BY KIM RIBBINK AND DENISE MYSHKO

Overcoming Diversity Obstacles: A CLINICAL IMPERATIVE

Traditional means of recruiting and retaining patients may not be enough to **OVERCOME AFRICAN AMERICANS' HISTORICAL RESISTANCE TO PARTICIPATING IN CLINICAL TRIALS**. Pharmaceutical company sponsors, contract research organizations, investigators, and investigator sites have to **WORK WITH COMMUNITY LEADERS TO ACTIVELY ADDRESS THE SPECIFIC CONCERNS OF THE AFRICAN-AMERICAN POPULATION** and overcome barriers to advance medical outcomes.

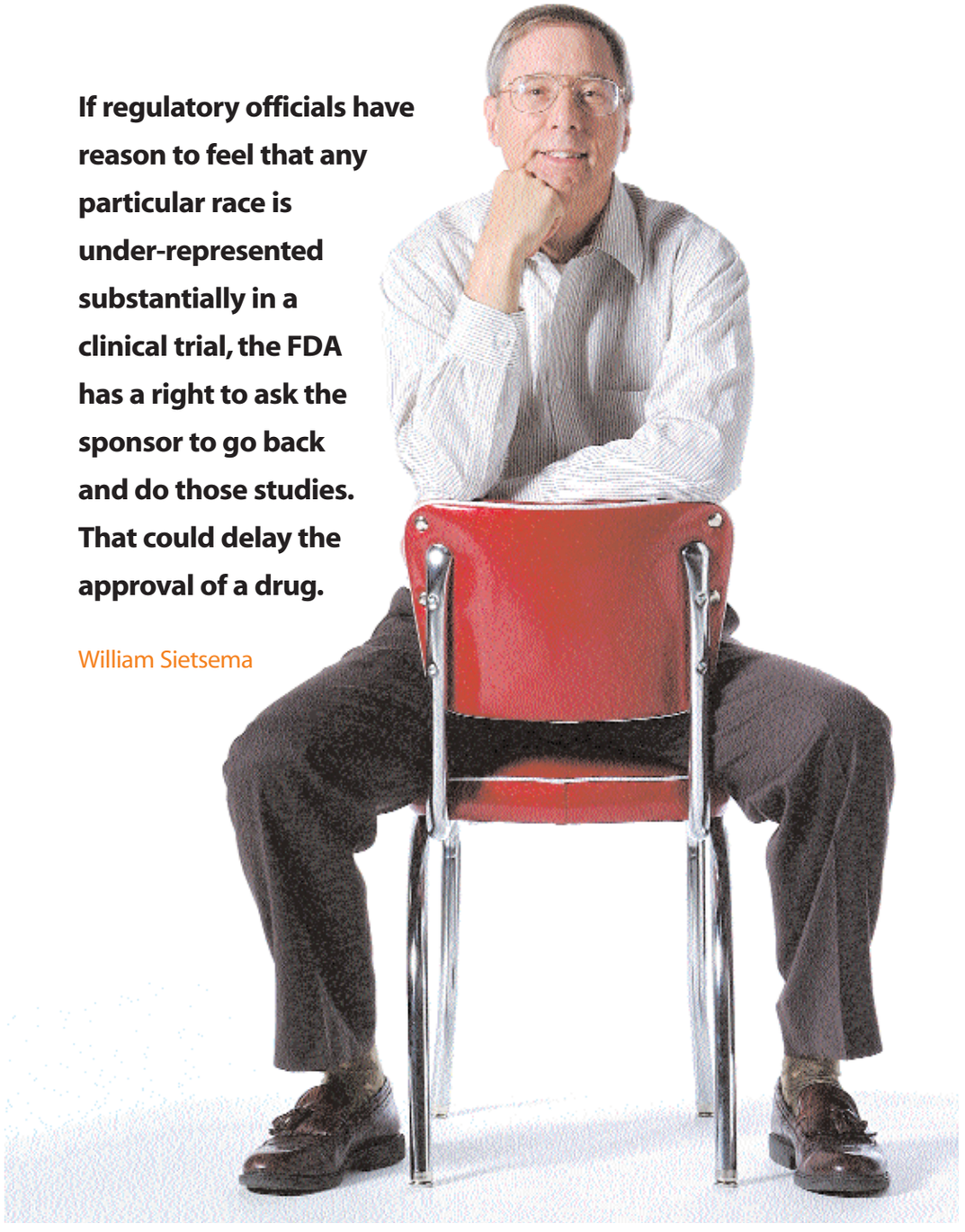
THE HUMAN GENOME PROJECT, research into responses to medicine, even the results of several clinical trials indicate that race and ethnicity do have bearing on the safety and efficacy of pharmaceuticals. Consequently, it is critical that pharmaceutical companies, CROs, and investigators ensure that a diverse selection of patients are represented in clinical trials.

Both the Food and Drug Administration and the National Institutes of Health in the mid-1980s began to look at policies for inclusion of women, and then minorities, in clinical-trial research. In 1997, the Food and Drug Administration Modernization Act (FDAMA) directed the FDA to examine issues related to the inclusion of racial and ethnic groups in clinical trials of new drugs.

Furthermore, in January 2003, the FDA published a draft guidance recommending categories for collecting effectiveness and safety data during clinical trials for ethnic and racial demographic groups. If adopted, this would create a standard for classifying the various races. FDA recommends that drug manufacturers use the categories for race and ethnicity established by the Office of Management and Budget during clinical-trial

If regulatory officials have reason to feel that any particular race is under-represented substantially in a clinical trial, the FDA has a right to ask the sponsor to go back and do those studies. That could delay the approval of a drug.

William Sietsema



data collection to ensure consistency in evaluating potential differences in drug response among racial and ethnic groups.

