

BiDil: Race Medicine Or Race Marketing?

Using race to gain a commercial advantage does not advance the goal of eliminating racial/ethnic disparities in health care.

by Pamela Sankar and Jonathan Kahn

ABSTRACT: Recent Food and Drug Administration (FDA) approval of the first drug with a race-specific indication has fueled the controversy over the meaning of race and ethnicity and raised questions over whether this move should be seen as an advance or a setback in the struggle to address disparities in health status associated with race. The drug, BiDil, combines two generics long recognized as benefiting patients with heart failure, irrespective of race or ethnicity. The push to bring these drugs to market as a race-specific treatment was motivated by the peculiarities of U.S. patent law and a willingness to exploit race to gain commercial and regulatory advantage.

ON 23 JUNE 2005 the U.S. Food and Drug Administration (FDA) granted formal approval to BiDil as a race-specific drug to treat heart failure. BiDil is a heart medication supposedly developed for African Americans and the first drug in the United States, and likely anywhere else, to be based on a patent formulated in terms of its benefit to a specific racial or ethnic group. In announcing the approval, Robert Temple, FDA associate director of medical policy, declared that BiDil “is a striking example of how a treatment can benefit some patients even if it does not help others.”¹ BiDil’s success, however, is one not of personalized medicine but of exploiting race to gain commercial and regulatory advantage in the pharmaceutical marketplace.

The uproar over BiDil has been that it reifies and biologizes racial groups, which it does, and much of the exchange has taken place over the meaning of race and the relation between race and biology.² But an additional risk posed by BiDil is that it will cheat consumers—African Americans as well as everyone else. Furthermore, it threatens to set in motion a trend in the pharmaceutical industry for turning other widely used and cost-effective generics into patented, expensive drugs in the name of alleviating health disparities.

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A Brief History Of BiDil

Heart failure is a debilitating and ultimately fatal condition that afflicts millions of Americans. Unlike a heart attack, it is not generally an acute condition but evolves over time as the heart progressively becomes less able to pump blood adequately. For years the standard therapy was simply a regimen of digoxin and diuretics that helped to manage blood pressure but did not do much to improve the condition of people suffering heart failure.

■ **An early combined form.** The 1980s saw the beginning of a revolution in the treatment of heart failure. Two cooperative studies administered through the Veterans Administration (now the Department of Veterans Affairs, or VA) led to important breakthroughs in heart failure treatment. The first of these, the Vasodilator Heart Failure Trial (V-HeFT I) found that a combination of two generic vasodilators—hydralazine and isosorbide dinitrate (H/I)—seemed to have a pronounced beneficial effect in treating heart failure.³ H/I would later be combined into a single pill to form BiDil.

A second trial in the late 1980s, V-HeFT II, found that the angiotensin-converting enzyme (ACE) inhibitor enalapril appeared to be even more effective in treating heart failure. At this point, ACE inhibitors became a new first-line therapy for treating heart failure.⁴

■ **Patenting BiDil.** In 1987, during the course of V-HeFT II, Jay Cohn, the lead cardiologist on the V-HeFT studies, submitted a “methods” patent on using the H/I combination to treat heart failure. Cohn could not get what is known as a “combination of matter” patent because the combined form of these two generic drugs did not act differently than using each separately. A methods patent would give the holder a monopoly on marketing the combination for a particular purpose—treating heart failure—but it would not give the holder the power to prevent generic manufacturers from producing and selling the individual drugs.

The 1987 methods patent, which expires in 2007, was not race-specific. It claimed that H/I was appropriate as a therapy to treat heart failure—period. No mention was made of race. Cohn licensed the patent to Medco, a North Carolina pharmaceutical company, which spent the early 1990s conducting bioequivalence studies on BiDil and preparing documentation for submission of a new drug application (NDA) to the FDA to get approval for marketing BiDil as a method to treat heart failure.⁵ Again, like Cohn’s underlying methods patent, Medco’s NDA for BiDil was not race-specific.

