

Participation of Racial/Ethnic Groups in Clinical Trials and Race-Related Labeling: A Review of New Molecular Entities Approved 1995-1999

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Few recent data are available from formal evaluations of approved new drug applications to address perceptions that racial and ethnic groups are under-represented in clinical trials of new drugs. This study reviews racial and ethnic group participation in clinical trials and race-related labeling for new molecular entities approved during a five-year period by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER).

This was a retrospective review of FDA medical officers' reviews of clinical trial protocols and product labeling for 185 new molecular entities (NME's) approved by CDER between January 1, 1995, and December 31, 1999. Enrollment data were obtained from the reviews and tabulated according to race/ethnicity. The approved product labeling was searched for statements related to product testing in various racial/ethnic groups. All data were compiled and analyzed using Microsoft Access. This study quantifies the participation of racial/ethnic groups in clinical trials by year and therapeutic category. Additionally, the study categorizes labeling based on the types of effects described as related to race/ethnicity.

Racial and ethnic groups appear to participate in clinical trials to varying degrees. African Americans participated in trials to the greatest extent; however, their participation steadily declined from 12% in 1995 to 6% in 1999. Among trials known to be conducted only in the U.S., African-American participation is comparable to their representation in the U.S. population. In all cases, participants designated as Hispanic appear to be far below their representation in the population. Some differences in participation for all racial and ethnic groups are seen when comparisons from year-to-year or among drug classes are made. Labeling for 45% (84/185) of the products contained some statement about race, although in only 8% (15/185) were differences related to race described. Fifty percent (50%) of the effects were pharmacokinetic, 39% were efficacy, and 11% were safety. One product label recommended a change in dosage based on racial differences. (*J Natl Med Assoc.* 2001;93(suppl):18S-24S).

Key words: clinical trials ♦ ethnicity
♦ product labeling

Responses to drugs can be altered by a wide variety of individual characteristics that affect the pharmacokinetics of a drug (differences in absorption, metabolism,

distribution, excretion, or the presence of other drugs) or the patient's response to the drug (differences in co-existing illness, etiology of disease, or again, the presence of other drugs, etc.). In some cases these differences have been related to demographic characteristics, such as gender or race. Women, for example, are unusually susceptible to drugs that prolong the electrocardiographic QT interval and the serious ventricular arrhythmia (Torsades de pointes) that can accompany this prolongation. They may also, because of their

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smaller size, have more adverse effects (e.g., edema with amlodipine) than men when both are given the same dose. There are documented racial differences as well. Whites are more likely than Asians to have abnormally low levels of an important liver metabolizing enzyme (cytochrome p450 2D6). African Americans respond poorly to several classes of antihypertensive agents (beta blockers, angiotensive converting enzyme (ACE) inhibitors, and angiotensin II antagonists) and appear to have a greater risk of angioedema when given ACE inhibitors. It is therefore important to include in drug development representation of the broad range of patients who will eventually receive the drug, including people of both genders, representatives of major racial/ethnic groups, and patients with a wide range of disease severity, concomitant illnesses, and use of concomitant treatments.

Attention to potential racial and ethnic differences in response to drugs is part of a larger effort by the FDA to ensure that the safety and efficacy of drugs are adequately studied in people who represent the full range of patients who will receive them upon marketing. FDA guidelines and regulations encourage the participation of racial and ethnic groups in all phases of drug development, promote collection of race-related data during research and development, and recommend analysis of the data for race effects. Following is a brief summary:

- The 1988 “Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications” emphasizes the importance of including analysis of demographic subset data in new drug applications. (<http://www.fda.gov/cder/guidance/statnda.pdf>)
- The 1998 “Final Rule on Investigational New Drug Applications and New Drug Applications (Demographic Rule) requires that analyses of effectiveness and safety data for important demographic subgroups, including race, be included in NDAs and that enrollment of subjects in clinical studies for drug and biological products be tabulated by important demographic subgroups in investigational new drug (IND) annual reports.¹

Draft guidance documents on population pharmacokinetics and the adverse reactions and clinical sections of the labeling also consider subgroup issues as summarized below.