"All studies have to collect data on racial make up," says William Sietsema, VP of clinical development at Kendle International Inc. "Reviewers will ask whether the racial break out in the trials differs much from the racial representation across the United States. If reviewers have reason to feel any particular race is under-represented substantially, the FDA has a right to ask the sponsor to go back and do those studies. This could significantly delay the approval of the drug. Or the FDA could tentatively approve the drug with restricted labeling that indicates there is insufficient information on a particular race."

According to Edward F. Ikeguchi, M.D., chief medical officer and cofounder of Medidata Solutions Inc., it is the responsibility of the pharmaceutical industry to know about disease disparity and incidence in diverse populations.

"The degree to which a company puts a concentrated effort into studying a population depends on the risk/benefit ratio," he says. "A company, however, doesn't want to wind up in a situation where at the end of the research process, it finds out that there is indeed a disparity in results in the drug profile from one racial group to another."

"Sponsors serious about recruiting patients from minority populations need to make a commitment to supporting the resources necessary to make the recruitment initiative successful," says Thomas Schnitzer, M.D., Ph.D., chairman of RRI. Dr. Schnitzer also is a professor of medicine at Northwestern University Feinberg School of Medicine. "This is not a

Leading Causes of Death for African Americans in the United States in 2000

1. Cardiovascular disease
2. Cancer
3. Stroke
4. Unintentional injuries
5. Diabetes
6. Homicide
7. HIV/AIDS
8. Chronic lower respiratory disease
9. Nephritis, nephrotic syndrome, and nephrosis
10. Influenza and pneumonia

Source: National Center for Health Statistics, 2002, Hyattsville, Md.
For more information, visit cdc.gov/nchs.

▶ TO RECRUIT AFRICAN-AMERICAN PATIENTS FOR CLINICAL TRIALS, WE NEED TO GO BEYOND SIMPLY DOING MORE RADIO ADS OR DIRECT MAIL. TO BE SUCCESSFUL, INVESTIGATOR SITES NEED TO DEVELOP LONG-TERM RELATIONSHIPS WITH REFERRAL GROUPS, WHETHER THESE ARE CLINICS, PHYSICIAN PRACTICES, OR COMMUNITY-BASED ORGANIZATIONS.

Dr. Thomas Schnitzer

▲ TWO KEY COMPONENTS OF HEALTHCARE ARE EDUCATION AND ACCESS. IF INDIVIDUALS CAN'T GET TO THE DOCTOR, THEY DON'T HAVE THE SAME ACCESS TO HEALTHCARE. I WOULD LIKE TO SEE A BROADER INTEGRATED DEFINITION OF HEALTHCARE, LOOKING AT HOW WE MANAGE HEALTHCARE AS A SOCIETY.

Stedman Stevens

▼ ONE OF THE MAJOR BARRIERS FOR RECRUITING AND RETAINING AFRICAN AMERICANS IS ACCESS TO MEDICAL CARE. IN UNDERSERVED COMMUNITIES PATIENTS DON'T HAVE AS GREAT AN ACCESS TO PHYSICIANS.

Deborah Kniuksta

▲ PHARMA COMPANIES TEND TO DO "ONE-SIZE-FITS-ALL" CLINICAL TRIALS, BUT NOW THERE IS GENETIC EVIDENCE THAT AFRICAN AMERICANS RESPOND DIFFERENTLY TO CERTAIN TYPES OF CLINICAL PREPARATIONS.

Dr. Michael Lenoir

▼ RECRUITMENT ADS HAVE TO BE CULTURALLY APPROPRIATE. THE BEAUTY OF THE MEDIA NOW IS THAT WE CAN SEGMENT TO SPECIFICALLY REACH THE AFRICAN-AMERICAN POPULATION, OR THE KOREAN POPULATION, OR THE CHINESE POPULATION.

Liz Moench

matter of simply doing more radio ads or direct mail; recruiting patients from diverse populations is much more difficult than traditional recruiting. To be successful, sponsors need to develop long-term relationships with the referring groups, whether these groups are clinics, practices, or organizations."

To achieve success, sponsors will have to overcome serious obstacles. Participation by African Americans in clinical studies typically is lower than by Caucasians. According to a FDA review of new molecular entities approved between 1995 and 1999, 83% of clinical-trial volunteers were white, 12% were black, and 3% were Hispanic. More recently, there have been several reports that have examined participation by different racial groups in studies being conducted for specific diseases. For example, a study published in the May 2002 issue of the *New England Journal of Medicine* revealed that African-American and Hispanic HIV patients are only about half as likely as non-Hispanic whites to participate in clinical trials of new HIV drugs. Together, African Americans and Hispanics comprise roughly 48% of HIV patients.

And while there have been studies that specifically address the African-American population — the most notable being the Jackson Heart Study, which is a single-site prospective epidemiologic investigation of cardiovascular disease (CVD) among African Americans from the Jackson, Miss., metropolitan area — for the most part, African Americans remain under-represented in clinical trials.

Despite FDA and NIH initiatives, little has been done to enforce enrollment of diverse populations.

"The FDA isn't enforcing any of the guidelines that it has been passing since the early 1990s," says Brian Stone, M.D., chief medical officer of The Black Health Network. "When a company knows that nothing punitive is going to happen, there really is no incentive for it to adhere to the guidelines especially if it requires additional effort."

A HISTORICAL BIAS

There are vast historical and current-day reasons that African Americans resist participating in clinical trials. In the most well-documented case, the Tuskegee syphilis study, 400 illiterate or low-literacy African-American male subjects in Alabama were systematically denied treatment by an agency of the U.S. government for more than 30 years.

"When I was growing up in Alabama, I heard stories about experimentation on slaves, about bodies being removed from black graveyards for medical schools, the U.S. Health Department syphilis experiment, experimentation on prisoners, the Willowbrook Hepatitis Experiment (in which uninfected mentally ill children were given viral hepatitis to study the course of the disease), and as recently as the 1970s, experimentation on Mexican-American women who were given birth-control pills without their consent," Dr. Stone says.

