Communication Strategies Must Be Tailored to a Medication’s Targeted Population: Lessons from the Case of BiDil

Chamika Hawkins-Taylor, MHA, PhD; Angeline M. Carlson, PhD

Background: The American population’s diversity continues to grow, and its racial and ethnic mixes are changing. The US healthcare system must confront this changing reality. The introduction of isosorbide dinitrate/hydralazine hydrochloride (BiDil) to the US marketplace was a move toward recognizing these changing consumer needs. BiDil was approved specifically as a secondary treatment for heart failure in African-American patients. It remains the first and only drug approved by the US Food and Drug Administration for a race-based indication. To ensure commercial success, a drug must be made “visible” to healthcare providers and to consumers.

Objectives: To describe and analyze the case of BiDil and its potential implications for drugs developed for targeted populations to help them avoid a similar fate of market withdrawal because of commercial considerations.

Method: This analysis is based on 12 comprehensive interviews with 5 clinical investigators, 1 minority healthcare provider, and 5 pharmaceutical representatives, as well as a review of the literature. Overall, 12 one-hour semistructured interviews were conducted. Of the 11 interviewees, 10 were interviewed once and 1 was interviewed once early in the process and then had a second interview by the end of the study. When the 12 scheduled interviews were completed, the recordings were transcribed and subjected to analysis through the use of a readily available computer software package, using concepts and themes collected from the literature and the interviewees’ responses.

Results: The interviewees lacked consensus regarding the unique nature of BiDil. The clinical researchers considered it innovative in identifying that taking the 2 drugs together produced the greatest clinical effect in African-American patients with heart failure. For them, BiDil represented an innovation in the emerging field of personalized medicine. However, they were dismayed to see that these beliefs were challenged by the medical community and their physician colleagues. They reported that practicing, mainly primary care physicians considered the development of a branded medication that combined 2 older drugs to be superfluous, because the same effect could be achieved by administering each agent individually at the same time. Obtaining a patent for BiDil, therefore, was seen simply as a desire for commercial gain. During the approval hearings, representatives of the sponsored company attributed these concerns to “misinformed physicians” and “uninformed patients.”

Conclusion: The case of BiDil demonstrates that a marketing strategy for a population with unique health issues requires an understanding of underlying cultural, social, and economic underpinnings. Ignorance of these dynamics within the African-American community was blatantly reflected at the launch of the drug. Although BiDil remains a treatment option, there is no marketing effort to promote its use. The failure to capture the targeted market for the drug has important implications for the future of commercial considerations in the development of race-based medications.
The diversity of the American population is continuing to grow. Not only is the American population aging, but its racial and ethnic mixes are also changing. In the next 30 years, a dynamic shift will occur within the US population, in which Caucasian Americans, once the majority population, are projected to become the minority, representing less than 50% of the population. In response, the American marketplace has become and will continue to become more diversified; what began as ethnically focused specialty businesses (eg, Asian or African groceries and African-American beauty salons) that are located in ethnically dominant neighborhoods have expanded, and will further expand, into the commercial mainstream.

The US healthcare system must also confront this changing reality. The US pharmaceutical industry has largely been focused on product development that delivers the most rapid and largest return on the substantial investment in research and development required to bring a drug to market. The industry has argued that large-market drugs (ie, drugs for prevalent diseases in developed countries) offset market losses for orphan and other small-market offerings. However, this may not have complete data sets to examine the response differences between population groups, and they are not available for low-income or uninsured populations. As the US population continues to diversify, the pharmaceutical and the healthcare industries will face increased pressures to ensure that the healthcare needs of multiple population groups are guaranteed and that access to targeted healthcare technologies is ensured.

**The Case of BiDil**

The move toward recognizing differences in healthcare needs for a specific population began in the early 2000s with the development, US Food and Drug Administration (FDA) approval, and introduction of isosorbide dinitrate/hydralazine hydrochloride (BiDil; Arbor Pharmaceuticals) into the US marketplace. BiDil was approved by the FDA on June 23, 2005, specifically as a secondary treatment for heart failure (HF) in African-American patients. It remains the first and only drug approved by the US Food and Drug Administration (FDA) for a race-based indication; the FDA noted that the generic drugs were not comparable to the branded agent in efficacy.

BiDil was launched into the US market with a marketing campaign focused exclusively on the African-American community.

Some patients were wary of a drug targeted to African Americans only, yet many could not afford the drug.

Physicians were reluctant to prescribe a drug using race-based terms with patients.

Ignorance of the social and cultural underpinnings of the African-American community was reflected at the launch of BiDil, which ultimately led to its market failure.