- The Guidance for Industry “Content and Format

of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics” is intended to assist sponsors in developing the adverse reactions section of labeling for human prescription drugs and biologics. It includes recommendations for presenting subgroup specific information. (http://www.fda.gov/cder/guidance/1888dft.htm#P109_5053)

- The Guidance for Industry “Population Pharmacokinetics” makes recommendations on the use of population pharmacokinetics in the drug development process to help identify differences in drug safety and efficacy among population subgroups. (<http://www.fda.gov/cder/guidance/1852fml.pdf>)
- The Guidance for Industry “Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format” states that the clinical studies section of the labeling should include a summary statement about the results of the required explorations of treatment effects in age, gender, and racial subgroups. (<http://www.fda.gov/cder/guidance/1890dft.html>)

The Food and Drug Modernization Act (FDAMA) of 1997 (<http://www.fda.gov/opacom/7modact.html>) also prompted FDA to examine issues related to the inclusion of racial and ethnic groups in clinical trials. Section 115 of the Act required the Secretary, “in consultation with the Director of the National Institutes of Health and the representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials...”

FDA established the FDAMA Women and Minorities Working Group to review and implement this section of FDAMA. In a report issued on July 20, 1998, the Working Group concluded that no additional guidance was needed. The report stated that the agency would implement procedures to enhance its ability to gather and evaluate demographic data and then decide whether additional guidance should be developed in the future. (<http://www.fda.gov/cder/guidance/women.pdf>)

FDA’s Office of Special Health Issues (OSHI) completed three projects that gathered and evaluated demographic data. The results of the first study were presented at the 2000 FDA Science Forum in a poster entitled “Special Populations: Testing and Labeling of New Drugs.” The study examined NME’s approved in 1995 and 1996.² Results demonstrated that African-American volunteers participated in studies for most

drugs but participation by other racial and ethnic groups was low. Similar results were found in an FDA review of demographic data for NME's approved from January 1998 to June 1991.

The results of the second study were presented at the 2001 FDA Science Forum in a poster presentation entitled "Race, Age, and Gender: A Review of Demographic Subgroups in Clinical Trials of FDA-Regulated Drugs and Biologics." The study examined the extent to which IND sponsors complied with the reporting requirements of the 1998 Demographic Rule and found that all required information was not submitted for 85% of IND protocols with data reported. Where race/ethnicity could be determined, African Americans represented 9% of the study participants. Hispanic/Latinos and the group consisting of Asians, Pacific Islanders, and Native Hawaiians each comprised 3%. Another 3% were designated as nonwhite, and less than 1% were American Indian and Alaska Natives.

This report presents the results of the third OSHI study "Participation of Racial/Ethnic Groups in Clinical Trials and Race-Related Labeling: A Review of New Molecular Entities Approved 1995-1999."

The objectives of this study were to assess to what extent racial and ethnic groups participated in clinical trials of drug products approved between 1995 and 1999 and to what extent sponsors presented race-related information in the approved product labeling.

METHODS

Data Sources and Collection

Data for this study were obtained from two primary sources. Information about clinical trial enrollment data was obtained from FDA medical officers' reviews of 185 new molecular entities (NMEs) approved by Center for Drug Evaluation and Research (CDER) between 1995 and 1999. (Medical officer reviews are documents in which the FDA officials responsible for oversight of specific products analyze the sponsors' data and explain their conclusions.) The reviews contained descriptions of 2,581 clinical trial protocols. The reviews were searched for FDA reviewers' descriptions of the race of study participants. Race categories used were those defined in the Office of Management and Budget Directive 15.⁴ Participation was quantified according to year of product approval and therapeutic class based on the FDA review division.

The labeling at the time of product approval was reviewed to determine whether assessments of racial/ethnic differences were being communicated to

practitioners. Exact wording from the label was captured. Labels describing racial differences were reviewed to determine the type of difference and whether the difference required a change in dosage for a particular racial/ethnic group.