■ **Rejecting the NDA.** In early 1997 the FDA’s Cardiovascular and Renal Drug Advisory Committee rejected Medco’s NDA for BiDil. It is important to emphasize here that the advisory committee did not determine that BiDil failed to work. To the contrary, several members of the committee specifically stated their opinion that BiDil was clinically efficacious. The problem was that Medco’s statistics were in too much of a muddle to meet the FDA’s criteria for new drug approval. As Cohn himself has acknowledged, this was because the V-HeFT trials were not designed as new

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drug trials but as “test of theory” trials.⁶ Cohn recognized the problem with the data at the time when he urged the FDA Advisory Committee to “keep in mind that this is a study designed 20 years ago. This was a VA cooperative study. This was not designed really as a regulatory study so that careful selection of criteria for endpoint were not as precise as one would see in a protocol designed today with the goal to come to this committee to ask for approval.”⁷ Thus, while providing sufficient evidence to convince the American Heart Association (AHA), among others, to recommend H/I as a heart failure therapy, the V-HeFT trials did not produce the type of statistical information that the FDA needed to approve an NDA.

■ **Race enters the picture.** After the FDA rejection, BiDil seemed dead in the water, and Medco let the intellectual property rights revert to Cohn. It was only at this point that Cohn, together with Peter Carson, a cardiologist with whom Cohn collaborated, went back to the now fifteen-year-old V-HeFT data and analyzed them by race. Significantly, Cohn had mentioned to the FDA advisory committee in 1997 that he had V-HeFT data available by race but that he did not think them relevant to present to the committee to obtain approval for BiDil.⁸ Race apparently became relevant only when it offered a means to revive the commercial prospects of BiDil.

So it was that in 1999 Carson was the lead author on a paper with Cohn that purported to show significant racial differences in response to H/I based primarily on the data involving the forty-nine African American subjects who were placed on H/I in V-HeFT I.⁹ The same month that this article appeared, Cohn relicensed the intellectual property rights for BiDil, this time to NitroMed, a Massachusetts biotechnology company specializing in nitric oxide-based therapies. The following year Cohn and Carson jointly applied for a race-specific methods patent to use H/I to treat heart failure “in an African-American patient.”¹⁰

With Carson’s article and the race-specific patent in hand, NitroMed approached the FDA. In early 2001 the FDA sent NitroMed a letter commenting on the ultimate approvability of BiDil as a race-specific drug, pending the successful completion of a confirmatory trial in African American subjects. Following the FDA’s letter, NitroMed, then still a privately held corporation, was able to raise more than \$34 million in private venture capital financing—this during the nadir of the NASDAQ bust. The bulk of this money was to be used to conduct the suggested confirmatory trial—known as A-HeFT (African-American Heart Failure Trial). In November 2003, with A-HeFT under way, NitroMed went public with an offering of six million shares and raised approximately \$66 million.¹¹

A-HeFT was designed to enroll just over 1,000 subjects, all African American, all with New York Heart Association class III or IV heart failure.¹² Subjects re-

mained on their current heart medication and then were randomized to receive, in addition, either a placebo or BiDil. The primary endpoint was a score that combined death from any cause, a first hospitalization, and change in quality of life.¹³ A-HeFT was predicted to run until sometime in 2005. Instead, its Data Safety Monitoring Board (DSMB) suspended the study in July 2004, several months early, declaring that its benefits were so substantial that continuing some subjects on placebo was unethical.¹⁴ Subjects taking BiDil experienced a 43 percent reduction in rate of death from any cause and a 33 percent reduction in first hospitalization resulting from heart failure.¹⁵ In the week following the announcement of the early suspension of A-HeFT, NitroMed stock more than tripled in value. In November 2004, when details of the study were released, the stock once again soared.¹⁶ A month later, subsequent to announcing that it was ready to submit an amended NDA to the FDA, NitroMed held a secondary public offering that raised nearly \$80 million (\$15 million beyond its stated goal) to fund the BiDil launch.¹⁷ Anticipating FDA approval, NitroMed hired an advertising agency, Vigilante, known for its work selling beer and cars, to handle the effort.¹⁸

The revised BiDil patent based on treating African Americans gives the company marketing rights until 2020. By testing BiDil in doses that are not available for its generic components (hydralazine and isosorbide dinitrate), NitroMed has discouraged doctors from easily devising ways for patients to get the same benefits from the long available, and much less expensive, generics.¹⁹ Additionally, NitroMed's race-specific methods patent will also prevent insurers from recommending to doctors that they use generic substitutes to save money.