The important message regarding the need to treat heart failure in African Americans with a combination of vasodilator therapies was lost in this controversial case.

The concept of personalized medicine, albeit mentioned, was never fully explored in relation to this drug.

The failure to capture the market with BiDil may signal that pursuing research to understand the underlying racial and ethnic responses to medical treatment is not commercially viable.

**Key Points**

- Isosorbide dinitrate/hydralazine hydrochloride (BiDil) was approved in 2005 as a secondary treatment for heart failure in African-American patients.
- It is the first and only drug approved by the US Food and Drug Administration (FDA) for a race-based indication; the FDA noted that the generic drugs were not comparable to the branded agent in efficacy.
- BiDil was launched into the US market with a marketing campaign focused exclusively on the African-American community.
- Some patients were wary of a drug targeted to African Americans only, yet many could not afford the drug.
- Physicians were reluctant to prescribe a drug using race-based terms with patients.
- Ignorance of the social and cultural underpinnings of the African-American community was reflected at the launch of BiDil, which ultimately led to its market failure.
- The important message regarding the need to treat heart failure in African Americans with a combination of vasodilator therapies was lost in this controversial case.
- The concept of personalized medicine, albeit mentioned, was never fully explored in relation to this drug.
- The failure to capture the market with BiDil may signal that pursuing research to understand the underlying racial and ethnic responses to medical treatment is not commercially viable.

BiDil’s story begins by looking at the burden of HF in African Americans.

Early epidemiology studies suggested that African Americans are at greater risk of developing HF because of their increased incidence of hypertension and related comorbid diseases. In addition, differential rates of obesity, a significant cardiovascular (CV) risk factor, were also reported based on racial and ethnic differences. Other studies reported the development of HF at an earlier age and with greater morbidity in the African-American population. African Americans also presented with advanced HF, which is characterized by more severe, left ventricular dysfunction that is exacerbated by decreased renal function and the presence of diabetes.

In the 1980s and 1990s, 2 clinical trials—Vasodilator-Heart Failure Trial (V-HeFT) I and V-HeFT II—were conducted to investigate protocols for the treatment of
HF that would bring about better patient outcomes and quality of life.\textsuperscript{12} A secondary analysis of the data from these 2 trials discovered a clear survival benefit with the use of vasodilator therapy as an adjunct treatment in HF that is more pronounced in African-American patients.\textsuperscript{13} These findings brought new interest to the 2 long-established vasodilators, isosorbide dinitrate and hydralazine hydrochloride, when used in combination for the treatment of HF.\textsuperscript{13-15}

The positive findings from these analyses also led to discussions among clinical investigators and representatives of NitroMed (Lexington, MA), the trial sponsor, about the commercial viability of a fixed-dose combination drug of isosorbide dinitrate and hydralazine hydrochloride. Ultimately, the decision was made to submit a New Drug Application to the FDA. The FDA requested a clinical trial that would confirm the secondary findings of the V-HeFT trials that would further establish the beneficial effects of isosorbide dinitrate and hydralazine hydrochloride when used in combination in African-American patients; hence the African-American Heart Failure Trial (A-HeFT), sponsored by NitroMed, was subsequently undertaken.\textsuperscript{6}

The A-HeFT trial compared the effect of isosorbide dinitrate/hydralazine hydrochloride combination on mortality, time to first hospitalization, and quality of life among 1050 African Americans with New York Heart Association (NYHA) stage III or IV HF.\textsuperscript{5} The combination therapy was shown to reduce all-cause mortality rates by 43% and time to first hospitalization by 39%, as well as improve quality-of-life outcomes in this patient population, as measured by the Minnesota Living With Heart Failure questionnaire, a 21-question self-administered instrument.\textsuperscript{6} Because of a significantly increased mortality rate in the cohort receiving placebo only, the study was halted early, after only 3 years.\textsuperscript{6}

With this further confirmation from A-HeFT and extensive scrutiny,\textsuperscript{6} the FDA approved BiDil for the treatment of African Americans with HF.\textsuperscript{5} For the first time in the history of FDA approvals, a drug was granted an indication for use in a specific, race-based population. The FDA specifically approved BiDil as an adjunct therapy for African Americans with severe HF (NYHA stage III or IV HF).\textsuperscript{5,16}

In the US pharmaceutical industry, FDA approval of a new drug sets into motion marketing plans for a commercial launch of that medication.\textsuperscript{17} To ensure commercial success, the consumers—doctors and patients—must understand the drug’s essential benefit and must see the drug as meeting a critical need for the treatment of an illness or disease. The failure to capture the targeted market for the drug may mean market failure if the percentage of targeted users remains low. Such failure could ultimately result in the withdrawal of the drug from the marketplace. In the case of BiDil, market failure could signal to researchers, the pharmaceutical industry, and to consumers that pursuing clinical investigations to understand the underlying racial and ethnic responses to medical treatment is not a commercially viable endeavor.