All data extracted were captured on a protocol extraction form and entered into a Microsoft Access database. An initial audit of each data field for 250 protocols assured the quality of the extracted data. A second audit was conducted for each data field for 100% of the protocols once the data were entered into the database.

Data Analysis

Race data were analyzed from clinical trial protocols described in FDA medical officer reviews of 185 NMEs.

RESULTS

Race/Ethnicity of Clinical Trial Participants

A total of 493,347 individuals were described in the medical officers' reviews as being enrolled in the 2,581 clinical trials for all products examined in this study. Race could be determined from the medical officers' reviews for 53% of the participants (Fig. 1). Race could not be determined for the remaining 47%. Of those for whom race and ethnicity could be determined ($n=263,704$), 88% were white; 8% were African American; 1% were Asian, Pacific Islander, or Native Hawaiian; 3% were Hispanic/Latino; and less than 1% were American Indian or Alaska Native. It must be noted that the Hispanic/Latino ethnicity is applicable to people of several races. Therefore, the possibility exists that in instances in which NDA submissions reported race without regard to ethnicity, Hispanics may have also been included, and the current figures may represent an undercount of the Hispanic ethnic group (Fig. 2).

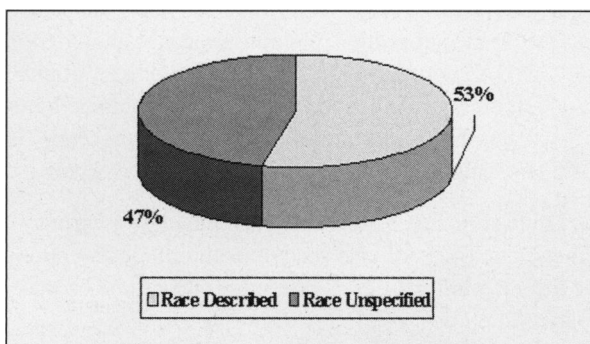


Figure 1. Total enrollees for study period 1995-1999.

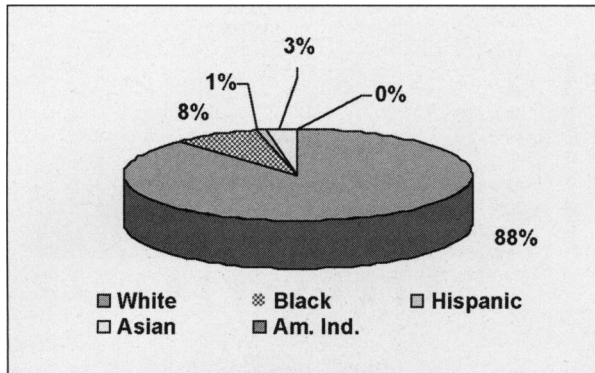


Figure 2. Clinical trial participants according to race (n = 263,704). Note, total number excludes 229,643 (47%) whose race was not described in the medical officer's review.

Of the 263,704 participants for whom race data were available, 75,357 of them were in trials known to be conducted only in the U.S. When evaluating those individuals, 83% were White; 13% were African American; 3% were Hispanic/Latino; 1% were Asian, Pacific Islander, or Native Hawaiian; and less than 1% were American Indian or Alaska Native (Fig. 3).

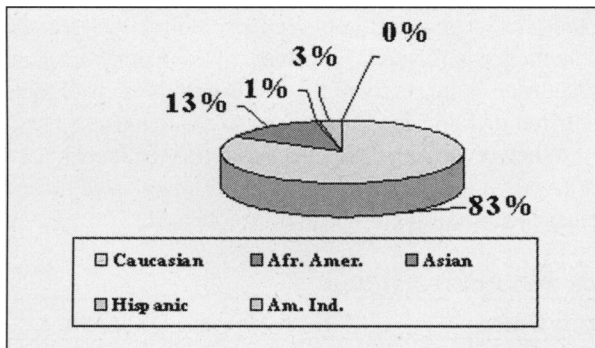


Figure 3. Participants in U.S.-based trials according to race. Note: total reflects ethnicity/race of 15% of total participants and 70% of participants from studies known to be conducted only in the U.S. Race could not be determined for the remainder.

