drug development for special populations have met with tremendous success, including incentivizing drug development for special populations through the Best Pharmaceuticals for Children Act (BPCA), the Rare Pediatric Disease Priority Review Voucher Program, and the Orphan Drug Designation Program. For example, as of May 5, 2014, the pediatric exclusivity incentives offered under the BPCA have directly resulted in 156 pediatric labeling changes.[2]

Finally, BIO believes that in instances where clinical trial enrollment of subpopulations is either not feasible or not warranted (based on preclinical, early clinical, and/or epidemiological data), alternative or "real world" data sources can be leveraged in the postmarket setting to attain a better understanding of relative benefit-risk profiles for specific subpopulations. Toward this end, BIO encourages FDA to engage stakeholders

[2] FDA New Pediatric Labeling Information Database, http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase

and develop consensus standardized methods for the utilization of alternative data sources.

**SPECIFIC COMMENTS:**

### *A. Demographic Subgroup Representation in Clinical Trials*

1. *What approaches might be used to encourage enrollment of representative proportions of subgroup participants in clinical trials consistent with disease prevalence in the underlying population being studied?*

BIO appreciates the Agency's interest in encouraging enrollment of representative proportions of subgroup participants in clinical trials consistent with disease prevalence and believes that in order to achieve this, Sponsors should employ inclusion and exclusion criteria that are scientifically justified and in accordance with this principle. However, BIO believes that Sponsors should also be afforded flexibility to balance practical considerations that affect the feasibility of clinical studies and ultimately have an impact upon public health by affecting access to medicines. As mentioned above in the General Comments, BIO believes that FDA should support the efforts of Sponsors to enroll representative proportions of subgroup participants in clinical trials, rather than employ a punitive system that may delay access to critical therapies for the broader population.

2. *What sources could be used to define disease prevalence among subgroups? Are there priority areas for study in terms of disease/condition, or in terms of demographic subgroup?*

In addition to standard epidemiological practice, BIO believes that claims databases and other alternative or "real world" data sources may be useful in defining disease prevalence among subgroups. BIO recommends that FDA engage stakeholders to develop consensus standardized methods for the utilization of alternative data sources in order to better estimate disease prevalence among subgroups.

3. *What are best practices and considerations for developing inclusion and exclusion criteria for clinical trials generally and for the early stages of research?*

BIO believes that safety should be the primary driver for developing initial inclusion and exclusion criteria for the early stages of clinical research. As the clinical safety profile of the investigational agent is elucidated, BIO believes that enrichment for populations most likely to experience benefit (prospective enrichment) or in which benefit can most easily be detected (prognostic enrichment) could also be beneficial to developing an initial understanding of the benefit-risk profile and promoting earlier access to therapies.

Again, BIO believes that overall, where feasible and practical, it is ideal for the population composition of clinical trials to be consistent with disease prevalence in the

general population. In striving to promote the enrollment and analysis of various subgroups, however, BIO notes that just as the study of a more restricted population will limit the generalizability of trial results, over-representation of a small subgroup in a clinical trial, whether intentionally or unintentionally, will also limit the generalizability of overall trial results, since the trial population would not be representative of the actual patient population.

4. *What approaches should FDA use to standardize the capture of race and ethnicity information, including for studies conducted outside the United States?*

The Agency has stated that for all submissions to FDA, the CDISC Study Data Tabulation Model (SDTM) RACE variable must contain a value from the published RACE codelist.[3] However, BIO believes that FDA has an opportunity to offer additional terminology and guidance for Sponsors and research organizations who submit data to multiple regulatory agencies, not just the FDA. There are cultural, as well as practical regulatory concerns about the current limited scope of Race categories. These concerns of practicality and utility are relevant for all racial designations, but for illustrative purposes, BIO will use the example of the "ASIAN" designation. Compiling all Asian subgroups into a single category is controversial and problematic, as described below:

- For trials limited to the US in terms of enrollment (and planned medical and/or regulatory applications of the data), the category "Asian" is not sufficient. According to the US Census Bureau, the Asian population in the US is projected to more than double, from 15.9 million in 2012 to 34.4 million in 2060, with its share of nation's total population climbing from 5.1 percent to 8.2 percent in the same period.[4] Predictably, clinical trial outcomes will have greater value for this growing US subpopulation, if Sponsors had the option to collect data with categories that better represent major Asian subgroups.

- For trials conducted globally with planned medical/regulatory applications inside or outside the US, the category "Asian" is also not sufficient. In some instances, for example, Sponsors have been informed that the Japanese Health Authorities would rather see the race listed as either JAPANESE or NON-JAPANESE, including study subjects enrolled inside or outside of Japan. Similarly, the Chinese Health Authorities have been open to review of clinical trial experience with certain Asian subjects enrolled outside of mainland China, and the relevance would be improved by the ability of Sponsors to elect to more consistently collect details of racial background beyond simply "Asian".

