
September 2003

PEDIATRIC DRUG RESEARCH

Food and Drug Administration Should More Efficiently Monitor Inclusion of Minority Children

**G A O**Accountability * Integrity * Reliability



Highlights of [GAO-03-950](#), a report to the Committee on Health, Education, Labor and Pensions, U.S. Senate, and the Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

Drug effectiveness and adverse events can vary between children and adults and among racial and ethnic groups. The Food and Drug Administration (FDA) is authorized under the pediatric exclusivity provision to grant drug sponsors 6 months of additional exclusive marketing rights for conducting clinical drug studies in children. The Best Pharmaceuticals for Children Act of 2002 (BPCA) expanded this provision to require FDA to take into account the adequacy of minority representation in pediatric exclusivity studies. BPCA also directed GAO to evaluate the representation of minorities in such studies. GAO examined the extent to which minority children are represented, whether drugs that treat diseases disproportionately affecting minority groups are studied under the provision, and FDA's monitoring of the representation of minority children in the studies. GAO reviewed related FDA documents, FDA requests for pediatric studies and final study results, and interviewed FDA officials and other experts.

What GAO Recommends

GAO recommends that FDA specify that drug sponsors use the standard racial and ethnic group definitions described in FDA's January 2003 draft guidance to identify study participants. FDA concurred with the recommendation.

www.gao.gov/cgi-bin/getrpt?GAO-03-950.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Janet Heinrich at (202) 512-7119.

PEDIATRIC DRUG RESEARCH

Food and Drug Administration Should More Efficiently Monitor Inclusion of Minority Children

What GAO Found

Compared with the proportions of children from racial and ethnic minority groups in the U.S. population, smaller proportions of children from minority groups were included in the pediatric clinical drug studies requested by FDA before the enactment of BPCA that GAO reviewed. However, FDA required, and drug sponsors included, larger proportions of African American children in clinical studies for hypertension drugs because there is evidence that hypertension is more prevalent and more severe among African Americans. Furthermore, FDA has requested that forthcoming studies for certain drugs include larger proportions of minority children.

Studies of some drugs that may be used to treat diseases or conditions that disproportionately affect minorities have been completed and additional such studies have been requested by FDA. From January 4, 2002, through March 6, 2003, FDA granted additional exclusive marketing rights to four drugs that may be used to treat conditions such as hypertension, type II diabetes, and sickle cell anemia—conditions or diseases that disproportionately affect minority children. During that time, FDA also issued written requests for studies of six drugs for these conditions.

FDA does not have a system in place to serve as a single source of data to allow the agency to efficiently determine the extent of participation of children by racial and ethnic group under the pediatric exclusivity provision. GAO found that some study reports submitted to FDA from drug sponsors did not specify the race and ethnicity of all study participants. Across all the studies for drugs granted additional exclusive marketing rights that GAO reviewed, 86 percent of study participants were identifiable by race or ethnicity, but the race or ethnicity of 14 percent of study participants was unknown. In January 2003, FDA issued draft guidance recommending that drug sponsors use standard definitions for race and ethnicity in drug studies. However, drug sponsors are not required to use these definitions. FDA has also begun to develop an agencywide system to monitor demographic characteristics of study participants, such as age, sex, and race.

FDA agreed with the GAO recommendation to specify the categories that sponsors should use to report minority representation as well as GAO's findings regarding the efficiency of its data collection systems. FDA expressed concerns about the GAO comparison of the proportion of minorities in drug studies to their proportion in the U.S. population. However, FDA had previously used the methodology GAO employed in its analyses of adult study participants.

Contents

Letter		1
	Results in Brief	4
	Background	6
	Smaller Proportions of Minority Children Were in Studies for Additional Marketing Exclusivity Requested before BPCA	11
	Drugs of Importance to Minority Children Are Being Studied in Response to Pediatric Exclusivity Provision Requests	14
	FDA Monitoring of Data on Minority Representation Needs Improvement	16
	Conclusions	18
	Recommendation for Executive Action	18
	Agency Comments and Our Evaluation	19

Appendix I	Scope and Methodology	21
-------------------	------------------------------	-----------

Appendix II	The Number of Children by Racial and Ethnic Group in Studies for Drugs Granted Exclusive Marketing Rights	23
--------------------	--	-----------

Appendix III	Comments from the Food and Drug Administration	25
---------------------	---	-----------

Appendix IV	GAO Contact and Staff Acknowledgments	29
	GAO Contact	29
	Acknowledgments	29

Tables		
	Table 1: Children, by Racial and Ethnic Group, in Clinical Studies for Drugs Granted Additional Exclusive Marketing Rights, January 4, 2002, through March 6, 2003	12
	Table 2: Children, by Racial and Ethnic Group, in Clinical Studies for Three Drugs for Which FDA Required Mixed Race Participation, and for All Other Drugs Granted Additional Exclusive Marketing Rights, January 4, 2002, through March 6, 2003	13

Table 3: Estimated Prevalence of Diseases or Conditions in Minorities That May Be Treated by Drugs for Which FDA Issued Written Requests or Granted Exclusive Marketing Rights, January 4, 2002, through March 6, 2003	15
Table 4: Children of Racial and Ethnic Groups, by Drug Class, in Clinical Studies for Drugs Granted Exclusive Marketing Rights, January 4, 2002, through March 6, 2003	24

Abbreviations

ACE	angiotensin converting enzyme
AIDS	acquired immunodeficiency syndrome
BPCA	Best Pharmaceuticals for Children Act
DIDR	Demographic Information and Data Repository
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
HIV	human immunodeficiency virus
NDA	new drug application
sNDA	supplemental new drug application

This is a work of the U.S. government and is not subject to copyright protection in the United States. It may be reproduced and distributed in its entirety without further permission from GAO. However, because this work may contain copyrighted images or other material, permission from the copyright holder may be necessary if you wish to reproduce this material separately.



United States General Accounting Office
Washington, DC 20548

September 26, 2003

The Honorable Judd Gregg
Chairman
The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Health, Education, Labor and Pensions
United States Senate

The Honorable W.J. "Billy" Tauzin
Chairman
The Honorable John D. Dingell
Ranking Minority Member
Committee on Energy and Commerce
House of Representatives

While children can be stricken with many of the same diseases afflicting adults and are often treated with the same drugs, only about one-third of drugs in use today have been studied and labeled for pediatric use.¹ A drug used to treat children that has not been tested or labeled for pediatric use may place children at risk of under- or overdosing, and when age-appropriate formulations of the drugs do not exist, such as liquids or chewable tablets, the drug may be improperly administered to children. To help address these concerns, in 1997 Congress passed a law that gives sponsors 6 months of additional exclusive marketing rights for their products in return for conducting clinical drug studies in children, commonly known as the pediatric exclusivity provision.² The Food and Drug Administration (FDA), the federal agency that approves drugs for marketing, is responsible for administering the law and has procedures for ensuring the study of drugs in pediatric patients. Specifically, if FDA officials believe that studying a drug may lead to health benefits for children, FDA issues a formal "written request" for clinical drug studies in

¹R. Roberts and others, "Pediatric Drug Labeling: Improving Safety and Efficacy of Pediatric Therapies," *Journal of the American Medical Association*, vol. 290, no. 7 (2003).

²Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, §111, 111 stat. 2296, 2305. Drug manufacturers may obtain marketing exclusivity through patents, patent term extensions to compensate for regulatory delays, approval of drugs containing new chemical entities, or approval of orphan drugs.

pediatric patients to the drug sponsor. If the sponsor agrees to comply with the terms of the written request and submits final study results to FDA that meet the terms of the request, FDA will grant the sponsor 6 months of additional exclusive marketing rights. Pediatric drug research has increased substantially since the enactment of the pediatric exclusivity provision.³

FDA officials are concerned that drug effectiveness and adverse effects can vary among children from different racial and ethnic groups. Although FDA has requested race and ethnicity data on subjects in clinical drug trials, no formal evaluations have assessed the extent to which children of different racial and ethnic groups are represented in clinical studies of new drugs, thus the extent to which these drugs have been tested on children in minority groups is unknown. Concern exists that if children from racial and ethnic minority groups are not included in adequate numbers in clinical studies of drugs, the administration of the drugs to children in these groups may result in atypical responses or unexpected side effects. In addition, no formal evaluations have assessed the extent to which drugs that were studied under the pediatric exclusivity provision may be used to treat diseases or conditions that disproportionately affect minority children.

To ensure that children of racial and ethnic minority groups are included in clinical studies for new drugs, the Best Pharmaceuticals for Children Act of 2002 (BPCA) expanded the pediatric exclusivity provision to require, among other things, that FDA “take into account adequate representation” of children from racial and ethnic minority groups when negotiating written protocols with the study sponsors of pediatric drugs.⁴ In addition, the act required that we study the adequacy of minority representation in studies covered by the pediatric exclusivity provision. As agreed with the committees of jurisdiction, we addressed the following questions: (1) to what extent are children of racial and ethnic minority groups represented in clinical studies for drugs granted exclusive marketing rights, (2) are drugs that are used to treat diseases that

³U.S. General Accounting Office, *Pediatric Drug Research: Substantial Increase in Studies of Drugs for Children, But Some Challenges Remain*, [GAO-01-705T](#) (Washington, D.C.: May 8, 2001).

⁴Pub. L. No. 107-109, § 18, 115 Stat. 1408, 1423. The pediatric exclusivity provision sunset on January 1, 2002. BPCA, which took effect on January 4, 2002, reauthorized the provision through October 1, 2007. BPCA, § 8, 115 Stat. 1414.

disproportionately affect racial and ethnic minority groups being studied for safety and effectiveness in children under the pediatric exclusivity provision, and (3) does FDA have appropriate management systems to monitor the representation of children of racial and ethnic groups in studies submitted for additional exclusive marketing rights?

To answer these questions, we reviewed recently completed and requested pediatric studies for inclusion of children from racial and ethnic minority groups and FDA's data systems, regulations, and guidance used to implement the pediatric exclusivity provision. To quantify the participation of racial and ethnic groups in completed pediatric clinical studies, we reviewed FDA pediatric study documents and collected data about racial and ethnic group representation in study participants for the 23 drugs that were granted additional exclusive marketing rights during the period January 4, 2002, through March 6, 2003.⁵ All of the studies for these drugs had been requested by FDA before BPCA took effect on January 4, 2002, and thus were not subject to the expanded pediatric exclusivity provisions under the law. The time lag between an FDA written request and a sponsor's submission of final study results ranges from 1 to 4 years. To determine the representation and reporting requirements that FDA required drug sponsors to follow concerning the participation of racial and ethnic minorities in pediatric studies since BPCA took effect, we reviewed the 22 written requests for pediatric drug studies that FDA issued from January 4, 2002, through March 6, 2003. To determine if drugs used to treat conditions disproportionately affecting minorities are being studied, we obtained data on the prevalence of selected diseases or conditions that disproportionately affect minorities. We then examined the list of drugs for which FDA had either issued study requests or granted additional exclusive marketing rights from January 4, 2002, through March 6, 2003, to determine if any of the drugs may be used to treat these diseases or conditions. To evaluate FDA's monitoring of data on demographic traits, such as race, in drug studies, we reviewed relevant documents and interviewed FDA officials. We also interviewed pharmacology experts and pediatric clinicians, including members of the American Academy of Pediatrics and the Pharmaceutical Research and

⁵We collected clinical study participation data for three racial groups (African American, Asian, and Caucasian) and one ethnic group (Hispanic) because these categories were commonly used in the clinical study documents that were submitted to FDA for exclusive marketing rights. The term pediatric study is defined as including at least one clinical investigation and may include studies on the absorption, distribution, metabolism, and excretion of a drug in pediatric age groups in which a drug is expected to be used.

Manufacturers of America. (For additional information on our methodology, see app. I.) We conducted our work from October 2002 through September 2003 in accordance with generally accepted government auditing standards.

Results in Brief

Compared with the proportions of children from racial and ethnic minority groups in the U.S. population, smaller proportions of children from minority groups participated in clinical drug studies for additional exclusive marketing rights that FDA requested before BPCA took effect. In clinical studies for the 23 drugs granted 6 months of additional exclusive marketing rights from January 4, 2002, through March 6, 2003, approximately 7 percent of study participants were African American, 5 percent were Hispanic, and 1 percent were Asian, whereas these groups comprised 15, 17, and 3 percent, respectively, of U.S. children under 18 years of age in 2000. However, FDA required, and drug sponsors included, larger proportions of minority children in studies for hypertension drugs because there is evidence suggesting a difference in drug metabolism or response in adult minority groups. Specifically, hypertension is more prevalent and more severe in African Americans, and African American children represented 22 percent of pediatric study participants in studies for three hypertension drugs. Similarly, FDA written requests for certain drugs issued since BPCA took effect require sponsors to increase minority representation. Specifically, in 4 of the 22 requests FDA required sponsors to increase the number of minorities in the study or analyze the effects of race and ethnicity for drugs that may affect minority groups differently. In 11 of the 22 requests, FDA directed drug sponsors to report the representation of pediatric patients of ethnic and racial minority groups when submitting final study results, and 7 written requests made no mention of race or ethnicity.

Some drugs that may be used to treat diseases that disproportionately affect minorities are being studied under the pediatric exclusivity provision. During the period January 4, 2002, through March 6, 2003, FDA granted exclusive marketing rights for four drugs and issued written requests for pediatric studies of six drugs that may be of particular importance to children in minority groups. For example, drug sponsors are either conducting or have completed studies on drugs to treat children with hypertension, type II diabetes, and sickle cell anemia—conditions or diseases that disproportionately affect children of racial and ethnic minority groups.

FDA does not have a system in place to serve as a single source of data to allow the agency to efficiently determine the level of participation of children by racial and ethnic group under the pediatric exclusivity provision. In addition, FDA lacks standard definitions for study sponsors to use in reporting racial and ethnic group participation in studies, and sponsors have reported these data using their own definitions for racial and ethnic groups. For example, in the completed studies for the 23 drugs granted additional exclusive marketing rights that we examined, the race or ethnicity of 86 percent of study participants was identified, but study sponsors did not specify the race or ethnicity of 960 children, or 14 percent of the studies' populations. FDA has taken action to start to address these issues. In January 2003, FDA issued draft guidance recommending that sponsors of drug studies use the definitions for race and ethnicity that the Department of Health and Human Services (HHS) has adopted for data collection and reporting systems funded or supported by HHS. However, FDA's guidance is not legally binding on clinical study sponsors. FDA has also begun to develop an agencywide system to monitor demographic variables, such as race, age, and sex in clinical studies.