Shortly before the FDA approval, NitroMed had predicted that BiDil revenues could reach \$120 million in its first year of sales, increase to \$350 million within a few years, and conceivably top \$1 billion annually.²⁰ This projection, by NitroMed chief executive officer Michael Loberg, was based in part on comparison to an existing heart failure drug, Coreg, which cost \$3.56 per day.²¹ A week after the FDA approval, BiDil's projected market opportunity nearly tripled to \$3 billion as NitroMed announced BiDil pricing at \$1.80 per pill, or \$10.80 per day, based on the target dose of six pills per day. This dwarfs the estimated cost of generic equivalents at \$0.25 per pill.²²

■ **The FDA changes its mind.** An important moment in BiDil's transformation from a possible alternative for patients who did not respond well to ACE inhibitors to the first so-called ethnic drug is the time between the FDA's 1997 rejection of the first NDA and its encouraging 2001 response to the amended one. Although there were no new studies showing BiDil's efficacy, there were several retrospective re-analyses of existing V-HeFT I and II data and of data from another large cardiac study (Studies of Left Ventricular Dysfunction, or SOLVD).²³ Each of these studies included Cohn or Carson as authors.

These three reanalyses purported to identify racial differences in cardiovascular disease rates and drug response. Their claims, however, were based on tenuous

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readings of questionable data. Thus, for example, an article by Daniel Dries and colleagues, on the SOLVD trials, incorrectly stated that overall mortality from heart failure was approximately twice as high for blacks as for whites, when, in fact, the best available current data showed the disparity to be approximately 1.08 to 1 (that is, negligible).²⁴ The study of racially differential response to H/I by Carson and colleagues was based on a post hoc retrospective analysis of fifteen-year-old data derived primarily from V-HeFT I, which enrolled only 180 African American subjects.²⁵ And the study of differential response to ACE inhibitors by Derek Exner and colleagues had found no racial difference in mortality, only in rates of hospitalization.²⁶ Moreover, this article’s broader claims about racially tailoring drug therapy for heart failure was later repudiated by one of its own coauthors.²⁷

This challenge to the data appeared after the FDA’s favorable 2001 response to NitroMed. Still, one wonders, given the FDA’s rejection of data accompanying the 1996 NDA and the novelty of NitroMed’s 2001 ethnic claim, why the FDA chose to encourage NitroMed at all.

Part of the explanation might lie in the changed political and social climate. Between 1996 and 2001 a strong mandate to respond to health disparities, racially framed, had emerged at the same time that the Human Genome Project had put the relationship of race and genetics back on the table for debate. Many researchers began to link these interests and to examine biological or genetic contributions to health disparities. Even historically black organizations such as Howard University participated by establishing their own gene banks composed entirely of samples from African Americans to use for research, particularly on conditions associated with health disparities.²⁸ And the Association of Black Cardiologists (ABC) threw its weight behind A-HeFT, without which one wonders if sufficient numbers of African American subjects could have been recruited or so well retained (not one of the 1,000-plus subjects was lost to follow-up).²⁹ What changed, then, from the FDA’s 1996 rejection of BiDil and its 2001 encouragement was the emergence of a strong demand to respond to health disparities coupled with a growing acceptance—among some, perhaps, a desire—that the response recognize rather than deny racial differences, conceived of as both genetic or biological and social. The question is, does BiDil respond to that demand?