The medical community must not only overcome past inequities and injustices but address current barriers that limit participation in clinical trials by diverse populations.

A 2002 report, Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care, conducted by the Board of Health Sciences Policy (HSP), Division of Health Sciences Policy (HSP), and Institute of Medicine (IOM) notes that minorities tend to receive lower-quality healthcare than whites do, even when insurance status, income, age, and severity of conditions are comparable. The sources of these disparities, according to the report, are complex and rooted in historical and contemporary inequities and involve many participants at several levels, including health systems, their administrative and bureaucratic processes, utilization managers, healthcare professionals, and patients. The study committee focused part of its analysis on the clinical encounter itself and found evidence that stereotyping, biases, and uncertainty on the part of healthcare providers can all contribute to unequal treatment.

According to the report, the conditions in which many clinical encounters take place — characterized by high-time pressure, cognitive complexity, and pressures for cost containment — may enhance the likelihood that these processes will result in care poorly matched to minority patients' needs. Minorities may experience a range of other barriers to accessing care, even when insured at the same level as whites, including barriers of language, geography, and cultural familiarity. Further, financial and institutional arrangements of health systems, as well as the legal, regulatory, and policy environment in which they operate, may have disparate and negative effects on minorities' ability to attain quality care.

Results from several clinical trials have pointed to differences in the way people of different ethnic and racial backgrounds respond to medicine, making it critical from a scientific point of view that people from both sexes and all ethnic and racial backgrounds are included in a trial protocol.

"Unfortunately, historic stereotyping, racial discrimination, and lack of experience in the multicultural marketplace are significant factors that have contributed to the omission and exclusion of racially and ethnically diverse segments in clinical trials," says Sheila Thorne, president of Multicultural Healthcare Marketing Group LLC.

Several studies over the past five years have tried to assess the attitudes of African Americans toward medical research. Most recently, a Harris Interactive survey in June 2003 found that 86% of whites were more likely to consider research participation compared with 70% of African Americans. Another report, published in the Nov. 25, 2002, issue of the *Archives of Internal Medicine*, contained results from a telephone survey of 527 African American and 382 white respondents. The study found that African Americans (41.7%) were less likely than white respondents (23.4%) to trust that their physicians would fully explain research participation; and 45.5% of African Americans believed that their physicians exposed them to unnecessary risks compared with 34.8% of white respondents.

The Unequal Treatment study concluded that a comprehensive, multilevel strategy is needed to eliminate disparities. Broad sectors — including healthcare providers, their patients, payers, health-plan purchasers, and society at large — should be made aware of the healthcare gap between racial and ethnic groups in the United States. Health systems should base decisions about resource allocation on published clinical guidelines, ensure that physician financial incentives do not disproportionately burden or restrict minority patients' access to care, and take other steps to improve access, including the provision of interpretation services where community need exists.

It is a business imperative that the industry embrace these suggestions to address the shortfall in patient recruitment among multicultural populations. Results from several clinical trials have pointed to differences in the way people of different ethnic and racial backgrounds respond to medicine, making it critical from a scientific point of view that people from both sexes and all ethnic and racial backgrounds are included in a trial protocol. Furthermore, different population groups often referred to as minorities — African Americans, Hispanics, Asian Americans, and Native Americans, among others — now comprise the majority population in several cities and even states. By 2050, African Americans, Hispanics, and Asian Americans will comprise 50% of the U.S. population, according the U.S. Census Bureau 2001 report.

BEHIND THE SCIENCE

African Americans and other minorities appear to respond differently to pharmaceutical products and are disproportionately susceptible to certain diseases than other patient populations. For example, antihypertensive agents such as angiotensin converting enzyme (ACE) inhibitors and beta-blockers are somewhat less effective in African Americans than in whites. At the same time, cardiovascular disease was the leading cause of death for African Americans in the United States in 2000.

Genetics may well play a role in how various populations metabolize certain drugs. Researchers are looking at the cytochromes P450 and, in particular, the enzymes 2C19 and 2D6 to assess response differences. 2D6, for example, is not present in some patient's livers. Some people have mutations in one or more of the nucleic acids in the DNA sequence of a particular enzyme. As a result, the enzyme may be absent or have low, or no, metabolizing activity for drugs that are usually metabolized by that enzyme. In the United States, whites are more likely than people of African or Asian heritage to have low levels of 2D6, which metabolizes antidepressants, antipsychotics, and beta block-

ers. Additionally, among some of the drugs in the psychotherapeutic class, slower enzyme metabolism has been observed in people of Asian descent. Other studies have shown that African Americans have a lower response rate to several classes of antihypertensive agents (beta blockers and ACE inhibitors).

About 3% to 5% of Caucasians and 20% of Asians and African Americans are poor metabolizers of 2C19, which controls the metabolic process for such products as diazepam (Valium), phenytoin (Dilantin), and omeprazole (Prilosec).

There are many complex factors that account for these differences, including diet, culture, and genetics, says Kenneth M. Borow, M.D., president and CEO of Covalent Group Inc.

"For example, African-American subjects are at a much higher risk than Caucasians for the development of adverse consequences of hypertension, congestive heart failure, stroke, and chronic renal disease," he says. "Some of this difference in incidence may be related to genetic differences in bioavailability of nitric oxide, an important mediator of endothelial function. It is important to study these disease states in African Americans to understand the pathophysiology and optimal treatment in this patient population. Another example of ethnic differences complicating treatment options is the nearly twice higher incidence of significant

Under-Represented Populations — Targets for Research

ASTRAZENECA HAS IDENTIFIED POPULATIONS THAT TYPICALLY HAVE BEEN UNDERSERVED IN CLINICAL RESEARCH AND DESCRIBES ITS THREE-PART STRATEGY TO ATTRACT RESEARCHERS INTERESTED IN THESE AREAS AND THE SUBMISSION OF INVESTIGATOR SPONSORED TRIAL (IST) PROTOCOLS IN THE NEXT TWO TO THREE YEARS.