Of greater importance, however, is the message that a drug combination that has been demonstrated in clinical trials to be the most effective therapy for a specific subpopulation, in this case African Americans, for the treatment of a condition that is prevalent in that population would be lost. The goals of this article are to describe how marketing missteps led to this fate for BiDil, and to explore the implications of this case for future drugs with a targeted subpopulation of patients. Interviews with key decision makers who were responsible for the commercial development and market launch of BiDil were conducted to shed light on its short-lived commercial experience to help to prevent drugs that are needed in targeted populations from experiencing a similar fate.

**Methods**

**Interview Strategy, Content, and Analytic Plan**

The sample cohort for this analysis included interviews with 5 clinical investigators, 1 minority healthcare provider, and 5 pharmaceutical representatives, including from upper and middle management, and a brand marketing team (Table 1).

Twelve, 1-hour semistructured interviews were conducted with adequate time for open, wide-ranging conversations. Each of the 11 interviewees was interviewed once. One interviewee, however, was interviewed early in the process and then submitted to a second interview to offer clarifications toward the end of the study. To ensure that interviewees represented a comprehensive range of job functions, each interview ended with a request for identification of any additional persons who would meet the definition of a key decision maker for the marketing of BiDil. This process of identifying qualified interviewees and eliciting input for additional interviewees is referred to as snowball sampling and is a well-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The Study Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interviewee category</td>
<td>Interviewees, N</td>
</tr>
<tr>
<td>Physician and/or A-HeFT researcher</td>
<td>5</td>
</tr>
<tr>
<td>Pharmaceutical representatives</td>
<td>5</td>
</tr>
<tr>
<td>Minority healthcare provider</td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{6}One of these 5 interviewees was interviewed twice. A-HeFT indicates African-American Heart Failure Trial.
accepted process for qualitative interviews.\textsuperscript{18}

The recorded and transcribed interviews began with the 5 clinical investigators who represented academic institutions and had integral roles in the design, data collection, analysis, and interpretation of the A-HeFT clinical trial outcomes. The dialogues continued with representatives of the pharmaceutical company NitroMed, which included 5 individuals of upper- and midlevel management, and 1 minority healthcare provider representing an organization that was advocating on behalf of BiDil. The concepts and themes explored in the interviews included the need for a medication therapy specifically targeted to African Americans with HF, and the company’s ability to market to African Americans in a socially and culturally acceptable manner.

When the total 12 scheduled interviews were completed, the recordings were transcribed and subjected to classical content analysis, which was facilitated by the use of a readily available computer software package (NVivo 8, qualitative data analysis software; QSR International Pty Ltd, Melbourne, Australia). NVivo, originally named NUD*IST, was developed in 1981 to aid in the organization and management of qualitative data.\textsuperscript{19} The software is designed to manage document collections (such as the BiDil interview transcripts) and to serve as a coding system where ideas and concepts are identified and stored in a thematic, hierarchical classification that is unique to the software.\textsuperscript{19}

\textbf{Results}

The thematic groupings identified by the software were compared with the themes that emerged during the literature review that were related to successful product marketing.\textsuperscript{20-23} The conceptual framework for the commercial success of BiDil was based on the brand equity model, using the model antecedents and the consequences of drug commercialization (Figure 1).\textsuperscript{24}

The themes identified based on the brand equity model are listed in Table 2,\textsuperscript{24} along with interview findings that illustrate those ideas.

\textbf{Table 3} summarizes the additional themes that emerged outside of the realm of the brand equity model and are not generally considered in the literature related to market success. These additional themes may be important considerations for establishing drugs for targeted subpopulations.

The interviewees lacked consensus about the uniqueness of BiDil or the need for it. The clinical researchers who had investigated BiDil considered it innovative and necessary, because they had identified that both agents taken together produced the greatest clinical effect in African-American patients. This group represented 45% of those who were interviewed. For them, BiDil represented an innovation in the emerging field of personalized medicine.\textsuperscript{5} This concept was acknowledged in the FDA’s announcement of the approval of the drug.\textsuperscript{5}

That conviction might have begun with an underlying...
physiologic premise about the differences in the way that blood vessels respond to stress in African Americans and in whites, which led to their proposal of the hypothesis that the vasodilator actions of 2 drugs used in combination would be a better therapeutic choice for African Americans with NYHA stage IV HF. The A-HeFT clinical trial investigated this hypothesis using a design that the researchers who were interviewed considered to be a rigorous strategy that resulted in compelling findings.