We are recommending that FDA revise the format of its written requests to specify that study sponsors must use the racial and ethnic categories described in FDA's January 2003 draft guidance to identify study participants in their reports to the agency. FDA can refuse to grant 6 months of additional exclusive marketing rights under the pediatric exclusivity provision for sponsors that do not fairly respond to FDA's written requests.

In commenting on a draft of this report, FDA concurred with our recommendation and reported that it has already begun to implement it. FDA also reaffirmed the importance of testing drugs used to treat children in clinical studies of that population and agreed that the agency needed to improve the efficiency of its system for tracking demographic information about study participants. However, FDA raised concerns about three aspects of our draft report. First, FDA was critical of our comparison of the proportions of minority children study participants to the proportions of minority children in the population. FDA commented that it would have been more appropriate for us to compare the proportions of minority children in clinical drug studies with the proportions of minority children with the specific condition each drug is intended to treat. We agree that such a comparison would have been useful, but both FDA and we found that the information needed for such comparisons was not available. Further, FDA has previously used the methodology we employed in its

analyses of adult study participants. Second, FDA was concerned about what it regards as the implications of our finding that the proportions of minority children in pediatric studies requested by FDA before the passage of BPCA were less than their proportions in the general population. Our report does not make any recommendations about the preferred study populations for any clinical drug trial. Third, FDA noted that the race or ethnicity of a high percentage of study participants was identified even before BPCA was enacted. While our findings agree with that assessment, we believe that FDA should have been able to identify the race or ethnicity of every study participant.

Background

Congress passed the pediatric exclusivity provision as part of the Food and Drug Administration Modernization Act of 1997 to address a long-standing concern about the low percentage of prescription medications on the market that had been tested and approved for use in children. BPCA, which reauthorized the pediatric exclusivity provision, also included a requirement that FDA take into account adequate representation of race and ethnicity in the development of patient groups in pediatric drug studies. FDA is responsible for administering the law and has procedures for ensuring the study of drugs in pediatric patients as well as guidance that encourages (1) the inclusion of children from minority groups and (2) the collection and analysis of race-related study data. In this role, FDA must balance its policy of minimizing the number of children exposed to a drug during clinical trials with the need to maintain adequate sample sizes, including adequate representation of minority children, for effectively assessing a drug.

Improvements Resulting from the Pediatric Exclusivity Provision

In May 2001, we testified before the Senate Committee on Health, Education, Labor and Pensions that, since enactment of the pediatric exclusivity provision, both the numbers of new drugs studied in children and the number of therapeutic classes these drugs represent have substantially increased.⁶ We reported that hundreds of studies were being done on drugs that are important to pediatric patients because the drugs treat a variety of diseases or conditions that afflict children. Some were tests on relatively small numbers of pediatric patients to determine the correct dose for a specified age group, while other tests were on larger numbers of pediatric patients and were more complex and costly

⁶[GAO-01-705T](#).

evaluations of a drug's safety and effectiveness in children of various ages.⁷ BPCA reauthorized and expanded the provision for 5 more years through October 1, 2007.

FDA Procedures for Ensuring the Study of Drugs in Pediatric Patients

The process for obtaining exclusive marketing rights can be initiated either by a drug sponsor or by FDA. A sponsor may submit a proposal to FDA to conduct drug studies. If FDA officials believe that studying a drug may produce health benefits for children, FDA issues a formal written request to the drug sponsor that includes, among other things, the type of studies to be conducted, the study design and goals, and the formulations and age groups to be studied. As of March 31, 2003, FDA had issued 272 written requests for pediatric studies. Of these, 220 were issued in response to sponsors' proposals. FDA may issue a written request without the sponsor's proposal if FDA identifies a need for pediatric data. FDA has issued 52 written requests without sponsors' proposals. A written request may require more than 1 study of a drug; the 272 requests covered 631 studies, and could involve more than 37,150 pediatric patient participants if they were all completed. Regardless of the final study results, if FDA determines that the data submitted fairly responds to the written request and the studies were conducted properly, it will grant the sponsor 6 months of additional exclusive marketing rights. From enactment of the pediatric exclusivity provision in 1997 through April 30, 2003, FDA granted an additional 6 months of additional exclusive marketing rights for 74 drugs. Sponsors are not required to include minority children in studies for pediatric exclusivity.

Findings from these studies have led to labeling changes for pediatric use for 50 drugs. For example, a study of fluoxetine (an antidepressant) confirmed its effectiveness to treat major depressive disorders in children 8 to 17 years of age and obsessive-compulsive disorder in children 7 to 17 years of age. In addition, studies for a new asthma drug—montelukast—led to new information on dosing and a new oral formulation permitting its use in children from the ages of 12 months to 5 years.

⁷More recently, FDA officials reported that the pediatric exclusivity provision has stimulated pediatric clinical studies resulting in improved understanding of drugs prescribed in pediatric medicine, important dose changes, and improved safety for children taking certain drugs. See R. Roberts and others, "Pediatric Drug Labeling: Improving Safety and Efficacy of Pediatric Therapies."

FDA also has a process in place to encourage pediatric studies of drugs that manufacturers choose not to conduct. For drugs on which the patent or exclusive marketing rights have expired, commonly referred to as off-patent drugs, the National Institutes of Health (NIH) in collaboration with FDA annually develop a list of drugs for which pediatric studies are needed and publish it in the Federal Register.⁸ FDA may select a drug from this list, issue a written request to the manufacturer that holds the approved application for the drug, and, if the manufacturer does not respond within 30 days, forward the written request to NIH to issue a contract to conduct the study. In fiscal year 2003, HHS announced that NIH would set aside \$25 million from its budget to conduct pediatric studies of off-patent drugs from this list. Similarly, if FDA issues a written request for a drug that is on-patent but the drug sponsor declines to test the drug in children, FDA can ask the Foundation for the National Institutes of Health, which supports the mission of NIH,⁹ to test the drug with funds raised from the private sector.

⁸The purpose of this list is to promote studies of pharmaceuticals in pediatric populations that would normally not be studied under the pediatric exclusivity provision. These include drugs that do not have specific patent protection or exclusive marketing rights that could be prolonged under BPCA.

⁹Originally established by Congress as the National Foundation for Biomedical Research, the Foundation was incorporated in 1996 as a nonprofit organization funded through private donations. In 1998 Congress changed its name to the Foundation for the National Institutes of Health.

Evidence Shows That Drug Effectiveness and Toxicity Can Vary among Racial and Ethnic Groups

An important reason to include minorities in pediatric drug studies is to examine the effect of race or ethnicity on the disposition and effects of drugs in children. In adults, the activity of some drug-metabolizing enzymes varies with race or ethnicity.¹⁰ For example, one commonly prescribed drug used to treat gastric conditions, esomeprazole (Nexium), is partly metabolized by the CYP2C19 enzyme. Studies have shown that from 15 to 20 percent of Asians lack the enzyme CYP2C19. As a result, some Asians metabolize the drug poorly and require lower doses because their bodies do not clear the drug as rapidly as individuals with this enzyme.¹¹ Also, compared with Caucasians, certain Asian groups are more likely to require lower dosages of a variety of different antipsychotic drugs used to treat mental illness.

