



November 20, 2013

The Honorable Margaret Hamburg, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-N-0745, Comments on FDASIA Section 907 Report: "Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products"

Dear Dr. Hamburg:

Our organizations are writing to offer comments on the Food and Drug Administration's (FDA) recent report, *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*. We appreciate the work that FDA, led by the Office of Women's Health in collaboration with the Office of Minority Health and other FDA offices, did on this important report. As Congress developed the Food and Drug Administration Safety and Innovation Act (FDASIA), our organizations worked closely with Congressional leaders on the enactment of Section 907, which required examination of the extent of data collection, analysis, and public reporting on how approved medical products affect women, minority racial and ethnic groups, and older adults. Our organizations strongly believe that research scientists, patients and their health care professionals must have access to this type of information in order to make the best decisions about their medical treatment and contribute to scientific advances.

In light of our efforts to date, we hope our joint comments and recommendations are incorporated into the FDA's Action Plan to address the findings of this report, which is also required by Section 907. Important progress has been made in the last two decades and in particular in the 15 years since FDA issued regulations to require data on participation in clinical trials be presented by age, gender, and race in annual reports for investigational new drugs. However, this report documents clear and continuing gaps in the participation of women, minorities, and the aged in clinical trials, the analysis of subgroup differences, and the availability of subgroup-specific data to clinicians, researchers, and patients. This is particularly evident with respect to minority participation and device trials.

Our comments will focus on highlighting existing gaps and recommended actions for FDA to address these gaps. We look forward to working with FDA on the drafting of the Action Plan that will guarantee greater diversity in all clinical trials conducted on the safety and effectiveness of new therapies. First we have general comments about the report.

General Comments on the Report

The FDA reviewed 72 product applications approved in 2011 for this report, and overall, the report includes data that highlights where gaps in demographic subgroup data persist. However, we are disappointed that the Executive Summary and the narrative throughout the report downplay the identification of shortcomings in subgroup analyses, representation in clinical trials, and the public availability of such information. The Executive Summary and the narrative give the misimpression that there is little or no room for further progress. Rather than highlighting examples where improvement was warranted, the FDA cites examples where subgroups were over-represented, even though these instances were atypical. For example, for medical device premarket approval (PMA) applications relying on multiple pivotal studies, 10 of the 16 studies included fewer than 5 percent of Hispanics, a low representation relative to their percentage in the overall population. Yet the narrative features one of the 6 studies in which Hispanics were overrepresented. Likewise, the report highlighted a facial wrinkle correction device study that enrolled predominantly Black participants, even though Blacks and other minorities were underrepresented in the majority of studies reviewed.

We are also concerned that the Executive Summary downplays the importance of demographic subgroup information. It is critical that patients and clinicians have information that describes the impact of genetic factors such as sex and race on the efficacy of new devices and treatments. The Institute of Medicine (IOM) in its landmark 2001 report answered the pertinent question, *Exploring the Biological Contributions to Human Health: Does Sex Matter?* with an emphatic “yes”. It is important from bench to bedside, from discovery of new compounds to biomarkers to the approval of new therapies. We are at the advent of personalized medicine where treatments are tailored to the genetic makeup of the individual, but we are still years away from achieving this goal if we do not seek the data necessary now.

Availability of Demographic Subgroup Information in Applications by Age, Sex, and Race

The report examined the tools FDA uses to ensure that age, gender, and race information is available in the applications for new drugs and biologics. In general, the report found that trial composition by subgroup was generally being reported by age, gender, and race in applications for FDA approval. Applications were credited with including this information even when the rates of participation for specific subgroups (particularly racial or ethnic subgroups) were very low or even zero. The point of requiring inclusion in the application of trials’ demographic make-up by subgroup was to identify and ideally correct gaps in participation. Achieving appropriate participation levels would provide the ability for FDA to analyze the data from the trials for demographic differences before products come to market. If the FDA just acknowledges that information exists without actually considering it during the approval process, a huge opportunity for improvement is lost. We’ll discuss the shortcomings of subgroup participation in the trials being relied upon for FDA approval of medical products later in our comments.