In contrast, the clinical investigators' beliefs about the importance of BiDil were challenged when they presented research findings to the medical community. The interviewees described reactions of their physician colleagues with dismay. They reported that practicing, largely primary care physicians considered the establishment of a single, branded drug that combined 2 older drugs superfluous, because the same effect could be achieved by administering each agent separately at the same time. Therefore, they maintained that obtaining a patent for BiDil was simply a desire for commercial gain.

**Discussion**

**Factors Influencing Commercial Success**

An important aspect of commercial success for a drug is obtaining a patent that, by definition, ensures market exclusivity. The importance of a patent was reinforced by the interviewees. The issuance of a patent by the FDA indicates that the drug is safe and effective and conveys the sense that the drug is innovative, and the market exclusivity is warranted to encourage new drug development. In the case of BiDil, market exclusivity depended on establishing the need for a medication that combined

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Research Themes Organized as Antecedents to Aaker’s Brand Equity Model*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>Theme</td>
</tr>
</tbody>
</table>
| Market-related | Perception of need | • Different treatments work in diverse groups  
• The disease cause may differ depending on the patient  
• Few understand the role heredity plays in how a disease is treated  
• High blood pressure occurs at younger ages for black patients; as a result, heart failure may be diagnosed at an early age |
| Market-related | Perception of innovation | • Dissenters said BiDil was the same as the available generics (taken together)  
• BiDil represents personalized care approaches |
| Social acceptance | | • Marketing failed to convince physicians and patients of BiDil’s necessity  
• Idea of a “blacks-only drug” made physicians and patients uncomfortable  
• Belief by patients that something is wrong with the drug |
| Firm-related | Diffusion of innovation | • Limited budget—more money spent on salaries than on actual marketing of the product  
• The company was small, with limited resources  
• Support from a large company partner may have helped to garner support and use |
| Marketing strategy | | • Better marketing messages should have been used to help people understand/accept the use of race-based marketing |
| Policy-related | Accessibility, cost | • Talking to private insurers could promote use  
• Use of a cost-savings program might have increased use  
• Introduction of Medicare Part D diminished BiDil’s visibility with pharmaceutical companies |
| Policy-related | Clinical trial success | • BiDil was considered a successful clinical trial (by FDA standards) because it had:  
• Ensured the rigor of trial design and protocol  
• Had a defined lead investigator (chair) who was involved in all research activities  
• Sound methodology  
• Early signals of positive response in African Americans  
• Scientific rigor  
• Safety and efficacy  
• Need for research |
| Market exclusivity | | • Early research results prompted the FDA to approve the drug for African Americans—not consultant feedback  
• The FDA said that no approved generic had the same effects as BiDil |


FDA indicates US Food and Drug Administration.
2 older, marketed drugs into a single tablet (ie, a fixed-dose combination).15

Concerns about the innovativeness of and the need for a fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride were not new and were clearly noted in the FDA transcripts.26 In fact, both of these concerns were expressed during the public hearings that are a required forum in the drug approval process. The open hearings were held on June 16, 2005, to obtain public comment and opinion to inform the FDA's final decision.26 NitroMed representatives attributed these and other concerns raised during those hearings to misinformed physicians and uninformed patients. One physician supporter from the National Minority Health Foundation who was at the hearing asked that dissenters become informed of the need for race to be considered in pharmaceutical treatment, and purported that the A-HeFT trial showed this requirement to be reasonable.26 Still, others at the hearings said that the drug did not represent an innovation, given that it had no absolute or implied correlation between social, racial, and genetic types.26 Even strong supporters of BiDil, such as the Association of Black Cardiologists and the National Association for the Advancement of Colored People (NAACP), questioned how a cost-prohibitive drug could benefit patients. Nevertheless, 1 week after the hearings were concluded, the FDA granted market approval for BiDil.5,15

**Marketing Efforts**

In June 2005, BiDil was launched into the US market with a nationwide campaign. Marketing representatives who participated in the interviews were part of a contracted sales force working to market BiDil to its targeted group. The representatives described a marketing strategy that at first suggested that BiDil would be a successful product; in its first 5 months, 3600 physicians wrote 14,000 BiDil prescriptions, and some Medicaid plans and a number of managed care plans began including BiDil on their formularies.27 During that same period, a partnership was formed between NitroMed and the NAACP, which would then advocate for BiDil’s health plan coverage,27 and advertisements began to appear in popular black magazines, such as *Ebony* and *Essence*.28,29 In contrast to the early favorable response, according to 1 interviewee from the pharmaceutical industry, and a report from the *Wall Street Journal*, sales reports for BiDil in late 2005 and throughout 2006 were “sluggish,” which was clear evidence of marginal market penetration (Table 4).