The first area the company addressed was to identify "who" the underserved populations are. In a recent AstraZeneca A2Z report, the company reviewed the disparity in health services for certain racial or ethnic minority groups. The report summarized the findings documented by the Institute of Medicine and other prestigious organizations, which were published in the *Journal of the American Medical Association*. AstraZeneca's IST team took a firm stand to alter its thinking in this area and to focus on the healthcare needs of these underserved populations.

In the same report, AstraZeneca outlined the percentage distribution of clinical-trial participants within the U.S. population (see chart below). The data reveal that a substantial portion of the population is underserved and the health of these demographic populations will impact medical services and costs of healthcare in the United States.

The populations identified, especially the senior group, are complex patients, typically being treated for several diseases simultaneously. These patients are under-represented in registration trials based on the study design and exclusion criteria. The purpose of the registration trials is to demonstrate efficacy and safety of drugs while controlling for other factors that may influence the results. Once the product is available in the market, its use expands to these more complex patients coming into the healthcare system to treat multiple disease complaints. Managed-care companies have reported that of all their plan enrollees, about 20% are using the majority of services.

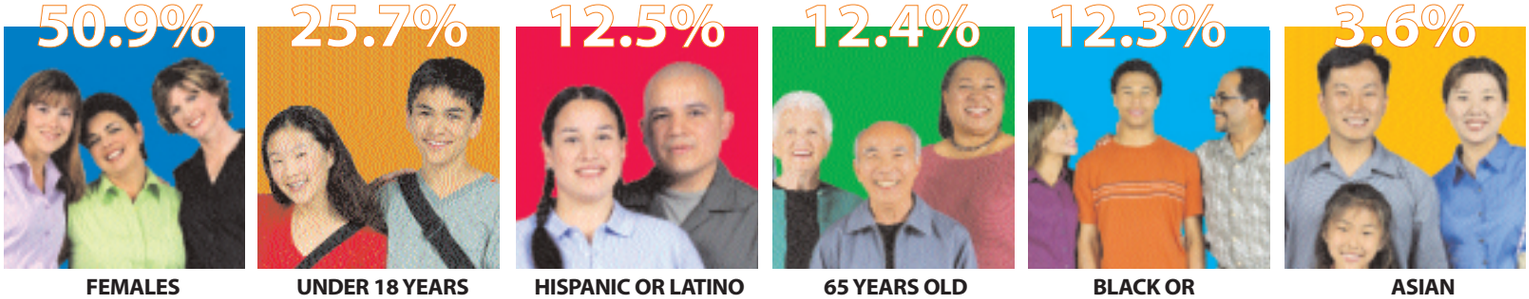
AstraZeneca also addressed "why" research involving these populations should increase. Although it has been stated in news and print for several years, the increase in the proportion of these sub-populations will have an impact on consumer markets as the "voice" and demands of these individuals will reach the "ears" of businesses.

In retail markets, the focus on customization of messages and variations in product lines has been a well-established strategy for doing business. The prediction from business research companies such as Tower Perrin is that healthcare will shift responsibility of medical care on to the consumer through cafeteria-type (multi-choice) coverage.

Two additional factors are, or will, change how healthcare is delivered. The first is the Internet. As a vehicle of information, the Internet provides access to global health data down to individual country reports of health benefits (i.e., low incidence of heart disease in France and Italy, longevity of life in Russia and China). This information can be easily accessed by

Face of America — Population Trends

Population Total — 281,421,906



Average percent of under-represented populations — **19.6%**

Source: AstraZeneca, Wilmington, Del., Nexium IST Team, June 2003. For more information, visit astrazeneca.com

obesity in black females compared with white females. If a drug is highly lipophilic, it may have very different bioavailability in obese subjects compared with leaner subjects. The result may be the need for higher dosing requirements in the more obese patient population. This would be most appropriately delineated by actually studying the patient population at risk. Another justification for including African Americans in clinical research trials is to assess if regional geographic differences in standard-of-care and or diet, for example salt intake, impact clinical-trial results."

In a report published in the *New England Journal of Medicine*, The Importance of Race and Ethnic Background in Biomedical Research and Clinical Practice, the authors note that gathering data on racial classification for use in medicine and biomedical research has given rise to debate. Some have suggested that racial classification may not be useful for biomedical studies, since it reflects a "fairly small number of genes that describe appearance" and "there is no basis in the genetic code for race." The report's authors note that excessive focus on racial ethnic differences runs the risk of under-

AstraZeneca has determined that the following resources will be required to meet its strategies for serving under-represented populations

TIME: Two to three years to increase IST submissions on these targets audiences (starting from 2002).

QUANTITY: A target percentage for these studies to grow steadily from 8% to 20%; 20% indicates the average of the demographic composite listed for women, minorities, children, and seniors, treating each subpopulation as independent. It is likely that some IST proposals will have overlapping underserved populations included (i.e., senior women).

INTERNAL RESOURCES: To be most effective, this project would be developed by a small working group of four to six people. Likely candidates for the group would be MIS/PDS field scientists who have access to investigators who are early advocates of the concept, and IST members with special interest in the project.

BUDGET: Larger strategic meetings cost about $160,000. Smaller regional focus groups cost about $40,000 to $60,000 each. The suggestion is to hold at least one meeting per region in the next two to three years.

patients in the United States, which is shifting the focus of the patient-physician interaction to one of customization of care.

The second factor is temporal. The impact of decisions by baby boomers has been often quoted as driving market trends due to this population's substantial voice in the market. Currently, baby boomers are entering their 50s, and in the next two decades they will account for the largest group of seniors in our country's history. Baby boomers are increasing the senior subpopulation of the demographic profile, as the current seniors are living longer due to advances in nutrition and medicine. Consequently, there will be an increase in the number of complex patients, who have multiple, simultaneous diseases, who will need medical care.