Research in adults over the past several decades has further characterized significant differences among racial and ethnic groups in the metabolism, clinical effectiveness, and side-effect profiles of many clinically important drugs. These differences in response to drug therapy can be traced to differences in the distribution of genetic traits that produce these differences among racial and ethnic groups.¹² These naturally occurring variations in the structures of genes, drug metabolism enzymes, receptor proteins, and other proteins that are involved in drug response affect how the body metabolizes certain drugs, including cardiovascular agents (beta-blockers, diuretics, calcium channel blockers, angiotensin converting

¹⁰An FDA review of demographic data for 185 new molecular entities approved between January 1, 1995, and December 31, 1999, found that labeling for 45 percent of the drugs contained a statement that race may affect how a patient responds to the drug, although in only 8 percent were any differences in response related to race described. For this small subset of drugs, information on differences in the drugs' effects among racial and ethnic groups noted that 50 percent were related to how drugs are processed in the body, 39 percent were related to efficacy, and 11 percent were related to safety. However, only one drug label, for a drug used to treat hypertension, recommended a change in dosage based on racial differences. It recommended that physicians increase the initial dose for African American patients. See B. Evelyn and others, FDA, Office of the Commissioner, Office of Special Health Issues, *Participation of Racial/Ethnic Groups in Clinical Trials and Race-Related Labeling: A Review of New Molecular Entities Approved 1995-1999* (Rockville, Md.: 2001). http://www.fda.gov/cder/reports/race_ethnicity/race_ethnicity_report.htm (downloaded Oct. 29, 2002).

¹¹H. Xie and others, "Molecular Basis of Ethnic Differences in Drug Disposition and Response," *Annual Review of Pharmacology Toxicology*; Vol. 41 (2001), 815-850, and R. Weinshilboum, "Inheritance and Drug Response," *New England Journal of Medicine*, vol. 348 (2003), 529-537.

¹²Institute of Medicine, *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* (Washington, D.C.: 2002).

enzyme (ACE) inhibitors, and central nervous system agents (antidepressants and antipsychotics).¹³

FDA's Efforts to Account for Minority Children in Clinical Drug Studies

BPCA requires that FDA take into account adequate representation of children from ethnic and racial minority groups when issuing written requests to drug sponsors. FDA regulations have required that in new drug applications, "effectiveness data (safety data) shall be presented by gender, age, and racial subgroups and shall identify any modifications of dose or dose interval needed for specific subgroups."¹⁴ Other FDA guidance encourages the participation of racial and ethnic groups in all phases of drug development, recommends collection of race-related data during research and development, and recommends the analysis of the data for race-related effects.¹⁵

FDA officials told us that if there is scientific evidence documenting possible mechanisms causing variation in drug response in minorities, such as a higher or lower prevalence of a specific drug metabolizing enzyme or drug receptor, then FDA's written request will require the study sponsor to increase minority representation in the study. The officials told us that it is particularly important to consider racial differences in pediatric patients under two circumstances: (1) when there is a possible difference in drug metabolism or response demonstrated in adult clinical studies or documented in the scientific literature or (2) if a drug is used to treat a disease that disproportionately affects minorities. Absent these conditions, the officials told us that FDA does not require that sponsors include particular numbers or proportions of minority children in its studies.

¹³There are over 100 examples in the medical literature in which inherited individual traits that contributed to atypical, exaggerated responses to drugs or to unusual effects or ineffectiveness of drugs. See for example, V.J. Burroughs, R.W. Maxey, and R.A. Levy, "Racial and Ethnic Differences In Response to Medicines: Towards Individualized Pharmaceutical Treatment," *Journal of the National Medical Association*, vol. 94, no. 10, Supplement (2002).

¹⁴21 C.F.R. 314.50 (d)(5)(v) and (vi) (a) (Content and format of an application for approval to market a new drug).

¹⁵Food and Drug Administration, *Guideline Format and Content of Clinical and Statistical Sections of an Application* (Rockville, Md.: July 1988); Food and Drug Administration, *Population Pharmacokinetics* (Rockville, Md.: 1999); Food and Drug Administration, *Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics* (draft) (Rockville, Md.: 2000).

Limitations of Pediatric Drug Studies

According to FDA officials, FDA's policy is to minimize the number of children exposed to a drug during clinical studies, while maintaining an adequate sample size to draw clinically meaningful conclusions. Most pediatric studies for extension of exclusive marketing rights are designed to give health care providers information on the appropriate dosage or formulation of a drug in a pediatric population.¹⁶ As a result, most pediatric clinical drug studies generally are on a smaller scale than the clinical studies drug sponsors conduct to gain FDA approval to market a new drug. FDA officials told us that both the small number of patients in most pediatric studies as well as the fact that most studies seek to determine the appropriate dosage and safety for pediatric patients have precluded any definitive conclusions about racial or ethnic differences in drug response among children. No completed studies under the pediatric exclusivity provision to date have led to findings or labeling changes specific to any racial or ethnic group.

Smaller Proportions of Minority Children Were in Studies for Additional Marketing Exclusivity Requested before BPCA

Compared to their proportions in the U.S. population, smaller proportions of children of racial and ethnic minority groups were included in the clinical drug studies we reviewed for additional exclusive marketing rights that FDA requested before BPCA took effect. However, for hypertension drugs where differences in racial response have been documented in adult drug studies, FDA required, and drug sponsors included, larger numbers of children from specific racial and ethnic groups. Most of FDA's written requests for studies that have been issued since BPCA took effect required drug sponsors to report the number of racial and ethnic minorities in their final study results. In addition, some requests required drug sponsors to analyze the effects of race and ethnicity or increase minority representation for certain drugs where differences in racial response have been documented in adult drug studies.

¹⁶FDA officials told us that about one-third of the studies requested under the pediatric exclusivity provision are for efficacy.

The Proportions of Children in Racial and Ethnic Minority Groups in Clinical Studies for Exclusive Marketing Rights Were Lower Than Their Proportions in the U.S. Population

Compared with their proportions in the U.S. population, smaller proportions of African American, Hispanic, and Asian children were included in clinical studies for the drugs that were granted 6 months of additional exclusive marketing rights by FDA from January 4, 2002, through March 6, 2003. Across all clinical studies for the 23 drugs we examined, 7 percent of pediatric patients were African American, 5 percent were Hispanic, and 1 percent were Asian. Most pediatric patients were Caucasian—69 percent—and the race and ethnicity were unknown for 14 percent. Compared with the frequency distribution of African American and Hispanic children under 18 years of age for the U.S. population as a whole in 2000, the proportions of these two groups included in clinical drug studies were 8 and 12 percentage points lower, respectively, than their proportions in the U.S. population. The proportion of Asian children in clinical drug studies was 2 percentage points lower than their proportion in the U.S. population (see table 1). (See app. II for the number of children in racial and ethnic groups included in clinical studies for drugs granted additional exclusive marketing rights from January 4, 2002, through March 6, 2003.)