The concerns that were first expressed during the FDA approval hearings and later to the clinical researches, trends, and patterns are summarized in Table 4 (Table 4).

### Table 3 Emerging Themes beyond the Brand Equity Model

<table>
<thead>
<tr>
<th>Themes</th>
<th>Interview findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulary-protected drug class</td>
<td>• Heart failure drug coverage should be mandated and added to the list of protected classes of therapeutic categories</td>
</tr>
<tr>
<td>Health disparities</td>
<td>• Understanding race as a factor in disease etiology and therapeutic response</td>
</tr>
<tr>
<td></td>
<td>• Real differences in how patients respond to therapies and how patients experience diseases as a function of race</td>
</tr>
<tr>
<td></td>
<td>• Differences in the etiology of disease as a function of race</td>
</tr>
<tr>
<td></td>
<td>• Need to understand genetic differences as they relate to disease incidence and treatment response</td>
</tr>
<tr>
<td></td>
<td>• BiDil is an acknowledgment of differences in the way healthcare is accessed</td>
</tr>
<tr>
<td></td>
<td>• Race references are only appropriate in discussions of civil rights, lead to poor physician–patient communication</td>
</tr>
<tr>
<td></td>
<td>• Lack of physician–patient rapport may result in compromised treatment</td>
</tr>
<tr>
<td>Social construct of race in America</td>
<td>• Historical distrust of white physicians by black patients</td>
</tr>
<tr>
<td>Physician decision-making</td>
<td>• Continuous engagement with physicians to increase chance of product buy-in</td>
</tr>
<tr>
<td></td>
<td>• Need for more effective communication with physicians</td>
</tr>
<tr>
<td>Social capital</td>
<td>• Potential benefits of partnership opportunities</td>
</tr>
<tr>
<td></td>
<td>• Role of opinion leaders in drug success</td>
</tr>
<tr>
<td></td>
<td>• Need to elicit government support and commitment or that of other influential source of support</td>
</tr>
<tr>
<td></td>
<td>• Media exposure</td>
</tr>
<tr>
<td>Target markets</td>
<td>• Ensuing growth of personalized medicine and the need to define target groups by a more substantial means than race or other surrogate characteristics</td>
</tr>
<tr>
<td>Wall Street effect</td>
<td>• Expectation that BiDil would be widely used and therefore be a strong performer in the stock market</td>
</tr>
</tbody>
</table>
ers resurfaced in an unlikely form. The BiDil controversy became a story line in the television drama *House*. In the pertinent episode (season 2, episode 203; 2005), Dr House’s resident, a black doctor, suggests BiDil to his patient. The therapy was only described as a drug that was proved to have positive effects in African Americans. The patient, a black man, responded in a manner that appeared to take the resident by surprise, “I don’t want any drug that’s for blacks only. Give me what the white folks are getting.”

This simple statement from a television show, which was characterized by 1 A-HeFT researcher as “shocking,” actually foreshadowed the forthcoming nonacceptance of BiDil by the African-American community and by healthcare professionals (Figure 2).

According to the interviewees, in 2006, a second marketing strategy emerged and included targeting physicians who treated significant cohorts of black patients with HF, health fair productions with blood pressure and blood glucose assessments, presentations in black churches, and radio advertisements on predominantly urban radio stations. Print advertisements were also scheduled over a 3-month period for African-American media in the cities of Detroit, MI; Houston, TX; and Washington, DC. A 60-second radio advertisement introduced BiDil as an FDA-approved treatment for HF in African-American patients. During the interviews, the clinical researchers, NitroMed management personnel, and the marketing professionals discussed the hesitancy of patients to use and