The third item addressed by AstraZeneca is "how" to revise an IST research strategy to focus on these underserved populations.

The primary goal for the company is to increase awareness of AstraZeneca's interests in having more research in these demographic areas through focused and frequent communication with its field scientists and its investigators.

This communication strategy has been designed in phases. Phase I (June-December 2002) was to inform and educate AstraZeneca field scientists about its interest in these areas. The company attempted to target frequent IST investigators, as they already have successfully completed other studies through the system. Notably, Dr. Phil Katz and Dr. Nimish Vakil have IST-approved target populations. AstraZeneca also was able to attract the attention of new IST investigators, namely Dr. Anthony DiMarino, Dr. Ken Vega, and Dr. Yvonne Romero who have active IST protocols and plan to submit additional protocols for review.

Phase II of the communication strategy is to increase awareness of the company's interests in these study populations. The IST team has completed a new brochure with special focus on the underserved populations, and Renata Maslowski, Ph.D., MBA, director, medical affairs, Nexium/Entocort, Paul Hoyle, Ph.D., director, medical affairs, AstraZeneca, and Henry Leher, Ph.D., product development scientist, gastrointestinal disease, have been presenting IST topic suggestions at regional gastrointestinal/MIS meetings since July 2002.

Secondly, Dr. Maslowski presented the trends in GI research and funding to an audience of fellows and young investigators at the 2002 GRG Methodologies in Outcomes Research Meeting, with a follow-up invitation to the 2003 meeting.

AstraZeneca now is moving into the next phase of its communication strategy, which includes increased contact with investigators who may not be aware of the company's interests. New IST brochures have been mailed to currently active IST investigators and hand-carried by MIS/PDS field scientists to additional targets. Dr. Romero and Dr. Alin Botoman have suggested nomination of Dr. Maslowski to the ACG committee on International and Minority Affairs to broaden the awareness.

Thirdly, Sandra Joshua-Gotlib, director, gastroenterology-health economics and outcomes research, has identified a need to address academic institutions that educate healthcare personnel from minority populations, and noted that how these populations are studied will be very important with regard to language and cultural variations in health/nutritional practices.

Phase III also will include identification of other "centers of excellence," or institutions that are recognized by the community as serving the specific needs of the under-represented populations.

Finally, a shift to include more research on these target populations is expected to increase the geographic specialization of care. Using information from the U.S. Census Bureau and migration patterns within the United States, both readily available resources from the Internet, will help identify optimal targets for these study strategies.

Source: AstraZeneca, Wilmington, Del. For more information, visit astrazeneca.com

▶ WHEN PHARMACEUTICAL COMPANIES ESTABLISH A PROCESS OF ENSURING INCLUSION OF RACIAL AND ETHNIC POPULATION SEGMENTS IN CLINICAL TRIALS, FDA APPROVAL OF PRODUCTS WILL BE ENHANCED.

Sheila Thorne

▶ THE FDA ISN'T ENFORCING ANY OF THE GUIDELINES THAT IT HAS BEEN PASSING SINCE THE EARLY 1990S. WHEN A COMPANY KNOWS THAT NOTHING PUNITIVE IS GOING TO HAPPEN, THERE REALLY IS NO INCENTIVE FOR IT TO ADHERE TO THE GUIDELINES ESPECIALLY IF IT REQUIRES ADDITIONAL EFFORT.

Dr. Brian Stone

▲ WE DESIGN OUR STUDIES TO REPRESENT A BALANCED POPULATION AND TO MIMIC THE 'REAL WORLD' IN BOTH THE DEMOGRAPHICS AND THE DISEASE ETIOLOGY. THE SELECTION OF INVESTIGATORS TO PARTICIPATE IN OUR TRIALS AND FIND THESE PATIENTS IS DONE WITH THE TREATMENT POPULATION GOAL IN MIND.

Lynn Baer

▼ EDUCATION INITIATIVES SHOULD HELP AFRICAN AMERICANS AND OTHER MINORITIES UNDERSTAND THE CRITICAL NEED FOR THEM TO PARTICIPATE IN TRIALS AND THE HEALTHCARE CONSEQUENCES FOR THE COMMUNITY WHEN THEY DON'T.

Jucinda Fenn-Hodson

◀ THERE IS A LONG HISTORY OF DISTRUST AMONG THE AFRICAN-AMERICAN COMMUNITY REGARDING CLINICAL RESEARCH, MUCH OF IT COMING OUT OF THE VERY REAL PROBLEMS ASSOCIATED WITH THE TUSKEGEE STUDY. ONLY A GENUINE AND SINCERE EFFORT INVOLVING EDUCATION AND COMMUNICATION WILL OVERCOME THIS CONCERN.

Dr. Kenneth Borow

valuing the great diversity that exists among persons within groups. The report states, however, that this risk needs to be weighed against the fact that in epidemiologic and clinical research, racial, and ethnic categories are useful for generating and exploring hypotheses about environmental and genetic risk factors, as well as interactions between risk factors, for important medical outcomes.

"Much of the new evidence that has resulted from the decoding of the human genetic map has shown that there are significant genetic polymorphisms between different ethnic groups, particularly blacks and Asians, as relates to drug metabolism, drug transport, and receptor expression," Dr. Stone says.

The *NEJM* report points out that discrepancies in racial and ethnic responses to disease are not purely genetic, but also are associated with access to quality of healthcare and education.

Cultural influences and traditions also must be taken into consideration when evaluating a drug's safety and efficacy in diverse populations.

"We can't just evaluate the science of the drug without taking into account how different populations take medicine, and how factors such as diet, environment, and culture impact patients while they are on a medication," says Lucille C. Norville Perez, M.D., past president of the National Medical Association (NMA). "There are many intangibles that physicians must consider in the treatment plan for their patients and being of the same 'race' doesn't necessarily assume sensitivity to all of the cultural nuances needed for the delivery of quality care."