Figure 4 presents a comparison of the average proportion of each race or ethnic group participating in total and in U.S. trials with their average representation in the U.S. population, across the years 1995-1999.

Participation by Year

The proportion of clinical trial participants from each racial/ethnic group varied from year to year. Overall, African-American participation in trials ranged from 12% in 1995 and steadily declined to 6% in 1999 (Fig. 5). Among trials known to be conducted only in

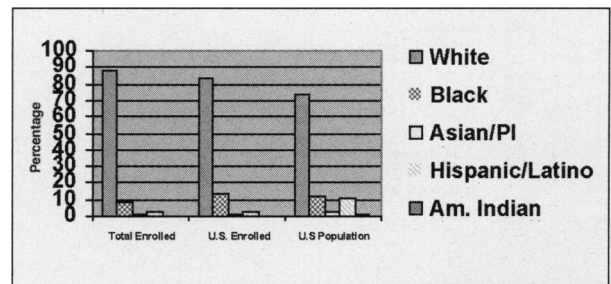


Figure 4. Comparison of average proportion of racial groups in total and U.S. trials and their representation in the U.S. population. Note: total reflects 15% of total participants and 70% of participants from trials known to be conducted in the U.S. Population Estimates Source: U.S. Census Bureau, 1995-1999

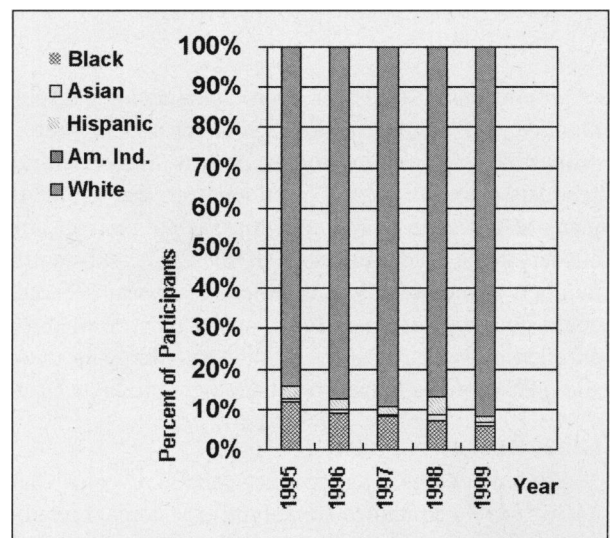


Figure 5. African American participation in clinical trials declined to 6% in 1999, but overall participation sometimes exceeded their representation in the U.S. population. Note: total number (n=229,643) excludes 47% whose race was not described in the medical officers' reviews.

the U.S., the representation of African Americans ranged from 18% in 1995 to 10% in 1999. Their representation occasionally exceeded their representation in the U.S. population. Hispanic representation appeared to be consistently well below their representation in the population (Fig. 6).

Participation by Drug Class

Drug classes were defined according to the division within the agency responsible for the product review. The categories of products for each division and designated abbreviations are listed in Table 1. Overall, racial and ethnic groups appeared to have participated in less

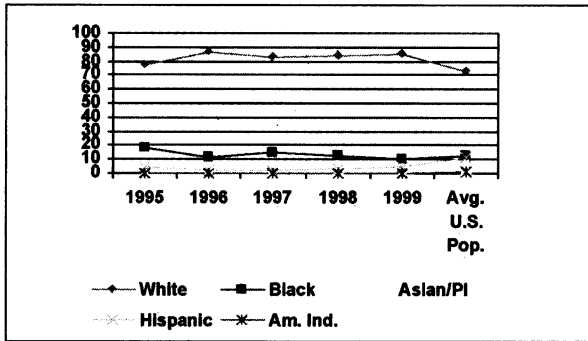


Figure 6. Hispanic participation in trials was consistently below their representation in the U.S. population. Note: total reflects 15% of all participants and 70% of participants from U.S.-based trials. Race could not be determined from the remainder. Population estimates obtained from the U.S. Census Bureau.