### Table 4  
**Targeted Drugs and Market Failure: Change in the Use of Isosorbide Dinitrate Alone, Hydralazine Hydrochloride Alone before versus after Market Introduction of BiDil**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Isosorbide dinitrate use only, before vs after introduction of BiDil</th>
<th>Total use, % (N = 288,559)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Northeast, %</td>
<td>Midwest, %</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2.19 vs 0.0</td>
<td>0.0 vs 0.41</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.13 vs 0.01</td>
<td>0.26 vs 4.02</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.7 vs 0.0</td>
<td>0.0 vs 0.0</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.0 vs 0.63</td>
<td>0.02 vs 1.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>Hydralazine hydrochloride use only, before vs after introduction of BiDil</th>
<th>Total use, % (N = 322,130)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Northeast, %</td>
<td>Midwest, %</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.0 vs 0.0</td>
<td>0.0 vs 0.39</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.0 vs 1.37</td>
<td>0.44 vs 0.13</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>9.80 vs 14.74</td>
<td>0.010 vs 0.0</td>
</tr>
<tr>
<td>Nonblack</td>
<td>3.95 vs 0.0</td>
<td>2.11 vs 0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients</th>
<th>BiDil or isosorbide dinitrate/hydralazine hydrochloride use, before vs after introduction of BiDil</th>
<th>Total use, % (N = 14,247)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Northeast, %</td>
<td>Midwest, %</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.0 vs 0.0</td>
<td>0.0 vs 7.40</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.0 vs 0.0</td>
<td>0.0 vs 0.0</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.0 vs 7.23</td>
<td>0.0 vs 0.0</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.0 vs 0.0</td>
<td>0.0 vs 0.0</td>
</tr>
</tbody>
</table>

**NOTE:** Use of drugs indicated for heart failure as reported in National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey data.
physicians to prescribe a drug that was for “blacks only,” because they possessed “discomfort with using that label.” In the opinion of these interviewees, African Americans did not want to be singled out in physicians' offices, and they offered the observation that "patients thought that maybe something was wrong with the drug." In the end, physicians rejected the marketing messages and ultimately did not embrace the use of BiDil.

NitroMed began planning advertisements that focused on quality of life rather than on black race, but such efforts never got under way. In 2009, BiDil's sponsoring company, NitroMed, was acquired by Deerfield Capital Management for $36 million and was ultimately dissolved as a pharmaceutical company. In 2012, Deerfield Capital Management sold the rights to BiDil to Arbor Pharmaceuticals, Inc. Today, although BiDil remains on the market, no active marketing campaign is apparent.

**Implications of the Findings**

BiDil's clinical development program and subsequent marketing activity have implications for a wider audience in the US healthcare system, for the pharmaceutical industry regarding the costs of newly introduced therapies, and for the pharmaceutical industry and consumers alike regarding marketing approaches for medical conditions in African-American and other targeted populations.

**Implications for conveying scientific findings.** Clinical researchers were convinced of the rigor of the trial design and the compelling nature of their findings. Effects were perceived as replicated, clinically important, and with potential applications to patients at excess risk for adverse CV outcomes. The treating physicians and the patients were not convinced. Instead of recognizing those differences in perception, and appropriately modifying the communication strategy, company representatives chose to identify the concerned stakeholders as misinformed or uninformed individuals. This stance presumed the underlying primacy of their clinical knowledge deduced from controlled studies and dismissed the experience and cultural perspectives that the perceived “nonscientists” (ie, physicians in practice and patients) possessed. Studies have shown that social factors, such as race/ethnicity, income, religiosity, social capital, and political identifications, are as important as knowledge and education in predicting trust in science.

Many of the crucial scientific and technological issues that citizens need to address do not involve technical details as much as the broader issues related to environmental injustice, involuntary impositions of risk, failures of scientific research to meet genuine social needs, and manipulations of scientific information by powerful interest groups. The failure to present the clinical trial results in a more usable format and to address the concerns being raised in the community meant that as time
went on, fewer prescriptions were written and therefore less patients received the medication. The presentation of science (clinical trial findings) in a socially identifiable and responsible manner is an important insight into marketing efforts for products that are introduced for population subgroups.

**Implications for the US healthcare system.** BiDil’s commercial demise also carries implications for the US healthcare system. The epidemiologic studies that consistently found that African Americans are at greater risk of developing HF because of their increased incidence of hypertension,35 and related comorbid diseases suggest that this may result in healthcare costs that would be avoidable with improved access to evidence-based care.

In 2010, the most recent year for which data are available, the United States spent an estimated $444 billion on CV disease treatment, medication, and lost productivity from disability related to CV disease.36 The proportion of this expenditure that can be attributed to the failure to appropriately treat the large CV burden in the African-American population has not been estimated, but it would be substantial given the unequal burden of the disease in this segment of the US population.8,35 It is known, however, that African Americans are less likely to receive drug therapy than whites who have similar diseases.17,38

The true harm done in the BiDil case is that by the inappropriate marketing of the drug, the important message—that the appropriate way to treat HF in the African-American population is with a combination of vasodilator therapies—was lost. The recommendation for this therapeutic strategy in this population exists in the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines, but the evidence for prescription utilization from a large database (ie, the Centers for Medicare & Medicaid Services Medicaid drug utilization database) indicates that the recommendation from the ACC/AHA was not followed in the years around BiDil’s active marketing period.7 If health equity between African Americans and white Americans is ever to be achieved, the burden of a disease such as HF relative to the costs to provide sufficient care and improved outcomes must be given serious consideration.