Statistics reveal that African Americans are more susceptible to certain diseases than other patient populations, including cardiovascular disease, diabetes, HIV, asthma, cancer, hyper-

tension, and infant mortality. (See related box on page 23.)

Lynn Baer, senior director and head of clinical-trial operations at Novo Nordisk Pharmaceuticals Inc., says, "Certainly diabetes, hypertension, and coronary artery disease are among those therapeutic areas that seem to affect the African-American population more acutely. Since diabetes touches all demographic groups, we seek a patient population in our trials that mimics the disease in the real world."

The challenge for pharmaceutical companies such as Novo Nordisk and their partners is filling trials to meet real-world scenarios.

Diana L. Anderson, Ph.D., president and CEO of D. Anderson & Co., concurs that recruiting the appropriate mix of patients for clinical trials is a challenge.

She cites her experience in relation to recruiting patients for a diabetes trial. "The target population for a diabetes trial is white, Hispanic, and black males," Dr. Anderson says. "Even though we have a fair number of people from minority populations respond to our initial patient-recruitment strategies, 80% of those who follow up to participate are white males."

IDENTIFYING THE BARRIERS

According to the HSP and IOM report, the healthcare workforce and its ability to deliver quality care for racial and ethnic minorities can be improved substantially by increasing the proportion of under-represented U.S. racial and ethnic minorities among health professionals. In addition, both patients and providers can benefit from education. Patients can benefit from culturally appropriate education programs to improve their knowledge of how to access care and their ability to participate in clinical-decision making.

Recruiting minorities, whether they are Hispanic, Asian, or African American, is difficult for many reasons, says Stedman Stevens, president and chief operating officer at Pharmaceutical Research Plus Inc.

"Proportionally there may be fewer African Americans signing up for clinical trials because of economic or logistic issues," he says. "There are much larger components, including the fact that patients are simply not aware of a trial, not aware of the benefits, and haven't been educated about trials."

This lack of awareness about clinical trials is a huge barrier to recruitment across all populations, says Deborah Kniuksta, assistant director of patient recruitment at Kendle International Inc.

"In the industry, we tend to think that everyone is very aware of clinical trials," she says. "Since we live and breathe clinical trials, we take them for granted. But the general population has a limited grasp of clinical trials and the drug-approval process. I think this is even more true in minority populations."

While the primary burden of education may lie with healthcare providers serving their communities, some say this burden should be shouldered by the pharmaceutical industry as

A Plan of Action

INCREASINGLY, PHARMACEUTICAL COMPANIES ARE RECOGNIZING THE NEED TO INCLUDE MULTICULTURAL GROUPS IN CLINICAL TRIALS FROM THE POINT OF VIEW OF SOCIAL RESPONSIBILITY, SCIENTIFIC SAFETY AND EFFICACY, AND BUSINESS IMPERATIVES.

One pharmaceutical company, GlaxoSmithKline, has begun to tackle diversity in clinical-trial recruitment through several initiatives.

"We have an 8,000-patient prostate cancer risk-reduction trial that's just started titled REDUCE," says Ronald Walls, M.D., medical director, clinical development and medical affairs for cardiovascular and urologic diseases, at GlaxoSmithKline. "We've put together an African-American recruitment and retention advisory board with the purpose of specifically addressing any culturally and regionally sensitive issues, to help develop culturally sensitive recruitment materials, to accrue as many African-American physicians as we can to participate in the clinical trials, and to retain patients once enrolled in the clinical trial."

Dr. Walls was the key member of that committee, which was chaired by Dr. Clarence Young, VP and global therapeutic area lead for anti-infectives at GlaxoSmithKline. The trial involves a GlaxoSmithKline product called dutasteride, which is approved under the brand name Avodart for the treatment of benign prostatic hyperplasia.

Dr. Walls says the group has just started its recruitment process, but its goal is to enroll as many African Americans as are reflected in the general population. "We've pulled together the world experts on accrual and retention of African Americans in the clinical-trial arena," he says. "Together, we've constructed the framework for an effective strategy for African-American patient and physician accrual and retention."

Dr. Walls says the team has a great interest to learn not only what measures and efforts have been successful, but also what have failed. Dr. Walls also emphasizes that there is a general lack of clinical-trial information on the African-American population. For this reason, it is critical to have African-American patients participate in clinical trials.

Recognizing the importance of African-American associations, GlaxoSmithKline has reached out to the National Medical Association (NMA) and other national and regional advocacy groups.

IN TERMS OF RETAINING AFRICAN-AMERICAN PATIENTS IN CLINICAL TRIALS, IT IS CRITICAL TO FIRSTLY BUILD THE RELATIONSHIP WITH THESE PATIENTS AND SECONDLY TO KEEP THESE PATIENTS INFORMED AS TO THE DEVELOPMENT OF CLINICAL TRIALS. THIS IS ESSENTIAL FOR RETENTION OF PATIENTS.

Dr. Ronald Walls

well. Traditionally, pharmaceutical companies have not made a concerted effort to reach out to diverse populations.

"I don't believe that we have, as an industry, directed our CRO partners to target populations of color as a strategic requirement," says Sarah Harrison, VP of customer strategy integration at AstraZeneca. "This does not apply only to populations of color, but to women, regardless of race or ethnicity; looking at the statistics of clinical-trial enrollees, women are not included to any great extent."

Michael Lenoir, M.D., principal investigator for the National Medical Association's (NMA) clinical-trials program, Project Impact, says pharmaceutical companies tend to do "one-size-fits-all" clinical trials, but now there is genetic evidence that African Americans respond differently to certain types of clinical preparations.

"Additionally, within the African-American community there has not been much discussion about what a clinical trial is, what the advantages are, or what the disadvantages are," Dr. Lenoir says. "So for the most part, African Americans don't know anything about clinical trials, with the exception of the Tuskegee study."

