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Division of Dockets Management
(HFA–305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852
E-comments: http://www.regulations.gov

**Comments of Living Well Black, Inc.
to the U.S. Food and Drug Administration in response to a
Notice of Availability of a Guidance for Industry entitled
"Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to
Support Approval of Human Drugs and Biological Products"
Docket Number FDA-2012-D-1145**

Introduction

Living Well Black, Inc. (LWB)[1] submits the following comments in response to the U.S. Food and Drug Administration's (FDA) Notice of Availability (Notice) of the "Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to Support Approval of Human Drug and Biological Products" (Draft Guidance).[2]

Background

In many areas of life, African Americans face a disproportionate burden of diseases and conditions. LWB is a nonprofit organization formed to mitigate and, ultimately, to help end such disparities. There are critical actions that could be used to narrow this gap, including developing regulatory policy decisions that are likely to improve, and not exacerbate these trends.

Although non-binding, this FDA Draft Guidance, when finalized, will represent the U.S. Food and Drug Administration's (FDA) "current thinking on the topic."[3] LWB is concerned that several approaches described by the FDA in its Draft Guidance (and

[1] Living Well Black, Inc. (LWB) is an organization formed in 2012 to promote policy decisions designed to reduce disparities. With an initial focus on health and injury prevention, LWB was created to provide African Americans with information and advice to overcome obstacles to health, wealth, and success.
[2] 77 Fed. Reg. 74670 (December 17, 2012). These comments also are submitted pursuant to the "Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products; Extension of Comment Period," extending the comment period through March 18, 2013. See 78 Fed. Reg. 7784 (February 4, 2013).
[3] See Draft Guidance, at 1, lines 8-9.

acknowledged as widely practiced)[4] are likely to disadvantage African Americans who suffer from the diseases and conditions intended to be treated by the human drugs and biological products contemplated by this Draft Guidance. In particular, LWB is concerned that the following enrichment strategies enumerated in the Draft Guidance may serve to disadvantage African Americans: (1) Decreasing heterogeneity; (2) Reducing participation by patients with concomitant illnesses; and (3) Excluding patients "who are likely to drop out for non-medical reasons (e.g., because they have difficulty getting to the study site)."[5]

Discussion

Drug developers often use methods to "enrich" clinical trial study populations in an effort to increase the likelihood that data collected during a clinical trial will demonstrate that a drug is effective. Using these "enrichment strategies," companies enroll patients who are more likely to demonstrate an effect, based on their demographics, clinical histories or other characteristics. One method employed to increase study power is "decreasing heterogeneity." In this approach, an attempt is made to decrease non-drug related variability. Too often, however, this approach results in the creation of a clinical trial study population not appropriately representative of the population the drug or biological product is intended to treat in the market.

1. "Decreasing Homogeneity"

a. The Population of the United States of America is Becoming Increasingly Diverse

This Draft Guidance reflects the current thinking of the FDA and, to a great extent, reflects methodologies that are "widely practiced" by industry. The approaches taken by the industry in the past may not be appropriate to address the changing demographics of the United States market, and the populations these therapies are likely to treat.

The population of the United States is becoming increasingly diverse, and the U.S. is projected to be a majority minority nation in 2043.[6] The Black/African American population was measured at 12.6% of the population of the United States by the 2010

[4] Id. at 3, line 102.
[5] Id. lines 121-122.
[6] See "U.S. Census Bureau Projections Show a Slower Growing, Older, More Diverse Nation a Half Century from Now," U.S. Census Bureau, December 12, 2012. http://www.census.gov/newsroom/releases/archives/population/cb12-243.html, viewed 3/17/2013.

census, with people self-identifying as Black or African American in combination with another race measured to be 13.6% of the population.[7]

b. Need to Ensure Appropriate Heterogeneity of Clinical Trials

LWB is concerned that ongoing efforts to streamline clinical trials have resulted in a lack of diversity in study populations. LWB urges, instead, that companies sponsoring clinical trials gather information appropriately representative of the population that its drug or biological product is intended to treat in the market.

Concerns about any presumed difficulty in attracting and retaining minority patients in clinical research should not be a sufficient reason to exclude them, or to fail to include them in sufficient numbers. We urge the FDA to ensure that a drug or biological product approved to treat certain conditions can appropriately do so in the broadest patient population. If the population of the clinical trial that serves as the basis for approval lacks sufficient breadth, the approved product's labeling should inform the patient and prescribing physician of the restricted nature of the patient population in which the drug was studied. In addition it should carry a warning box informing that others using the product may experience different risks and dissimilar benefits due to a lack of statistically significant outcomes information.