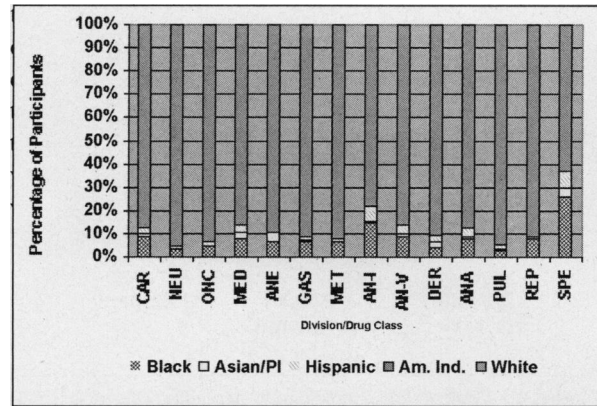


Figure 7. Racial/ethnic group trial participation based on drug class. Total participants excludes 229,643 (47%) whose race was not described in the medical officers' reviews.

er proportions in trials for neuropharmacological, pulmonary, and oncologic drug products and in greater proportions for special pathogen and anti-infective drug products (Fig. 7). No statistical analyses were done. In many instances in which nonwhite racial/ethnic groups appear to be underrepresented, there are substantial numbers of individuals whose race could not be determined for as many as 70% of those enrolled in the trials for the pulmonary/allergy products and 54% of those in trials for oncologic products.

Label Review Findings

Review of the 185 product labels revealed that 84/185 (45%) contained some type of statement related

statements indicated that no studies had been conducted to determine if there were differences related to race/ethnicity. Eight percent (8/98) indicated that studies were inadequate to detect any racial differences. Thirty percent (29/98) of the statements indicated that no differences were found. Eighteen percent of the statements (18/98) indicated that differences related to race had been identified. Ten percent (10/98) of the statements indicated that there were similar racial responses. A summary of the labels with race statements is listed in Table 2.

When reviewing differences found in the label by the drug class, the greatest proportion of race-based differences occurred in cardio-renal products (8/22 or 36%),

Table 1. Product Categories and Abbreviations

Abbreviation	Review Division/Drug Class	FDA Review Division
CAR	Cardio-renal	110
NEU	Neuropharmacological	120
ONC	Oncologic	150
MED	Medical Imaging	160
ANE	Anesthetic	170
GAS	Gastrointestinal/Coagulation	180
MET	Metabolic/Endocrine	510
AN-I	Anti-Infective	520
AN-V	Antiviral	530
DER	Dermatological/Dental	540
ANA	Analgesic	550
PUL	Pulmonary/Allergy	570
REP	Reproductive/Urologic	580
SPE	Special Pathogens	590

analgesics (2/13 or 15%), neuropharmacology (3/21 or 14%), and metabolic/endocrine (2/25 or 8%). No race/ethnicity-based differences were noted in the labels of oncologic, anesthetic, gastrointestinal, anti-infective, anti-viral, dermatological and dental, pulmonary and allergy, reproductive and urologic, or special pathogen drug products (Table 3).

Fifteen product labels contained 18 statements about differences related to race/ethnicity. Of the 18 effects described, 50% (9/18) were pharmacokinetic, 39% (7/18) were efficacy, and 11% (2/18) were safety. Three product labels described more than one effect related to race. Ten product labels described differences for African Americans; one of those also described a difference for Hispanics. Five labels described differences for Asians. One product, an antihypertensive agent, recommended a change in the dosage based on racial differences: an increased initial dose for African-American patients.