With respect to devices, the FDA report found that, while device manufacturers generally addressed trial composition by age and sex in their PMAs, race and ethnicity information was not

consistently available. In fact, 10 of the 33 PMA applications did not report any information on racial or ethnic composition. There is no requirement that product sponsors report representation of ethnic subgroups in trials to the FDA in a standard way.

Recommendations for the Action Plan

- To ensure that age, sex, and racial and ethnic subgroup information is being consistently reported by manufacturers, FDA should issue regulations that require new device applications and investigational device exemption reports to present safety and effectiveness data by sex, age, and race/ethnicity, similar to the regulations that already exist for drugs and biologics. FDA should also finalize the draft guidance for sex-specific analysis that they proposed in 2011 and issue similar guidance for racial and ethnic minorities and the aged.
- FDA regulations, guidance, and actions should make clear that lack of inclusion of required demographic subgroup data will result in withholding of product approval until such data is provided.
- FDA regulations should require the separate collection and reporting of ethnicity and race, as recommended by the FDA's guidance *Collection of Race and Ethnicity Data in Clinical Trials*, so that future analysis can determine whether specific ethnic groups are underrepresented in research.

Subset Analyses by Sex, Age, and Race

The report also examines the extent to which demographic subset data was analyzed to determine if and how differences in product performance by subgroups could be detected. Although the report finds that drug and biologic applications generally addressed subset analyses and that device applications addressed subset analyses to a lesser extent, we object to the definition the report uses to define analysis.

The Executive Summary acknowledges this shortcoming: "Inclusion (of subset analysis) did not necessarily mean that the data on patient subgroups was sufficient for meaningful analysis or to detect relevant subgroup effects" [emphasis added]. In other words, as long as the application mentioned demographic subsets in some way, FDA considered that a subgroup analysis was conducted. In our view, subgroup-specific analyses should be conducted for primary safety and efficacy endpoints for all products, unless a reasonable justification exists for why such analyses cannot be conducted for a specific product (such as a product is only approved for use in men or children).

Despite the low threshold that applicants need to meet for this subgroup analysis requirement, the report reveals that compliance is still uneven. To quote from page 11 of the report, "Although there is no statutory or regulatory requirement to include demographic subgroups as participants in clinical trials, FDA guidance documents encourage, and regulations clearly require, presentation and inclusion of analysis of demographic data in marketing applications [emphasis added]". Therefore, we would expect 100 percent of applications to have conducted at least these minimal analyses. Yet that is not the case. For example:

- For devices, 12 percent of PMA applications did not contain sex analysis, 30 percent did not contain an age analysis; and 73 percent did not contain race or ethnicity analysis.
- For drugs and biologics, there were numerous instances where subset analysis information wasn't found in either the labeling or other documents in the public domain. In 20 cases where no analysis information on pharmacology, safety, or efficacy was found in the labeling or review documents, we presume that no such analysis was provided or conducted.

There were many more examples where subset “analysis” was conducted, but there were not actually enough participants in that category to conduct a meaningful analysis:

- Thirteen of the 31 applications reviewed for drugs and biologics lacked meaningful geriatric subgroup safety or efficacy analysis.
- Five of the 31 applications for drugs and biologics lacked meaningful geriatric subgroup clinical pharmacology analysis because there weren't enough older participants in the trial.
- Eight of the 30 drug and biologics applications reviewed, lacked data to conduct meaningful safety subgroup analysis by sex.
- Ten of 31 drug and biologics applications reviewed for racial subset analysis, included no meaningful clinical pharmacology subgroup analysis.
- Sixteen of 31 drug and biologics applications contained no meaningful safety subgroup analysis.
- Six of 31 drug and biologics applications included no efficacy subgroup analysis because there was insufficient data to detect differences.
- Fifty percent of medical device applications included a summary statement about racial or ethnic subgroup analysis that could draw meaningful conclusions based on an adequate number of subgroup participants. There were also instances where sex and age subgroup analyses were not able to be meaningfully conducted.