OVERCOMING THE BARRIERS

Industry leaders say one strategy to recruit and retain African Americans in clinical trials is to focus on recruiting African-American physicians to conduct the studies. In an analysis conducted by CenterWatch in February 2002, 3% to 4% of the total number of board-certified minority physicians — about 1,500 physicians worldwide — participate in clinical research. Recent data show the percentage of African-American physicians in the U.S. is 3.7%, about the same as 75 years ago.

Recruiting minority physicians as principle investigators, however, requires that sponsors and CROs make special efforts to train these physicians for research participation.

"It is our belief that to improve the number of African Americans engaged in clinical trials, it is important to first increase the number of African-American investigators," Dr. Lenoir says.

To this end, Project Impact — Increase Minority Participation and Awareness of Clinical Trials — has been working to introduce the issue of clinical trials to the African-American physician community through a series of nationwide seminars.

"African-American patients are more likely to engage in clinical trials if African-American investigators are involved," he says. The NMA then works to connect those investigators with the pharmaceutical industry.

According to the 2002 report by HSP and IOM, cross-cultural curricula should be integrated early into the training of future healthcare providers, and practical, case-based, rigorously evaluated training should persist through practitioner continuing medical education programs.

"The industry should be involved in helping to train minority physicians to meet the qualifications that we need," Ms. Harrison says. "And, if we're going to use a CRO to facilitate the recruitment, then we have to provide our CRO partner with the necessary resources and incentives. We can take an active role in supporting and sponsoring medical schools that are traditionally minority based and help graduate physicians who are ready to do clinical trials the way we want them and need them to be done."

Dr. Perez stresses that it is critical to start training at the college level. "We need to start to bring the historically black colleges and universities into the mix in relation to research."

There are 119 historically black colleges and universities, four of particular note are, Howard School of Medicine, Meharry Medical College, King-Drew School of Medicine, and Morehouse School of Medicine.

Physician education is one aspect of bridging the gap. According to Ronald Walls, M.D., medical director of clinical development and medical affairs for cardiovascular and urologic diseases at GlaxoSmithKline. The proper infrastructure within the physician office to participate in clinical trials is critical. It is equally important that pharmaceutical companies and CROs help physicians make sure that the proper support is in place by having culturally sensitive materials available to help enroll patients and by

making sure that there is a suitably trained and dedicated study manager.

To help ease the financial recruitment burden on sites and investigators, some suggest that economic incentives should be considered for practices that improve provider-patient communication and trust, and reward appropriate screening, preventive, and evidence-based clinical care for minority populations.

"It is important to acknowledge that clinical-research sites may have to put more effort into the recruitment of African-American subjects compared with Caucasian subjects," Dr. Borow says. "This extra effort is often required to overcome potential distrust on the part of African Americans regarding clinical trials. These subjects in particular must feel that they are clinical-trial participants with a well-defined and understood purpose rather than merely 'test subjects' or 'guinea pigs.' Open and honest communication between the physician and the subject is essential. Patient education and a true willingness on the part of study site personnel to address subjects' questions and anxieties is essential. The result may be the need for the sponsor to pay the study site an additional stipend reflecting the additional time required with the subject. This is not meant as an undue incentive to the study site to recruit subjects, but rather it is an acknowledgement that there may be more time required by the site to explain the benefits and risks of the study to the subject, thereby helping to overcome the subject's skepticism and fear of the clinical-research process."

Ms. Kniuksta agrees that there is a need for companies to overcome suspicions of the government and scientists that may be held by some communities.

"Even more important is the cultural sensitivity of the research staff in dealing with different ethnic groups," she says. "Cultural sensitivity is probably more important than the actual race or ethnicity of the investigator."

Ms. Baer says Novo Nordisk has found several approaches to be effective in raising awareness about clinical trials for its therapies among diverse populations.

"These include patient-education venues, advertising designed to raise awareness about clinical trials being conducted, and working with large clinics that serve various demographic groups," she says. "In addition, Novo Nordisk

Diversity and the Bottom Line

GETTING TO MARKET AS FAST AS POSSIBLE, BEARING IN MIND SAFETY, EFFICACY, AND REGULATORY GUIDELINES, IS THE GOAL OF ALL PHARMACEUTICAL COMPANIES.

In January 2003, the Food and Drug Administration published a draft guidance recommending categories for collecting effectiveness and safety data during clinical trials for ethnic and racial demographic groups. If adopted, this would create a standard for classifying the various races. FDA recommends that drug manufacturers use the categories for race and ethnicity established by the Office of Management and Budget (OMB) during clinical-trial data collection to ensure consistency in evaluating potential differences in drug response among racial and ethnic groups.

The 2003 guidance, however, came too late to help Bristol-Myers Squibb. Last year, in a review of the company's hypertension therapy Vanlev (omapatrilat), the Office of Drug Safety (ODS) raised concerns about the therapy. In controlled hypertension trials submitted in the original NDA filed in 1999, eight patients were hospitalized for angioedema associated with omapatrilat. Of those patients, six were black and two were non-black patients. In March 2000, FDA's Division of Cardio-Renal Drug Products informed Bristol-Myers Squibb that additional research was needed to assess this adverse event.

The company initiated a larger study, the OCTAVE Trial, in which 25,000 hypertensive patients were randomized to either omapatrilat or enalapril. The company's evaluation of angioedema risk revealed a two- to three-fold increase in risk for black patients and for current smokers. A one- to two-fold increase in risk also was identified for female patients, patients with seasonal allergies, and former smokers. On May 8, 2002, Bristol-Myers Squibb submitted a proposal for risk-management strategies to be implemented during marketed use of omapatrilat.

The ODS, however, noted several shortcomings of the proposed post-marketing surveillance plan, including doubts about whether severe angioedema associated with omapatrilat can be adequately managed by a program primarily focused on education. Last October, Bristol-Myers Squibb acknowledged receipt of a letter from the FDA specifying that additional actions must be taken before the agency would consider approval of Vanlev. The company reported it was evaluating its options.