There are several issues to consider in answering this question, some that date back to a critical juncture in the early history of BiDil’s development. In V-HeFT I, H/I (notably not yet BiDil) outperformed placebo and an alpha adrenergic blocker called prazosin. In V-HeFT II, however, an ACE inhibitor, enalapril, outperformed H/I. A next obvious step might have been research that assessed combining the

two treatments. However, absent a way to argue that the sum was greater than its parts or that two generics combined differed essentially from the two generics separated, there was no patent to apply for, no NDA forthcoming, thus no money to be made, and so no research conducted. Indeed, Cohn himself bemoaned the lack of relevant intellectual property rights as undermining industry interest in conducting such a trial.³⁰ Instead, industry initiated another trial, V-HeFT III, which combined enalapril with a patented calcium channel blocker—to no great effect. In profit-driven drug development, there is nothing remarkable about the choice to abandon pursuit of an apparently efficacious treatment for a potentially profitable one, but this particular choice is important for the role it played in BiDil's development.

■ **Important features obscured.** Popular press coverage of the A-HeFT story tended to obscure certain important features. Some articles characterized A-HeFT as proving the efficacy of a new therapeutic (calling BiDil a “new drug combo” and a “new heart drug therapy”), while others implied that BiDil alone, rather than BiDil in conjunction with established standard therapies, produced the trial's dramatic results.³¹ As fuller accounts detail, however, BiDil's efficacy was established twenty years before A-HeFT by the V-HeFT I trial and not as a substitute for, but as a complement to, standard therapy. Some BiDil proponents dismiss such popular press misstatements as insignificant, emphasizing instead A-HeFT's dramatic success in proving that BiDil works better for blacks than whites. The problem is, A-HeFT established no such thing—as even its lead investigators admit.³²

The study did not compare blacks to whites. It enrolled only blacks. It proved that (black) subjects given BiDil, along with their standard heart medication, did better than (black) subjects given a placebo along with their standard heart medication. A study of white heart patients; Californian heart patients; or even of patients with no particular racial, ethnic, or geographic labels might have returned the same finding. Whether H/I helps heart patients was not a question, nor has it been for more than twenty years. The goal of A-HeFT was not to prove that H/I was effective; it was to prove BiDil's efficacy in such a way that patent law could protect it and an NDA could succeed. A study could have been conducted instead in a racially diverse population using the generic drugs (H/I), which might have resulted in the broader availability of a good, lower-cost medication. But in the absence of a potential for substantial profit, NitroMed showed no interest in that inquiry.

■ **Race not relevant to BiDil's performance.** This points up both a paradox of the A-HeFT trial and an underlying problem with how commercial considerations shape drug development in this country. On the one hand, the data from A-HeFT are valuable. They seem to strongly support the claim that BiDil, layered on top of existing therapies, greatly helps people with heart failure. Critical to getting funding to support the A-HeFT study were the tortured efforts to show a racial difference in the cause and progression of heart failure. Hence the importance of the inaccurate or

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misconstrued studies by Dries, Exner, and Carson—and ultimately of Cohn and Carson’s race-specific patent. Without playing the race card, NitroMed might never have raised the money needed to conduct A-HeFT. On the other hand, the value of the A-HeFT results has been greatly diminished by commercial considerations that have shaped the data presentation to imply improperly that the race of the subjects was a relevant biological variable in the study.

If the investigators had really wanted to find out if BiDil worked differently or better in blacks than in another population, they would need to have enrolled another population such as whites or Asians and to have designed a study to compare them. Such a study, however, while likely to have confirmed A-HeFT’s findings that BiDil worked, would have risked also showing that BiDil worked for everyone, not just blacks, thus negating the basis for the NDA and of NitroMed’s control of the market based on its race-specific patent. Moreover, the newer race-specific patent protects NitroMed until 2020, thirteen years beyond the general methods patent supporting BiDil, which expires in 2007.

■ **Market exclusivity.** The great irony here is that NitroMed admits that BiDil might work in people who aren’t African American, and many of the A-HeFT investigators themselves have expressed the hope that the drug is prescribed to anyone who might benefit from it, regardless of race.³³ NitroMed, it seems, is perfectly happy with this apparent contradiction—so long as the actual approval from the FDA is race-specific. With the FDA approval of BiDil’s NDA based on race-specific indication, only NitroMed will be able to publicly market it as a therapy for heart failure. Generic manufacturers will still be able to sell hydralazine and isosorbide dinitrate separately, but they will not be able to advertise them as treatments for heart failure. The advertising limit comes with FDA approval and gives NitroMed three years of what is known as “market exclusivity” to market its product for the new indication. After three years, NitroMed’s race-specific patent will still prevent anyone else from marketing the generic component drugs as a “method” to treat heart failure in African Americans until 2020. Moreover, to the extent that public discussion and the professional literature argues that BiDil should be used regardless of race, it allows NitroMed, with a wink and a nod, to take advantage of a potentially huge market of so-called “off label” prescribing to non-African American heart failure patients.