Recommendations for the Action Plan

To ensure that meaningful subset analyses are being conducted and that FDA reviewers are taking this information into account when making approval decisions for medical products, we recommend:

- FDA should consistently enforce its existing regulations and guidance requiring the analysis of subgroup data.
- FDA should exercise its regulatory authority to reject applications that do not include the required information or that do not have sufficient numbers to draw relevant conclusions when necessary.
- The FDA should strengthen its existing regulations and guidance to require subgroup-specific analyses to be conducted for primary safety and efficacy

endpoints for all products, unless a reasonable justification exists for why such analyses cannot be conducted for a specific product.

- Sponsors of applications for biologics approved by the Center for Biologics Evaluation and Research should be required to report summary subgroup data, similar to what is required for biologics approved by the Center for Drug Evaluation and Research.
- We also recognize that postmarket surveillance can be a valuable source of information about how a product performs in a specific subgroup once it is being used in a much larger population. Although we do not believe that postmarket surveillance should be a substitute for pre-approval demographic subgroup analyses for safety and efficacy, we encourage FDA to ensure adequate monitoring and enforcement of postmarket surveillance studies.

Subgroup Representation in Clinical Trials

At the heart of the gaps in information identified in the preceding pages is the underlying problem that women, racial and ethnic minorities, and the aged are not adequately represented in clinical trials. A close examination of the data in this report indicate many instances where the number of women, minorities, and the elderly in trials is not representative of the prevalence of the disease in these subgroups:

- Although the report's text indicates that the percentage of geriatric patients participating in drug studies "tended" to reflect the prevalence of the disease by age, we found numerous instances where that appears not to be the case:
 - Hypertension is more prevalent as people age; according to the Centers for Disease Control and Prevention (CDC), 70 percent of people over age 65 have hypertension. Yet fewer than 30 percent of trial participants for a new hypertension medication were over 65. (Figure 1-1)
 - The report stated that Hodgkin lymphoma occurs more commonly in younger patients and thus geriatric representation was expected to be low. Yet according to National Cancer Institute (NCI) data, 17.7 percent of new cases of Hodgkin lymphoma are in people over age 65; fewer than 5 percent of patients in the trial were over age 65.
 - According to the Leukemia and Lymphoma Society, although acute lymphoblastic lymphoma (ALL) is most common in the first decade of life, there is an increase in incidence in older adults. No older adults were represented in the ALL study, according to Figure 1-1.
- Women make up approximately 61 percent of total chronic obstructive pulmonary disorder (COPD) patients, according to the CDC, yet in two trials for new COPD medication, women made up only about 25 percent and 31 percent of participants, according to Figure 1-2.

- Taking a look at drug efficacy trial composition by race, there were several examples where Blacks were underrepresented:
 - For a type 2 diabetes trial, African-American representation in clinical studies was only 2 percent, even though they make up 13 percent of the overall population and nearly 19 percent of African-American adults have type 2 diabetes, according to the NIH/CDC National Diabetes Education Program.
 - African-American representation in two different COPD trials was only 2 percent, even though 8 percent of those with COPD are African-American, according to CDC data.
 - There were several other studies, such as for hereditary angioedema and age-related macular degeneration, in which Blacks were not included at all.
- With respect to the sex composition of medical device trials, there were 18 out of the 33 PMAs reviewed in which participation of women in the studies was below 50 percent, and for seven studies, women’s participation rate was below 30 percent. More specifically:
 - The explanation for the 18 percent participation rate by women in a trial for an endovascular occlusion device was particularly troubling. The report says, “investigators often select patients with larger coronary size and less diffuse nature of coronary disease” – in other words, investigators purposely select men for these types of trials, even though the device will be used for women.
 - For three coronary drug-eluting stent (DES) submissions, in four of the six pivotal studies used, participation by women was at or below 30 percent and two were below 40 percent, even though 42 percent of coronary heart disease patients are women, according to American Heart Association statistics (Figure 2-6)
- Similarly, the inclusion of African-Americans in the DES trials appears to be very small (less than 5 percent) although 14 percent of CHD patients are Black (AHA). Also, participation of Hispanics in the DES studies appears to be below 5 percent, even though Hispanics/Latinos represent 17 percent of the population (and for one study ethnic composition was not reported at all).