While recognizing that, for drugs intended to treat a small patient population, this may not be possible, for other trials, LWB strongly urges the FDA to stress the importance of clinical trial sponsors ensuring that efficacy data generated from its clinical trials originates from a cross-population of participants. Similarly, pharmacovigilence must be robust enough to take into consideration the genomic makeup of varying populations. Where African Americans are part of the population burdened by the disease or condition the drug or biological product is expected to treat, companies should use best efforts to solicit African American pharmacogenomic information during clinical trials.

Ideally, the collection of diverse genotypes should be the defining characteristic of a responsibly conducted trial. If differences exist, the question to be answered is what are the functional genotypes of those who respond differently to a drug or biologic. Where, for valid and justifiable reasons, there is insufficient information of this kind generated during clinical trials conducted to support approval, companies should solicit African American pharmacogenomic information after the drug is on the market. In these instances, we strongly urge the FDA to impose the "postmarket commitments or requirements," as described in section VII.A.2 of the Draft Guidance to "better define the

[7] "The Black Population: 2010," 2010 Census Briefs, See http://www.census.gov/prod/cen2010/briefs/c2010br-06.pdf (viewed 3/17/2013).

full extent of a drug's effect (including efficacy and safety studies and trials in a broader population)."[8]

2. Eliminating Subjects with Concomitant Illnesses

Another strategy employed includes eliminating patients with concomitant illnesses.[9] LWB concurs with the statement in the Draft Guidance, that:

> *…it is not clear that concomitant illnesses that do not affect survival or other endpoint measurement or concomitant drugs unrelated to a test drug really do interfere with assessment of a treatment effect. Therefore, the implication of using these strategies should be carefully considered before they are used.*[10]

LWB agrees with the concern that avoiding enrolling people with multiple illnesses can result in the collection of data that does not appropriately reflect the full range of people likely to be treated by a drug or biologic product when it is on the market. These strategies may negatively impact African Americans, in particular, who tend to be sicker with more co-morbidities. Where achievable, we strongly urge clinical trial sponsors to avoid eliminating subjects with concomitant illnesses. Where eliminating such patients is unavoidable, FDA should require sponsors to conduct postmarket studies in patients with co-morbid conditions.

3. Eliminating Subjects Likely to Experience Trouble Reaching Trial Site

An additional method of enrichment discussed in the Draft Guidance is to restrict clinical trial enrollment to those patients believed to be most likely to comply. One strategy described is "Excluding patients who are likely to drop out for non-medical reasons (e.g., because they have difficulty getting to the study site)."[11] For obvious reasons, employing this strategy is likely to disadvantage lower income potential trial subjects who, if burdened by the illness the therapy is expected to treat, are representative of the population the drug or biological product is intended to treat in the market. Eliminating subjects anticipated to have difficulty reaching the study site likely will negatively impact lower income potential subjects, and disproportionately impact minorities and the diversity of clinical trials.

These potential challenges can and should be dealt with early in a study design. It is no surprise that a low level of education and income could present a potential barrier to participation. However, best practices of companies sponsoring clinical trials must anticipate that if certain subjects likely will experience difficulty with transportation,

[8] Draft Guidance at 32, lines 1300-1301.
[9] Draft Guidance at 3-4, lines 123-125.
[10] Id.
[11] Id. at 3, lines 121-122.

assistance can be provided in the form of vouchers for taxis or the use of shuttle buses. As additional solution, the study protocol could include participation by a healthcare worker available to make home visits to those unable to reach the study site. It is important to note that there are clinical trial site sponsors in operation today that use these approaches. With a commitment to diverse study populations, these clinical trial sponsors are successful at recruiting and retaining minority patients due to their ongoing investment of the resources necessary to retain patient participants. In addition, these site sponsors develop community outreach programs, and cultivate relationship with local residents by, for example, offering wellness and health screening events and programs.

Finally, the availability of more clinical trial sites accessible to a more diverse population could decrease the potential impact on those with limited transportation. Additionally, recruitment of diverse doctors, and clinical trial study site coordinators with a diverse patient population would increase the likely access to potential clinical trial subjects that would better represent a cross-population of participants.

Conclusion

We request that the FDA consider the foregoing recommendations in preparing its Final Guidance in order to recognize the need for diverse populations in studies to determine the safety and efficacy of human drugs and biological products.

Respectfully submitted,

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Living Well Black, Inc.