Table 1: Children, by Racial and Ethnic Group, in Clinical Studies for Drugs Granted Additional Exclusive Marketing Rights, January 4, 2002, through March 6, 2003

Race/ethnicity	Number in clinical studies	Percentage in clinical studies	Percentage in U.S. population under age 18
African American	488	7	15
Asian	94	1	3
Caucasian	4,783	69	69
Hispanic	355	5	17
Other	272	4	NA
Unknown	960	14	NA
Total	6,952	100	104^a

Sources: FDA and Department of Commerce.

Notes: GAO analysis of final study reports for the 23 drugs granted additional exclusive marketing rights; and U.S. Bureau of Census, Census 2000 Summary File 1, "Total Population by Age and Sex for the United States: 2000."

NA means not applicable.

^aIndividual entries do not sum to 100 percent because the Department of Commerce, in collecting U.S. Census data, permitted individuals to report that they belonged to multiple race groups. Consequently, the total of all race groups exceeds the population total.

Pediatric Studies for Hypertension Drugs Included More Children of Racial and Ethnic Minority Groups

FDA required that sponsors increase representation of children of ethnic and racial minority groups in clinical studies for drugs used to treat diseases that disproportionately affect children in such groups or where evidence from studies on adults suggests that for certain classes of drugs differences in metabolism or response for racial or ethnic groups exist. For example, because hypertension is more prevalent and more severe in African Americans than in Caucasians, and adult responses to some hypertension therapies appear to be different in African American and non-African American populations, FDA’s written requests for these drugs require that the patient recruitment protocol be designed to ensure a mixture of African American and non-African American patients. Therefore, in pediatric clinical studies for three cardiovascular drugs used to treat hypertension, African American children represented 22 percent of study participants (see table 2).

Table 2: Children, by Racial and Ethnic Group, in Clinical Studies for Three Drugs for Which FDA Required Mixed Race Participation, and for All Other Drugs Granted Additional Exclusive Marketing Rights, January 4, 2002, through March 6, 2003

Race/ethnicity	Numbers in percent		
	In clinical studies for 3 drugs when mixed race required	In all other clinical studies	In U.S. population under age 18
African American	22	6	15
Asian	1	1	3
Caucasian	54	70	69
Hispanic	17	4	17
Other or unknown	6	19	NA
Total	100	100	104 ^a

Sources: Department of Commerce and FDA.

Notes: GAO analysis of 23 new drug applications (NDAs) or supplemental new drug applications (sNDAs) and FDA medical officer reviews and Department of Commerce, Bureau of the Census, Census 2000 Summary File 1, “Total Population by Age and Sex for the United States: 2000.”

NA means not applicable.

^aIndividual entries do not sum to 100 percent because the Department of Commerce, in collecting U.S. Census data, permitted individuals to report that they belonged to multiple race groups. Consequently, the total of all race groups exceeds the population total.

FDA Written Requests Issued since BPCA Require Sponsors to Increase Minority Representation for Certain Drugs

For some written requests issued since BPCA took effect, FDA required sponsors to increase the participation of minority children. Specifically, 4 of the 22 written requests for such studies directed sponsors to increase the proportion of minority children participants or to analyze the effects of race and ethnicity. In 11 of the 22 requests, FDA directed drug sponsors to report the representation of pediatric patients of ethnic and racial minority groups when submitting final study results, but did not request that sponsors include a particular proportion of minority children or analyze the effects of race and ethnicity. The remaining 7 written requests made no mention of race or ethnicity.

FDA's four study requests that directed sponsors to increase the proportion of minority children participants or to analyze the effects of race or ethnicity took varied approaches. One written request by FDA required that the sponsor include a mixture of African American and non-African American patients for a study of a drug used to treat hypertension. Two other requests, for diabetes drugs, required the study sponsors to ensure that 50 percent of the study populations were composed of African American, Native American, and Hispanic patients because of a greater prevalence of diabetes in these groups. In the fourth written request, for a drug used to prevent bone loss, FDA required that the study sponsor examine potential demographic covariates, such as race.

Drugs of Importance to Minority Children Are Being Studied in Response to Pediatric Exclusivity Provision Requests

Some drugs that may be used to treat diseases or conditions that disproportionately affect children of racial and ethnic minority groups are being studied under the pediatric exclusivity provision. In response to FDA written requests, drug sponsors are conducting or have completed pediatric studies on drugs that might be used to treat hypertension, type II diabetes, sickle cell anemia, and other conditions that disproportionately affect minorities.

From January 4, 2002, through March 6, 2003, FDA granted exclusive marketing rights or issued written requests for studies of 10 drugs that might be used to treat diseases or conditions that disproportionately affect minority children. Specifically, 4 of the 23 drugs for which FDA granted additional exclusive marketing rights might be used to treat diseases or conditions that are more prevalent in minorities, such as asthma and hypertension (see table 3). In addition, 6 of the 22 written requests for new studies that FDA issued to drug manufacturers during this period also included treatments for diseases or conditions disproportionately affecting minorities, such as type II diabetes, hypertension, sickle cell anemia, HIV, and hepatitis B.

Table 3: Estimated Prevalence of Diseases or Conditions in Minorities That May Be Treated by Drugs for Which FDA Issued Written Requests or Granted Exclusive Marketing Rights, January 4, 2002, through March 6, 2003

Disease/condition	Estimated prevalence among selected racial and ethnic groups	Drug(s)	Study status
Asthma	Asthma prevalence of 82/1,000 in African American children compared to 76/1,000 in Hispanic and 65/1,000 in Caucasian children. ^a	Budesonide	Exclusive rights granted.
Diabetes mellitus (type II diabetes)	National age-adjusted rates for all types of diabetes show that it is more frequent in African Americans and Hispanics than Caucasians. ^b In addition, one study found that over 70 percent of type II diabetes cases among children were in African Americans. ^c	Metformin Pioglitazone	Written request issued. Written request issued.
Hepatitis B	Age-adjusted rates of Hepatitis B in African Americans are more than 2.5 times greater than in Hispanics and 4.5 times greater than in Caucasians. ^d	Adefovir	Written request issued.
HIV infection and AIDS	Prevalence rate of 1.4/100,000 African American children was 7 times greater than in Hispanics and 14 times greater than in Caucasians and Asians. ^e	Tipranavir	Written request issued.
Hypertension	A study found that a sample of African American children in California had higher blood pressure than Caucasian children. ^f	Losartan Quinapril Fosinopril Metoprolol	Exclusive rights granted. Exclusive rights granted. Exclusive rights granted. Written request issued.
Sickle cell anemia	Occurs in 1 out of every 700 African American births, 1 of every 46,622 Hispanic births, and 1 of every 158,127 Caucasian births. ^g	Hydroxyurea	Written request issued.

Sources: FDA and publications identified below.

^aL.J. Akinbami and K.C. Schoendorf, "Trends in Childhood Asthma Prevalence, Health Care Utilization, and Mortality," *Pediatrics*, vol. 110, no. 2 (2002), 315-322.