Finally, it is our understanding that this report only reviewed Phase III clinical trials used to evaluate final product approval. However, subgroups are often even further underrepresented in early phase trials for drugs, biologics, and devices. For example, a 2010 study found that the percentage of women participating in early phase trials has increased only to 31 percent.¹

The FDA must take steps to address inadequate representation of subgroups in the clinical trials used for approving medical products. Otherwise, a lack of adequate information about how these

¹ FDA. Status of Women’s Participation in Clinical Trials. *Journal of Women’s Health*, 2010; 19:1771.

therapies perform in women and men, racial and ethnic minorities, and older Americans will continue to persist.

Recommendations for the Action Plan

- FDA should require that representative proportions of women, minorities and older Americans be included in clinical trials, consistent with the disease's prevalence in the underlying population, as the NIH required 20 years ago. This requirement should extend to their representation in trials in all phases. While we certainly understand the need to conduct clinical trials in a timely and cost-effective manner, adequate representation of patient subgroups that will ultimately be using the drug or device is critical to ensuring that it is safe and effective for all people. Dosing has long remained an issue for women whom it has frequently been shown metabolize drugs differently and have greater side effects and adverse events than men.
- It is also critically important that FDA put in place a system of real-time, transparent compliance so that gaps in information do not continue. We support a recommendation called for by Drs. Rita Redberg and Sanket Dhruva in a *Journal of the American Medical Association* editorial: "Real-time transparency, with reporting through FDA-TRACK at monthly intervals for clinical trials that are actively recruiting, would increase the likelihood that adequate numbers of women are enrolled. Tracking should involve specific information about the percentage of women enrolled in studies."² The same applies to minorities and the aged.
- Study sponsors should be required to proactively and prospectively develop a plan to enroll sufficient proportions of women, minorities, and older adults in clinical research. While there may be reasons why these populations do not participate in clinical research at levels equal to white men, there are strategies proven to bolster the participation of underrepresented people, and more should be done to encourage these efforts.
- The FDA should consider establishing an FDA Advisory Group for groups underrepresented in clinical research studies to make recommendations to improve participation rates.
- FDA should take steps to ensure that representative proportions of women, minorities, and the aged are included in early phase trials.

Public Availability of Demographic Subgroup Information

Finally, Congress required that the report analyze the extent to which product safety and efficacy subgroup data is "readily available to the public in a timely manner by means of the product labeling or the Food and Drug Administration's Internet Web site." In this report, FDA considered information to be publicly available if it was included in the product labeling or

² Dhruva SS and Redberg R. Evaluating Sex Differences in Medical Device Clinical Trials: Time for Action. *JAMA*. Published Online: February 29, 2012. doi:10.1001/jama.2012.254.

included in the review packages or Summaries of Safety and Effectiveness Data (SSEDs) that are posted on the FDA's website. Although we recognize that the reviews or SSEDs are technically available to the public, we do not believe this information is "readily" accessible nor do we think it reasonable to expect patients and clinicians to find and search through these highly technical documents to determine whether the product has been found to be safe and effective for their demographic subgroup.

We are also concerned about contradictory statements about when information might actually be included in the product's labeling that is more readily available to the public. According to the report, this determination is made based on whether it would be informative or whether there are sufficient numbers for meaningful analysis and whether differences based on subgroup were noted. The problem of course is that if there is not sufficient data to conduct meaningful analysis and look for evidence that differences based on subgroup might exist, then it cannot really know what informative information might be missing from the label. The FDA wants patients and health care professionals to assume that if there is no information included in the label about a product's safety or efficacy in specific subgroups, it is because there are no differences in how it performs in those populations. In reality, however, the absence of such information is just as likely to mean that FDA does not know whether such differences exist because it did not have enough information to draw such a conclusion.