**Cost implications for the pharmaceutical industry.** Health economists estimate the current cost of drug development in the United States to be between $1.3 billion and $1.7 billion.39 Because of the increasing cost of drug development, the cost of a marketed drug to the consumer may be considered exorbitant. Unless a new drug has a noticeably successful market launch based on a sophisticated communication platform, it may encounter challenges in adoption that hinder its market reach to patients who require it. The drug’s cost may be perceived as high and may therefore result in a lack in formulary placement and insurance payer coverage and with limited perceived value relative to other alternatives. Even if the newly marketed drug is covered by a payer, it may have an unfavorable formulary position and have high out-of-pocket costs or copayments for a patient.30

Furthermore, as it faced the typical challenges of a newly marketed drug, BiDil’s cost of therapy for chronic illness carried a harsh message. To recoup the costs of research and development and to realize a profit, NitroMed introduced BiDil at a cost of $16.20 daily. However, a 30-day supply of isosorbide dinitrate 20 mg and hydralazine hydrochloride 25 mg purchased individually was less than half of the cost of BiDil. BiDil’s higher price was not affordable for this patient population.

The true harm done in the BiDil case is that by the inappropriate marketing of the drug, the important message—that the appropriate way to treat HF in the African-American population is with a combination of vasodilator therapies—was lost.

The target population for BiDil, while experiencing a higher burden of CV disease, also has a significant economic disadvantage, with high rates of unemployment compared with whites and therefore many patients are uninsured or underinsured.40 Whether physicians and patients accepted the arguments for the need for BiDil, its cost would still be considered prohibitive for its targeted population.40 The inability of a large portion of the African-American population to afford a $486 monthly prescription is problematic.

**Implications for managing medical conditions in targeted populations, including African Americans.** If marketing to a subpopulation is to be successful, BiDil’s story indicates that it requires a clear understanding of the underlying social concerns of the targeted group. For BiDil, this can be translated into an understanding of the underlying racial dynamics that exist in the United States. At its very origins, BiDil had its commercialization strategy contaminated by a long history of perceived and genuine racial exploitation of black patients and racially biased inequities. Misinformation and failure to inform physicians and patients about the importance of clinical trial results in a fashion that was culturally appropriate, and the concordance of these findings with clinical guidelines, might have been the main culprits for unearthing old stigmas, fears, and national disgraces that
The clinical development and commercialization failures of BiDil clearly demonstrate that to market a pharmaceutical agent to a subpopulation with unique healthcare issues, their underlying cultural, social, and economic dynamics must be understood.

The concerns about BiDil’s race-based indication began as early as the FDA’s public hearings. However, the company did not appear to give appropriate credence to what they heard in these meetings about a drug that was specifically designed for a racial subgroup. Even though NitroMed may have ignored those concerns, the physician and patient communities did not. Through editorials in professional journals, practicing physicians expressed their reluctance to prescribe BiDil, pointing largely to the idea of physicians’ discomfort using the terms “black,” “white,” or “race/ethnicity,” and inquiring about a patient’s race.

Conclusions
The clinical development and commercialization failures of BiDil clearly demonstrate that to market a pharmaceutical agent to a subpopulation with unique healthcare issues, their underlying cultural, social, and economic dynamics must be understood. By their own admission, the group of decision makers interviewed for this study, who were in part responsible for the development, market launch, and promotion of BiDil, did not appreciate the cultural and racial perspectives that influence the interpretation of data, and the resulting patient and physician adoption of the therapy for which they ultimately sought and obtained FDA approval.

Without the acceptance of the African-American community—an acceptance that could have only been gained by overcoming long-held distrust of the medical community, presenting clinical research in a socially responsible way that recognizes the socioeconomic challenges of access to and affordability of medical care, and the presentation of clinical research in a manner that addresses the health beliefs of the community—BiDil ultimately was a market failure. Ignorance of the social and cultural underpinnings of the African-American community was reflected at the launch of BiDil, and its market failure contains important lessons for the future. The events with BiDil could signal that pursuing research to understand the underlying racial and ethnic responses to medical treatment is not a commercially viable strategy. ■

Author Disclosure Statement
Dr Carlson is a Consultant to Medtronic Neuromodulation, BioMimetic Therapeutics, and Bayr HealthCare. Dr Hawkins-Taylor reported no conflicts of interest.