^bAge-adjusted rates from the National Center for Chronic Disease, Diabetes Public Health Resources, available at <http://www.cdc.gov/diabetes/statistics/index.htm#prevalence> (downloaded Apr. 11, 2003).

^cA study in Arkansas found that 74 percent of type II diabetes in children was in African Americans. C. Scott and others, "Characteristics of Youth-onset Noninsulin-dependent Diabetes Mellitus and Insulin-dependent Diabetes Mellitus at Diagnosis," *Pediatrics*, vol. 100, no.1 (1997), 84-91.

^dAge-adjusted rates from the National Health and Nutrition Examination Survey III (1988-1994) in G.M. McQuillan and others, "Prevalence of Hepatitis B Virus Infection in the United States: The National Health And Nutrition Examination Surveys, 1976 through 1994," *American Journal of Public Health*, vol. 89, no. 1 (1999), 14-18.

^eBased on a total of 175 AIDS cases reported in children aged 13 and younger in December 2001, from National Center for HIV, STD and TB Prevention, <http://www.cdc.gov/hiv/stats/hasr1302/table18.htm#tab18> (downloaded Apr. 11, 2003).

^fM.L. Cruz and others, "Insulin Sensitivity and Blood Pressure in Black and White Children," *Hypertension*, vol. 40, no. 1 (2002), 18-22.

^gA. Ashley-Koch, Q. Yang, and R.S. Olney, "Sickle Hemoglobin (Hb S) Allele and Sickle Cell Disease: A HuGE Review," *American Journal of Epidemiology*, vol. 151, no. 9 (2000), 839-845.

FDA Monitoring of Data on Minority Representation Needs Improvement

FDA does not have a system in place to serve as a single source of data to allow the agency to efficiently determine the extent of minority enrollment in drug studies under the pediatric exclusivity provision. Further, we found that some study reports submitted to FDA from drug sponsors did not specify the race and ethnicity of study participants. For example, in the completed studies for the 23 drugs granted additional exclusive marketing rights that we examined, the race or ethnicity of 86 percent of study participants was identified, but study sponsors did not specify the race or ethnicity of 960 children, or 14 percent of the studies' populations. Recently, FDA issued draft guidance to improve drug sponsors' reporting of racial and ethnic minority representation data, and FDA is planning to develop a database to monitor demographic variables in drug trials across the agency.

There Is No Single Source of Data about Minority Representation

There is no single data source at FDA to allow the agency to tabulate the overall numbers of racial and ethnic minorities in clinical studies. For example, to quantify the participation of racial and ethnic groups in studies for the 23 drugs granted additional exclusive marketing rights since January 2002, FDA had to extract and tally race data from about 50 separate final study reports that included nearly 7,000 children.

Reporting of Minority Representation Data Is Not Standardized

Final study results submitted to FDA from sponsors do not always fully describe the race and ethnicity of children who participated in clinical drug studies. In addition, FDA has not established uniform definitions for reporting racial and ethnic minorities in drug studies. In reviewing the study results for the 23 drugs granted additional exclusive marketing rights from January 4, 2002, through March 6, 2003, we found wide variation in how study sponsors presented and defined data regarding minority participation. Study sponsors reported minority representation according to non-standard definitions, which were often ambiguous. For example, one study classified its 200 participants as "mostly Caucasian" and included no further data on the remaining population. Similarly, in studies included in three applications involving more than 1,500 children, sponsors only identified the number of Caucasian patients and did not identify the racial or ethnic groups of non-Caucasian children. Across all studies for drugs granted exclusive marketing rights from January 4, 2002, through March 6, 2003, the race or ethnicity of 960 children, or about 14 percent of all study participants, was unknown. Eighty-six percent of study participants were identified by race or ethnicity. Further, we could identify the specific race or ethnicity for only 30 of the 268 subjects classified as "other" in study reports. FDA officials told us that they do not

know which populations are included in the “other” category and that it likely includes children whose race was not determined.

FDA Is Taking Steps to Improve Data Management

Recently, FDA has begun to take steps to address data management issues. In January 2003, FDA issued draft guidance for industry¹⁷ recommending that study sponsors collect and report racial and ethnic representation using definitions developed by the Office of Management and Budget, which HHS adopted for use in HHS funded and sponsored data collection and reporting systems.¹⁸ FDA stated in its draft guidance that using uniform categories would enhance the consistency and comparability of data across studies and other HHS agencies, as well as promote the early identification of differences in physiological response among racial and ethnic groups. FDA’s draft guidance recommended that sponsors collect race and ethnicity data for clinical study participants using five racial groups (African American/Black, American Indian/Alaska Native, Asian, and Native Hawaiian/Other Pacific Islander, and White) and two ethnic groups (Hispanic/Latino and not Hispanic/Latino). However, FDA guidance is not legally binding for either FDA or the sponsor.

In addition, FDA has started to develop an agencywide system called the Demographic Information and Data Repository (DIDR) to electronically manage information regarding demographic characteristics of clinical trial participants, including age, sex, and race.¹⁹ DIDR is part of FDA’s response to a congressional report requesting that FDA monitor the representation

¹⁷See Food and Drug Administration, *A Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials* (Rockville, Md.: January 2003) <http://www.fda.gov/cber/gdlns/racethclin.htm> (downloaded Jan. 28, 2003).

¹⁸See Department of Health and Human Services, *A Policy Statement on Inclusion of Race and Ethnicity in DHHS Data Collection Activities* (Washington, D.C.: October 1997).

¹⁹In a prior report, we recommended that FDA develop management tools to ensure that the collection, presentation, and analyses of data related to sex differences are addressed and monitored. See U.S. General Accounting Office, *Women’s Health: Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement*, [GAO-01-754](#) (Washington, D.C.: July 6, 2001).

of women in clinical studies.²⁰ The conference report accompanying FDA's 2002 appropriations identified a \$500,000 increase in funding for FDA's Office of Women's Health to begin work on this system. FDA officials told us that it would be several years before the system is operational.

Conclusions

To have optimal effectiveness for all children, a drug should be tested in clinical studies that include pediatric patients representing the full range of population groups likely to receive the drug once it is marketed. In addition to age, genetic factors related to race and ethnicity may play important roles in the variability of patients' responses to a drug. Pediatric clinical drug studies with sufficient representation of minority groups are necessary to detect the presence or absence of differences in responses to certain drugs. The changes under BPCA to the pediatric exclusivity provision require that FDA take into account the adequate representation of children of racial and ethnic minorities in written requests for drug studies. However, it is too early to tell whether FDA's written requests issued since enactment of BPCA will result in better reporting or a broader mix of participants. Currently, FDA is unable to accurately determine whether and to what extent minority groups are accounted for in final study results because it does not require sponsors to use uniform definitions. Though FDA's draft guidance on standard definitions for reporting race and ethnicity is helpful, sponsors will not be obligated to use these categories to identify study participants unless FDA requests that they do so. The standardized collection of demographic data, such as race and ethnicity, would help ensure that FDA's forthcoming DIDR will have the required data needed to evaluate the risks and benefits of a drug in specific demographic groups.