Race, Commerce, Health Disparities, And BiDil

Make no mistake, BiDil will benefit heart patients. Some of them will be black. Cohn, the drug’s champion for nearly thirty years, has achieved a valuable objective. He also is likely to make a lot of money. Indeed, in addition to royalties and li-

censing fees, Cohn received \$1 million in milestone payments for approval and first marketing of BiDil.³⁴ Most of the other coauthors of the article announcing A-HeFT's findings also could benefit from a BiDil launch. Nine of eleven have direct financial ties to NitroMed (K. Ferdinand and M. Taylor do not).³⁵ Some report receiving research funding, and several disclose that they are stockholders. Careful management of these conflicts likely protected A-HeFT data from bias. However, conflicts of interest do not influence research only by biasing results. They also can assert themselves into research by allowing potential financial gain to distort the design and trajectory of research in ways that might ultimately undermine broad and affordable access to important therapies that help eliminate health disparities.

Thus, in addition to considering how BiDil's approval reifies race, it is essential also to examine its emergence at the intersection of commerce and health disparities. The problem with BiDil is not only that it biologizes race but also that it uses race as biology to create the impression that the best way to address health disparities is through commercial drug development. By exploiting race in the service of product promotion, it distorts public understanding of health disparities and of efforts to address them.

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NOTES

1. U.S. Food and Drug Administration, "FDA Approves BiDil Heart Failure Drug for Black Patients," Press Release, 23 June 2005, www.fda.gov/bbs/topics/NEWS/2005/NEW01190.html (5 July 2005).
2. A. Ahuja, "We Can Treat Your Heart Disease, If You're Black," *Times*, 29 October 2004, www.timesonline.co.uk/article/0,,8123-1334916,00.html (15 September 2005); L. Boyce, "Are 'Ethnic Drugs' a Form of Racial Marketing?" *Charlotte Post*, 2 December 2004; V. Cheng, "Can We Medicate by Race?" *News and Observer*, 18 November 2004, www.newsobserver.com/lifestyles/v-printer/story/1839354p-8158207c.html (2 January 2005); S.J. Landers, "New Drug Combo Intensifies Race-based Medicine Debate," *American Medical News*, 6 December 2005; A. Pollack, "Drug Approved for Heart Failure in Black Patients," *New York Times*, 20 July 2004; and R.S. Cooper, J.S. Kaufman, and R. Ward, "Race and Genomics," *New England Journal of Medicine* 348, no. 12 (2003): 1166-1170.
3. J.N. Cohn et al., "Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure. Results of a Veterans Administration Cooperative Study," *New England Journal of Medicine* 314, no. 24 (1986): 1547-1552.
4. J.N. Cohn et al., "A Comparison of Enalapril with Hydralazine-Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure," *New England Journal of Medicine* 325, no. 5 (1991): 303-310.
5. "Medco Research Finds Bidil Bioequivalent and Re-Acquires Rights from Boehringer-Manheim Pharmaceuticals; Plans to Submit NDA," PR Newswire, 2 April 1996.
6. J. Kahn, "How a Drug Becomes 'Ethnic': Law, Commerce, and the Production of Racial Categories in Medicine," *Yale Journal of Health Policy, Law, and Ethics* 4, no. 1 (2004): 1-46; and AHeFT.org, "Questions about the A-HeFT Study," 2005, www.aheft.org/questions.asp (21 April 2005).
7. Kahn, "How a Drug Becomes 'Ethnic'."
8. *Ibid.*
9. P. Carson et al., "Racial Differences in Response to Therapy for Heart Failure: Analysis of the Vasodilator-Heart Failure Trials," *Journal of Cardiac Failure* 5, no. 3 (1999): 178-187.
10. J. Cohn and P. Carson, U.S. Patent No. 6,465,463 (issued 15 October 2002).