[3] http://evs.nci.nih.gov/ftp1/CDISC/SDTM/SDTM%20Terminology.pdf
[4] http://www.census.gov

- Irrespective of region for conduct of trials and planned applications of the data, the evaluation of safety, pharmacology, efficacy, and other clinical trial outcomes can be more precisely analyzed using RACE categories that are clinically relevant.

A goal remains to employ RACE terminology that is meaningful, practical and scalable for collection. A practical approach for this particular example could be to include an optional algorithm[5] to further subcategorize Asians into major ethnic distributions, which has been used by some Sponsors for Case Report Forms and data collection by trial participants. This approach would enable subsequent data analyses requested by some Health Authorities (*e.g.,* Japanese vs. Non-Japanese) and captures Asian subpopulations into a practical number of categories.

### *B. Analysis of Demographic Subgroup Data*

*1. What are the statistical challenges in analyzing clinical trial data to evaluate subgroup differences?*

BIO wishes to emphasize that, in general, treatment effect is assessed in a pre-specified primary analysis set (or sets), which often is based on the entire enrolled population rather than the demographic subsets. While assessment of demographic subsets may be carried out as a pre-specified analysis or part of sensitivity analyses in assessing primary treatment effect, such subset analyses cannot trump analysis based on the entire enrolled population.

---

[5] Suggested option for data collection:

ASIAN
If Asian, check one of the following:

1. Indian subcontinent Asian
Ethnic origins from Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan or Sri Lanka

2. Southeast Asian
Ethnic origins from Cambodia, Laos, Myanmar, Thailand, Vietnam, Brunei, East Timor, Indonesia, Malaysia, Philippines

3.1. Far East Asian – Japanese

3.2 Far East Asian – Korean

3.3 Far East Asian – China or Taiwan

4. Hawaii and Pacific Islander

5. Asian - Other

From a statistical analysis and reporting perspective, BIO believes that an important issue related to subgroup analysis is the potential loss of treatment group comparability if randomization is not stratified by the subgroup factor. Bias can be introduced due to this loss of treatment comparability, which can be both difficult to detect and difficult to handle by statistical approaches. However, when conducting a clinical trial, it would be a practical challenge to stratify for all subgroup factors of interest. Other important statistical challenges with subgroup analyses include multiplicity control and lack of power if a clinical trial is not designed to test on subgroups. If the results of subgroup analyses are to be presented in a confirmatory manner (*e.g.,* in the label), the statistical characteristics of such analyses such as bias, multiplicity control, precision, and reproducibility need to be taken into consideration.

2. *Given that it is not feasible to power most studies to detect subpopulation differences, what approaches should be used to analyze subgroups to explore clinically relevant information?*

BIO believes that Exposure/Response and Exposure/Safety models will enhance reliability, as they can adjust for other key baseline differences. BIO also encourages FDA to employ greater acceptance of model-based approaches, especially those using continuous endpoints. This may require the acceptance of different endpoint outcomes in subgroups versus the overall population.

3. *How might additional clinically relevant information about subgroups be obtained in the postmarket setting?*

BIO believes that additional Agency efforts to support the collection and analysis of clinically relevant information about subgroups in the postmarket setting would be very beneficial. Specifically, in order to improve the ability of Sponsors to collect and analyze these data in the postmarket setting, BIO encourages FDA to work with stakeholders to develop consensus standardized methods to evaluate alternative, "real world" data sources. BIO cautions FDA, as above, about the development of a punitive system that would require Sponsors to collect data that may not, at present, be feasible and that could potentially delay the availability of therapies to the larger population.

### *C. Communication of Demographic Subgroup Information to the Public*

1. *What information regarding demographic subgroups is helpful to health care professionals to make informed decisions about the use of medical products? To consumers/patients? To researchers?*

BIO believes that communicating information regarding demographic subgroups similar to the data reported for the overall population would be useful to inform the decisions of health care professionals; however, BIO cautions FDA to avoid the unintended consequence of limiting access to potentially beneficial therapies based solely upon analyses of statistically insignificant data sets. BIO also believes that there should be

greater acceptance of model-based approaches, allowing to Sponsors discuss 'estimates' or 'ranges.'

2. *What is the best way for FDA to communicate and make accessible such information to health care professionals? To consumers/patients? To researchers?*

BIO believes that the product label could be an appropriate tool for communicating this information by the inclusion of a special section detailing clinical trial results in demographic subgroups. In addition, BIO member companies are committed to responsibly sharing clinical trial data for qualified research requests and are supportive of efforts to develop and share factual summaries of clinical trial results with research participants.[6]

**CONCLUSION:**

BIO appreciates this opportunity to comment on the "Action Plan for the Collection, Analysis, and Availability of Demographic Subgroup Data in Applications for Approval of Food and Drug Administration-Regulated Medical Products; Notice of Public Hearing; Request for Comments." We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew W. Womack, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

[6] *BIO Principles on Clinical Trial Data Sharing* (2014), http://www.bio.org/articles/bio-principles-clinical-trial-data-sharing