References
4. BiDil (isosorbide dinitrate and hydralazine hydrochloride) tablet [prescribing information]. Atlanta, GA: Arbor Pharmaceuticals; March 2013.
15. Cheng JW. A review of isosorbide dinitrate and hydralazine in the management...


STAKEHOLDER PERSPECTIVE

Much More than Biomarkers: Sociodemographic Variables in Personalized Medicine

By Michael F. Murphy, MD, PhD
Chief Medical Officer and Scientific Officer, Worldwide Clinical Trials, King of Prussia, PA

In a literature replete with references to personalized medicine tailored to variations in genetic- and disease-related phenotypes, the case study presented by Hawkins-Taylor and Carlson in this issue of the journal emphasizes the importance of incorporating sociodemographic variables into this definition. The adoption of new therapeutics results from interactions between patients and healthcare systems in a mosaic wherein scientific data must be congruent with cultural and ethnic perceptions of medication and health status. Neither a regulatory strategy facilitating approval, evidence of utility in well-controlled trials, nor the existence of unmet needs based on epidemiologic data assured acceptance of BiDil by patients and physicians in the absence of values that are relevant to the targeted population.

RESEARCHERS: Data leading to the approval of BiDil for the treatment of heart failure in self-identified African-American patients followed a development pathway that is recognized in other therapeutic areas. In investigations with overall favorable results, biologically plausible secondary findings within a subgroup consisting of self-identified African Americans prompted a confirmatory study yielding a statistically significant, clinically important effect in a meaningful composite end point. In addition, BiDil was approved as adjunctive therapy for a clinical condition in which neither of the constituent agents in isolation had previously demonstrated utility. Failure to achieve meaningful adoption after approval, Continued
STAKEHOLDER PERSPECTIVE Continued

despite a methodologically rigorous pedigree, emphasizes the importance of ensuring clinical and commercial stakeholder convergence during, not after, the drug development process.

The content and analytic plan by Hawkins-Taylor and Carlson employed “snowball sampling.” Used for specialized populations, this non–probability-based sampling method generated a hierarchical classification scheme contrasting variables particularly related to social acceptance and clinical trial success that offered plausible explanations for failure to achieve product adoption. Potential qualitative and quantitative interactions by region, sex, and race suggested avenues for additional inquiry. Survey methodology, including factorial designs evaluating a respondent’s choice, would inform designs of interventional trials regarding sample composition, the use of proxies (eg, extended family), and variables to support product positioning at introduction.

Payers: An inability to secure adoption of a fixed-dose combination drug based on 2 compounds with established efficacy and safety is counterintuitive, given the attributes of a single daily medication, and disheartening, given the implications for healthcare utilization. Fixed-dose combination products may reduce the complexity of use, counteract therapeutic inertia, and enhance adherence in the control of hypertension, as well as adherence to therapy in patients who have risk factors for cardiovascular disease.5,6

Historically, models for drug adoption placed emphasis on the physician, the specialty, and/or the intervention. The impact of gatekeepers, such as administrators and payers, on this decision-making process was not formally considered.7 “One-to-one” communication was influential, and strategies to promote the adoption of medical evidence trended toward comparability with repetition, even if techniques were initially characterized as ineffective (dissemination of published information or didactic sessions) or influential (eg, academic detailing, audit and feedback, educational outreach).8,9 The additional dimensions of race and ethnic concerns provided by this research thus create a Gordian knot of interrelated variables impacting adoption and compliance programs that are of interest to payers. Nevertheless, structures can be created in which survey methodology is used for hypothesis generation,10 whereas quasi-experimental designs (eg, stepped-wedge, pre–post designs) can evaluate the effectiveness of communication strategies for subgroups within a membership to enhance adoption.

Patients: Although insurance coverage is an important antecedent to prescription medication access, even with comparable benefits and disease status, minority patients underutilize therapy.11 Medicaid policy affecting the behavior of prescribing physicians in minority areas demonstrates spillover effects into the non-Medicaid population in that community.12 In addition, patient perceptions of disease status affect adoption and adherence, such as semistructured interviews identifying a cultural model for breast cancer within low-income African-American women (ie, a stigmatizing and shameful condition) expressing sentiments very different from those associated with Caucasian patients (ie, a disease to be conquered).13,14 Facilitating access to novel medication through changes in healthcare policy for targeted populations is effective only with knowledge of the underlying social concerns and provides impetus for continued research.