Recommendation for Executive Action

To help the agency more efficiently monitor the participation of children of racial and ethnic groups in studies for additional exclusive marketing rights, we recommend that the Commissioner of FDA specify in written requests that study sponsors must use the racial and ethnic categories

²⁰The conference report for the 2002 FDA appropriations act expressed concern that FDA has paid insufficient attention to gender-based research and directed the agency to develop an agencywide database focused on women's health activities to include demographic data on clinical trials. See H.R. Conf. Rep. No. 107-275, at 82-83 (2001) (accompanying Pub. L. No. 107-76, making appropriations for Agriculture, Rural Development, Food and Drug Administration, and Related Agencies programs for the Fiscal Year Ending September 30, 2002, and for other purposes).

described in FDA's January 2003 draft guidance to identify study participants in their reports to the agency. FDA can refuse to grant 6 months of additional exclusive marketing rights under the pediatric exclusivity provision for sponsors that do not fairly respond to FDA's written requests.

Agency Comments and Our Evaluation

FDA comments on a draft of this report reaffirmed the importance of clinical studies of drugs used to treat children. FDA agreed that the agency needed to improve the efficiency of its system for tracking demographic information about study participants. FDA also agreed with our recommendation and reported that it has already begun to implement it.

FDA raised concerns about three aspects of our draft report. First, FDA was critical of our comparison of the proportions of minority children study participants to the proportions of minority children in the population. FDA commented that it would have been more appropriate for us to compare the proportions of minority children in clinical drug studies with the proportions of minority children with the specific condition each drug is intended to treat. We agree that such a comparison would have been useful, but both we and FDA found that the information needed for such comparisons—the racial and ethnic group distributions of children with many of the specific conditions treated by the drugs studied for additional exclusive marketing rights—was not available. Further, FDA has previously used the methodology we employed in its analyses of adult study participants.²¹

Second, FDA was concerned about what it regards as the implications of our finding that the proportions of minority children in pediatric studies requested by FDA before the passage of BPCA were less than their proportions in the general population. FDA incorrectly suggested that we advocate that “the percentage of children in each clinical drug trial would or should track the percentage of children in the general population.” Our report does not make any recommendations about the preferred study populations for any clinical drug trial. Further, we did not disagree with FDA's current policy requiring larger proportions of children from racial and ethnic minority groups when a studied drug treats a condition that

²¹For example, see B. Evelyn and others, *Participation of Racial/Ethnic Groups in Clinical Trials and Race-Related Labeling: A Review of New Molecular Entities Approved 1995-1999*.

disproportionately affects minorities or when it is known from adult studies that the effects of a drug may be different in persons from different racial or ethnic groups.

Third, FDA noted that the race or ethnicity of a high percentage of study participants was identified even before BPCA was enacted. Our findings agree with that assessment—we reported that the race or ethnicity of study participants was identified for 86 percent of study participants—but we believe that FDA should have been able to identify the race or ethnicity of every study participant.

FDA's written comments are reprinted in appendix III of this report. FDA also provided technical comments, which we considered and incorporated where appropriate.

We are sending this report to the Commissioner of FDA and to other interested persons. We will also provide copies to others upon request. In addition, the report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staffs have any questions about this report, please contact me at (202) 512-7119. Another contact and major contributors to this report are listed in appendix IV.

A handwritten signature in black ink, reading "Janet Heinrich". The signature is written in a cursive, flowing style.

Janet Heinrich
Director, Health Care—Public Health Issues

Appendix I: Scope and Methodology

To assess the extent to which children of racial and ethnic groups are represented in clinical studies for drugs granted exclusive marketing rights, we reviewed data for the 23 drugs that were granted exclusive marketing rights from January 4, 2002, through March 6, 2003. For these 23 drugs, we determined the total number of children in four racial and ethnic groups enrolled in each study from Food and Drug Administration summary documents, and new drug applications (NDA) or supplemental new drug applications (sNDA) submitted to FDA for this time period. We collected clinical study participation data for three racial groups (African American, Asian, and Caucasian) and one ethnic group (Hispanic) because drug sponsors commonly used these categories.¹ However, the clinical studies included in the NDAs or sNDAs submitted during this period were conducted before the effective date for the Best Pharmaceuticals for Children Act of 2002 because the time lag between when FDA issues a written request for a pediatric study and when sponsors submit final study results ranged from 1 to 4 years. To assess the extent to which FDA required drug sponsors to take into account the adequate representation of children of racial and ethnic groups in clinical studies for drugs for which written requests have been issued since BPCA took effect, we reviewed the 22 written requests issued for pediatric drug studies by FDA from January 4, 2002, through March 6, 2003.

To determine whether drugs used to treat conditions or diseases disproportionately affecting minorities are being studied under the pediatric exclusivity provision, we obtained data on the prevalence of selected diseases or conditions that disproportionately affect minorities and examined the list of drugs for which FDA has either granted exclusive marketing rights or issued study requests from January 4, 2002, through March 6, 2003, to determine if any of these drugs may be used to treat these diseases or conditions. We compiled data on the estimated prevalence of the diseases and conditions by race and ethnicity from the National Centers for Health Statistics, National Center of HIV, STD, and Tuberculosis Prevention, and research in scientific journals reporting the prevalence of these diseases and conditions in minority children. We interviewed National Institutes of Health officials, pharmacology experts, and pediatric clinicians, including members of the American Academy of

¹We classified as “other” any study participants that were specified by some other race or ethnicity. If no race was indicated, we classified those participants as “unknown.” For example, one study classified its 200 participants as “mostly Caucasian” and included no further data on the remaining population. We classified the entire study population as unknown.

Pediatrics and the Pharmaceutical Research and Manufacturers of America to gain their perspectives on the representation of minorities in drug studies and the study of drugs of importance to these populations.

To evaluate FDA's management of pediatric clinical study data on minority representation and its guidance to sponsors on reporting such data, we reviewed FDA's policies, guidance, and rules for inclusion and reporting of minority representation in drug studies. We interviewed FDA officials within the Office of Counter-Terrorism and Pediatric Drug Development to determine how they interpret and implement these policies for the pediatric exclusivity program. We spoke with officials in the Office of Women's Health who were responsible for establishing a database to monitor demographic variables to determine how an agencywide demographic database might affect the monitoring of minority participation in drug studies. We also reviewed FDA's response to a congressional request to develop an agencywide demographic database.²

We conducted our work from October 2002 through September 2003 in accordance with generally accepted government auditing standards.

²"Response to Congressional Request on FY 2002 Funding to Develop an Agency-wide Database Focused on Women's Health Activities," Conference Action, Pub. L. No. 107-76, FDA, June 2002.

Appendix II: The Number of Children by Racial and Ethnic Group in Studies for Drugs Granted Exclusive Marketing Rights

We obtained the number of children by race or ethnic group who participated in the clinical drug studies for the 23 NDAs or sNDAs for exclusive marketing rights in our sample by reviewing the portions of final study reports that provide information on the demographic representation in the study. Table 4 represents the number of children of racial and ethnic groups, by drug class, in clinical studies for drugs granted exclusive marketing rights from January 4, 2002, through March 6, 2003. It is important to recognize that the FDA written requests outlining the study design for the 23 NDAs or sNDAs that we examined preceded the passage of BPCA on January 4, 2002. The time between when FDA issued written requests for pediatric studies and sponsors conducted and submitted final study results for FDA review and approval ranged from 1 to 4 years.