DISCUSSION

Participation of Racial/Ethnic Groups

Overall, during the five-year period examined, non-white racial/ethnic groups participated in clinical trials at various rates. No comparisons were done to determine the types and proportions of products approved that might provide insight into year-to-year differences. No comparison was done, for example, to determine whether more anti-infective or cardiorenal products were approved in years where these groups were present in larger numbers. Nonwhite racial/ethnic groups rate of participation varies by drug class.

Label Reviews

The review of the labels showed that half of the products contained race-related statements and indicates that many sponsors are aware of the need to look for race-based effects. Only a minority of drugs where

race/ethnicity was assessed showed a difference based on race/ethnicity. The race effects described in the labeling were primarily pharmacokinetic differences. One product, an antihypertensive agent, recommended a different initial dosage for a specific racial group.

Limitations

There are several limitations to this study. First, the study was conducted using medical officers' reviews and product labeling only. There were large numbers of participants whose race could not be determined from the reviews. Second, the data presented do not reflect the race representation and analysis in the complete submission by the sponsors. The documents used may not represent the complete FDA analysis. Additional information, such as meeting records, memos, and supervisory, clinical pharmacology, or statistical reviews, was not included. Third, the study reviewed only approved products, which are a subset of all products reviewed by FDA staff. Fourth, neither sponsors nor reviewers were required to use the pre-defined race/ethnicity categories used in this study. The number of Hispanics could be underestimated if they were counted in other racial groups. Fifth, the study did not determine whether the proportion of a racial subgroup's participation in clinical trials of specific drug classes was comparable to the prevalence of a particular disease in a racial group. Lastly, race/ethnicity could not be determined for 47% of the participants; therefore, it is impossible to say whether the demographics obtained are generalizable to the entire sample of participants reviewed in this study or to participants in all clinical trials.

CONCLUSION

This study implements, in part, the July 1998 FDAMA Working Group initiative to gather and evaluate demographic data. Overall participation by racial and ethnic groups was small; however, African-American representation closely approximated their

Table 2. Label Review Findings

Statement	Number (%)
• No studies conducted	33/98 (34%)
• Studies inadequate	8/98 (8%)
• No differences found	29/98 (30%)
• Differences found	18/98 (18%)
• Similar racial response	10/98 (10%)
Total	98*

A total of 84 products had statements about race. Eleven products contained multiple statements.

*Excludes 229,643 (47%) subjects whose race was not described in the medical officers' reviews.

Table 3. Frequency of Race Differences by Drug Class

Div	Drug Products	Differences	Found in Label
110	Cardio-Renal	8/22	36%
120	Neuropharmacology	3/21	14%
150	Oncology	0/18	0%
160	Medical Imaging	0/11	0%
170	Anesthetic	0/6	0%
180	Gastrointestinal/Coagulation	0/11	0%
510	Metabolic/Endocrine	2/25	8%
520	Anti-Infectives	0/12	0%
530	Antivirals	0/17	0%
540	Dermatologic/Dental	0/8	0%
550	Analgesics	2/13	15%
570	Pulmonary/Allergy	0/7	0%
580	Reproductive/Urologic	0/6	0%
590	Special Pathogens	0/8	0%

representation in the U.S. population. Hispanics appeared to be most underrepresented in comparison to their representation in the U.S. population; however, they might have been counted among other racial groups. Few product labels contained statements about whether racial effects were known.

Attention to race by CDER medical officer reviews is variable. The recently launched Clinical Review Template will be implemented over the next year and will facilitate consistency among reviews. The template is intended primarily to standardize the ordering and placement of topics within reviews. The section on Special Populations will discuss how many people of various racial/ethnic groups were exposed to the investigational product during clinical trials and how well the data were analyzed for differences between them.

Additional studies using actual sponsor submissions may be needed to determine if FDA should provide

additional guidance to industry regarding demographic subgroup analysis in NDAs. Other studies may also be needed to determine whether the proportion of a racial subgroup's participation in clinical trials of specific drug classes was comparable to the prevalence of those diseases within racial groups.

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