In our review of the report, we found numerous examples where safety and efficacy information by subgroup was not readily available to the public through the product labeling or in some cases, wasn't available at all. More specifically, we found:

- For 80 percent (24 of 30) of drug and biologic products, efficacy information by sex was not readily available to the public through the labeling and for 83 percent (25 of 30) of applications, safety information by sex was not readily available through labeling. In 3 cases, this safety information wasn't available publicly at all, even through the review packages. (Figure 1-8)
- For 77 percent (24 of 31) of drugs and biologics approved in 2011, efficacy information by race was not available at all or more readily available through the labeling, and for 94 percent (29 of 31) of drugs and biologics, safety information by race was not available through the labeling. For 9 (29 percent) drugs/biologics, this safety information wasn't publicly available at all. (Figure 1-9)
- With respect to devices, summary demographic information (defined as inclusion in the labeling and/or the SSED), was publicly available even less consistently. According to the report, 37 percent of PMA applications did not publicly report sex-specific data, 43 percent did not publicly report age-specific data, and 84 percent did not report race or ethnicity-specific information.

Recommendations for the Action Plan

- The FDA should require that sex and race/ethnicity demographic information be required sections in labeling, as is the case for pediatrics and geriatrics information, even if subgroup-specific analyses suggest no difference in outcomes.
- If the proportion of subgroup members participating in product studies is not sufficient to evaluate whether differences exist, we recommend that FDA require this be stated on the label.
- FDA should develop standard label content requirements for medical devices.

Conclusion

In closing, we appreciate the FDA's work in preparing this report, and we are eager to work with FDA on the drafting of the Action Plan to address the gaps that are identified. Implementing an effective plan of action will result in making subgroup-specific data more widely available and ultimately increase the participation of women, minorities, and the elderly in clinical trials.

To summarize our major recommendations for inclusion in the Action Plan:

- FDA should consistently enforce its existing regulations and guidance requiring the analysis of subgroup data and exercise its authority to reject applications that do not submit the required information.
- The FDA should strengthen its existing regulations and guidance to require subgroup-specific analyses be conducted for primary safety and efficacy endpoints for all products, unless a reasonable justification exists to exempt a specific product from such analyses.
- FDA should require that representative proportions of women, minorities and the elderly be included in clinical trials, consistent with the disease's prevalence in the underlying population, as the NIH required 20 years ago, and then enforce these regulations.
- FDA should also put in place procedures to track and publicly report compliance with these recommendations on a regular basis and take further action as needed to ensure compliance.
- The results of subgroup-specific analyses should be included in the labeling so that it is accessible to researchers, clinicians, and patients.

If you have any questions or need any additional information, please do not hesitate to contact one of our staff: Stephanie Mohl, Senior Government Relations Advisor at the American Heart Association, at (202) 785-7909 or stephanie.mohl@heart.org; Martha Nolan, Vice President, Public Policy at the Society for Women's Health Research (SWHR), at 202-496-5007 or Martha@swhr.org; Susan Campbell, Director of Public Policy at WomenHeart: The National Coalition for Women with Heart Disease, at 202-728-7199 or scampbell@womenheart.org; or Kate Ryan, Senior Program Coordinator at the National Women's Health Network, at 202-682-2640 or kryan@nwhn.org.

Thank you for your consideration of our comments.

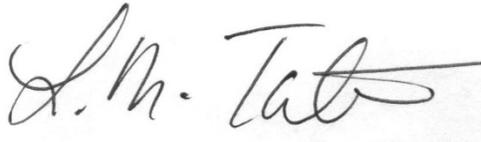
Sincerely,



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