Some people say part of the problem may be a dearth of African-American patients in initial studies industrywide.

"Just as Vanlev was approaching FDA approval, researchers started to notice that adverse events were occurring in African Americans," says Edward F. Ikeguchi, M.D., chief medical officer and cofounder of Medidata Solutions Inc. "That put a big monkey wrench in Bristol-Myers Squibb's plans. The company had to go back and look at its recruitment of African Americans for the trial, which was dismal."

COMPANIES DON'T WANT TO WIND UP IN A SITUATION WHERE AT THE END OF THE RESEARCH PROCESS, IT BECOMES CLEAR THAT THERE IS A DISPARITY IN TERMS OF WHAT THE DRUG PROFILE IS FROM ONE RACIAL GROUP TO ANOTHER.

Dr. Edward Ikeguchi

offers a patient-assistance program to help people who do not have private health insurance and who do not qualify for private, local, state, or federal prescription reimbursement."

Word of mouth is regarded by some experts as the best avenue for reaching out to members of the African-American community, by working through opinion leaders and peer counselors, and putting together a support network for patients. When speaking to members of a community, companies also need to provide patients with the short-term benefits of joining a trial program, such as assuring them of the best medical care, not having to wait to see doctors, and having personal contact with healthcare professionals.

"In addition, position those who enroll in trials as community heroes," Ms. Thorne says. "Companies should develop public-relations initiatives to showcase clinical-trial participants so the community can associate a familiar face with the clinical-trial process, which will enhance community receptivity."

According to Dr. Walls, one of the approaches that has proved most successful in terms of prostate cancer clinical-trial recruitment has been to use prostate cancer survivors in the recruitment material. Prostate cancer affects African Americans at twice the rate of that of white Americans, and African Americans have the highest incidence of prostate cancer in the world. (See related box on page 30.)

Dr. Ikeguchi says there is a strong connection related to the level of trust between the physician and the patient and the physician's ability to put forth a good argument that an African-American patient should participate in the clinical trial.

"This is part of the whole concept of cultural affinity," he says. "We are trying to get through to the pharmaceutical sponsors that it's worth their while to focus on the training, the education, and the development of clinical sites with African-American physicians as investigators. We are pushing the fact that there are well-established relationships in communities between minority physicians and groups such as the NMA, the Black Health Network, and the Association of Black Cardiologists. These groups are cultural intermediaries that already have a strong, long-lasting bond with doctors."

Dr. Lenoir says the NMA tries to overcome the African-American community's healthy paranoia with regard to clinical trials by educating prospective participants on what a clinical trial is, what the restrictions are, why to engage in it, why not to engage in it, and how to be involved in the clinical-trial process.

It is a business imperative that the industry address the shortfall in patient recruitment among multicultural populations.

REACHING OUT

The location of the clinical trial also can have an economic and cultural bearing on the success in recruiting and retaining patients from diverse backgrounds.

"Sponsors and CROs often don't choose sites that are in the community being targeted," Ms. Thorne says. "Sites are usually geographically not in the communities of the target ethnic audience and therefore inconvenient and unfamiliar to target ethnic patients."

"The most effective way to target any subpopulation is to go where these patients live," Mr. Stevens says. "We need to go to their churches, to the YMCA, to the local pharmacy. That's what we do with our local outreach programs. We tie in wellness events at all those venues. We also will do interviews with community physicians on local radio and tie these into nearby community events. So even though we as an organization are remote, we're tying into the local physician, into the local patient, and into the local community."

Another possible way that pharma companies might reach out to African-American physicians is through pharmaceutical detail reps, Ms. Thorne says.

"Reps know the key opinion leaders who are African American in those respective communities," she says. "Reps should seek out these leaders to learn what organizations they belong to, who their colleagues are who would be helpful, and whether they potentially could be investigators."

According to some statistics, 85% of people in America are not even aware that clinical trials exist. Thus, part of local outreach programs must include basic education about clinical trials for physicians and patients.

And these education efforts need to be specifically designed for specific patient communities, says Liz Moench, president of MediciGroup Inc.

"Within the African-American population, for example, the education communications process must be a steady, understandable, and ongoing process and the process has to take into account specific cultural aspects," she says. "The African-American community, by and large, has a matriarchal structure; there may be a grandmother or siblings who will have a lot of involvement. Patients need materials that they can share with other family members. These family members will be in a position to ask questions and/or may even second guess the process. Investigators, study coordinators, and sponsors have to work harder at fostering relationships. Patients need to feel in control."

Education efforts also need to dispel some of the myths and misunderstandings about clinical trials, says Jucinda Fenn-Hodson, VP of multicultural marketing at Palio Communications. "Education efforts should address issues of the past, but also assure patients that trials are now heavily regulated," she says. "Education initiatives should help African Americans and other minorities understand the critical need for them to participate in trials and the healthcare consequences for the community when they don't."

Recruitment is just one aspect, since there also are issues related to retention and adherence to the protocol, including diet. Ms. Thorne says many African Americans, Asians, and Hispanics eat highly seasoned food that can impact the efficacy of the project. She says it would be important to include dieticians who can design menus so these patients can still maintain their dietary preferences from a cultural perspective without impacting the taking of the drug.

In addition, according to Ms. Harrison, sponsors need to communicate to the targeted population that the patient's needs — be that transportation, childcare, or other accommodations — will be considered.

"There are things that may need to be added to the patient component to incentivize more patients to participate," she says.

The fact is that for industry the primary goal has been to get drugs approved fast, bearing in mind safety and efficacy. To do that, Ms. Harrison says the industry relies on CROs to get enrollees in a trial as quickly as possible.

"CROs first go to all the experienced investigators who they know, and these mostly white investigators are going to put people into trials who come to their office all the time, and who are cooperative, and who they know will be able to get back into the clinic," she says. "This is just an example of the way things are done. We must have a strategic objective to have populations of color fully represented in trials." ✦

PharmaVoice welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

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