11. K. Pihl-Carey, "NitroMed, Preparing for BiDil Launch, Publicly Raises \$80M," *BioWorld Online*, 9 December 2004, www.bioworld.com (2 January 2005, subscriber access only).
12. A.L. Taylor et al., "Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure," *New England Journal of Medicine* 351, no. 20 (2004): 2049–2057.
13. *Ibid.*
14. Pihl-Carey, "NitroMed."
15. Taylor et al., "Combination of Isosorbide Dinitrate and Hydralazine."
16. Pihl-Carey, "NitroMed."
17. *Ibid.*
18. "Nitromed Selects Vigilante as Ad Agency for Heart Drug Benefiting African-Americans," *Target Market News*, 6 December 2004, www.targetmarketnews.com/Top%20Stories%20of%2004.htm (22 September 2005).
19. "Race and Medicine" (Editorial), *Newark Star-Ledger*, 17 November 2004.
20. A. Pollack, "Drug Approved for Heart Failure in Black Patients," *New York Times*, 20 July 2004; and Pihl-Carey, "NitroMed."
21. M. Loberg, Remarks on Behalf of NitroMed Inc. at the Pacific Growth Equities 2005 Life Sciences Growth Conference, San Francisco, 6 June 2005.
22. S. Saul, "Maker of Heart Drug Intended for Blacks Bases Price on Patients' Wealth," *New York Times*, 8 July 2005.
23. D.L. Dries et al., "Racial Differences in the Outcome of Left Ventricular Dysfunction," *New England Journal of Medicine* 340, no. 8 (1999): 609–616; D.V. Exner et al., "Lesser Response to Angiotensin-Converting-Enzyme Inhibitor Therapy in Black as Compared with White Patients with Left Ventricular Dysfunction," *New England Journal of Medicine* 344, no. 18 (2001): 1351–1357; and Carson et al., "Racial Differences."
24. Dries et al., "Racial Differences"; and Kahn, "How a Drug Becomes 'Ethnic'."
25. Carson et al., "Racial Differences."
26. Exner et al., "Lesser Response."
27. D.L. Dries et al., "Efficacy of Angiotensin-Converting Enzyme Inhibition in Reducing Progression from Asymptomatic Left Ventricular Dysfunction to Symptomatic Heart Failure in Black and White Patients," *Journal of the American College of Cardiology* 40, no. 2 (2002): 311–317.
28. J. Kaiser, "African-American Population Biobank Proposed," *Science* 300, no. 5625 (2003): 1485.
29. NitroMed, "First Heart Failure Study in African-Americans Shows 43 Percent Improvement in Survival," Press Release, 8 November 2004, www.nitromed.com/11_08_04c.shtml (2 January 2005).
30. Kahn, "How a Drug Becomes 'Ethnic'."
31. "Heart RX: Medication Should Be Approved for Blacks, Studied for Other Races" (editorial), *Columbus Dispatch*, 18 November 2004; and M. Brady-Myerov, "Race-Specific Drug Raises Ethical Questions," *Voice of America*, 18 November 2004.
32. D. Rotman, "Race and Medicine," *MIT Technology Review*, April 2005, technologyreview.com/articles/05/04/issue/feature_medicine.asp?p=1 (2 January 2005).
33. M. Branca, "Race and Genomics: Marketing Ploy or a Route to Individualized Therapy?" *BioWorld Online*, 30 April 2003, www.bioworld.com (2 January 2005, subscription required); NitroMed, "NitroMed SEC Filings," Form 10K, 10 March 2005, investors.nitromed.com/phoenix.zhtml?c=130535&p=IROL-sec (2 January 2005); and Reuters, "Study: Heart Failure Drug Helps Black Patients," 8 November 2004, www.msnbc.msn.com/id/6435861 (2 January 2005).
34. NitroMed, "NitroMed SEC Filings," Form 10K, 10 March 2005.
35. Taylor et al., "Combination of Isosorbide Dinitrate and Hydralazine."