**Appendix II: The Number of Children by
Racial and Ethnic Group in Studies for Drugs
Granted Exclusive Marketing Rights**

Table 4: Children of Racial and Ethnic Groups, by Drug Class, in Clinical Studies for Drugs Granted Exclusive Marketing Rights, January 4, 2002, through March 6, 2003

Drug	Indication	African American	Asian	Caucasian	Hispanic	Other	Unknown	Total
A	Allergic Rhinitis	6	0	46	0	5	398	455
B	Allergic Rhinitis	47	2	146	0	24	0	219
C	Allergic Rhinitis	51	0	222	0	33	0	306
D	Cancer	0	0	30	0	0	45	75
E	Cancer	13	4	151	10	7	0	185
F	Cancer	—	—	26	—	—	112	138
G	Cancer	1	0	12	6	5	0	24
H	Cardiovascular	3	3	172	0	9	0	187
I	Cardiovascular	0	0	311	6	2	0	319
J	Cardiovascular	2	6	203	0	3	24	238
K	Hypertension ^a	52	5	152	35	9	0	253
L	Hypertension ^a	50	3	54	21	8	0	136
M	Hypertension ^a	33	0	125	48	21	0	227
N	Ophthalmologic	3	2	89	0	40	0	134
O	Ophthalmologic	3	2	89	0	40	0	134
P	Psychiatric	16	49	265	34	12	0	376
Q	Psychiatric	6	0	1,101	0	4	249	1,360
R	Psychiatric	52	4	391	48	23	0	518
S	Psychiatric	0	0	367	0	0	89	456
T	Psychiatric	86	8	583	72	19	43	811
U	Other	18	1	86	26	1	0	132
V	Other	5	2	15	5	1	0	28
W	Other	41	3	147	44	6	0	241
Total		488	94	4,783	355	272	960	6952
Percentage of children in clinical studies		7	1	69	5	4	14	100
Percentage of U.S. population under age 18		15	3	69	17	NA	NA	104 ^b

Sources: Department of Commerce and FDA.

Notes: GAO analysis of 23 NDAs or sNDAs and FDA medical officer reviews; and U.S. Bureau of Census, Census 2000 Summary File 1, "Total Population by Age and Sex for the United States: 2000."

NA means not applicable.

^aDrugs are those for which FDA required greater minority representation.

^bIndividual entries do not sum to 100 percent because in collecting U.S. Census data, the Department of Commerce permitted individuals to report that they belonged to multiple race groups. Consequently, the total of all race groups will exceed the total population.

Appendix III: Comments from the Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

September 5, 2003

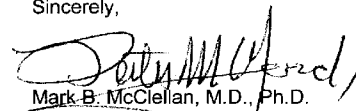
Janet Heinrich
Director, Health Care-Public Health
United States General Accounting Office
441 G Street, NW
Washington, DC 20548

Dear Ms. Heinrich:

Please find the enclosed comments from the Food and Drug Administration on the GAO draft report entitled, PEDIATRIC DRUG RESEARCH: Food and Drug Administration Should More Efficiently Monitor Inclusion of Minority Children (GAO-03-950). The Agency provided extensive technical comments directly to your staff.

We appreciate the opportunity to review and comment on this draft report before its publication as well as the opportunity to work with your staff in developing this report.

Sincerely,


Mark B. McClellan, M.D., Ph.D.
Commissioner of Food and Drugs

Enclosure

General Comments By The Department of Health And Human Services' Food and Drug Administration on GAO'S Draft Report, *PEDIATRIC DRUG RESEARCH: Food and Drug Administration Should More Efficiently Monitor Inclusion of Minority Children* (GAO-03-950)

FDA appreciates the opportunity to comment on GAO's draft report that focuses additional attention on the area of needed research of drugs used to treat children. Our general comments are as follows:

General Comments

1. **Support of Clinical Studies of Pharmaceuticals in Children:** FDA appreciates and concurs fully with the interest of GAO and the Congress in assuring that all of the children of the United States benefit appropriately from the significant advances taking place in medicine. For children to benefit from these advances, practitioners and parents need to know when and how best to use these medicines in the different stages of childhood. To do this, well-designed, ethically conducted, clinical trials are needed to give the community the information required to make appropriate health care decisions. For too long, practitioners and parents have had to treat children without the type of safety, efficacy, and dosing information in children that are routinely available for adults. FDAMA and BPCA have gone a long way in rectifying this situation. To fully meet our obligations to our children in this respect, FDA and HHS fully support the bipartisan legislation now before Congress regarding pediatric studies of pharmaceuticals.
2. **Agreement on Need for More Efficient Tracking System:** FDA currently monitors the inclusion of racial and ethnic minorities in pediatric studies and has been systematically compiling this information since January 4, 2002, when the BPCA was signed into law. However, FDA agrees with the GAO that the current system used to track the demographic information on study participants needs to be made more efficient and less resource intensive. FDA is in the process of developing improved knowledge management capabilities to track sub-population participation in clinical trials and to track variability in response, both in terms of efficacy and safety, to medications by people of different racial and ethnic groups.
3. **Doing What is Scientifically Rational and Ethically Appropriate:** Two of the three determinations Congress directed the GAO to make under the BPCA are: 1) to determine the extent to which children of ethnic and racial minorities are adequately represented in studies, and 2) to determine whether drugs used to address diseases that disproportionately affect racial and ethnic minorities are being studied for their safety and effectiveness. FDA believes these two issues are inherently interconnected. In several areas throughout the document GAO comments on the "smaller proportion" of minorities in the studies when compared with the proportion of children from racial and ethnic minority groups in the U.S. population. While this might be factually correct, FDA questions whether this is the metric by which one should determine if children in minority ethnic and racial populations are "adequately

benefiting” from this legislation. FDA believes there is no scientific or public health rationale to expect or mandate that the percentage of children in EACH of these trials would or should track the percentage of children in the general population.

One might infer from the GAO report that GAO advocates that sponsors should enroll children of racial or ethnic minorities in these studies in the same proportion seen in the general population. Using the general population as the comparator is not the correct metric to assess minority children’s “adequate” representation in the particular diseases being studied.

For example, it is not scientifically appropriate to enroll a majority percentage of Caucasian subjects in trials for diseases that predominately affect African Americans (e.g., sickle cell disease). A trial that enrolls predominately African American patients for this disease would be scientifically appropriate, even if other minority groups were not included. In contrast, it would be equally inappropriate to enroll a specified percentage of African Americans in a trial for a disease that is prevalent in Ashkenazi Jews of eastern European descent, such as Tay-Sachs disease.

An accurate assessment of the extent to which children of ethnic and racial minorities are adequately represented in studies cannot be obtained by using averages referencing the general population. To effectively assess whether these children are adequately represented in studies, the more appropriate comparison would be to the number of minority children in the population with the specific disease being studied.

In addition, there is a lot FDA already knows about the approved drugs being studied for pediatric indications that guide decisions about drug effect based on race and ethnicity, and even more that we are learning through pharmacogenomics. Race and ethnicity may serve as a crude predictor of disease and drug response in medical practice because we know that some genes and propensities can cluster in this way. There are however times where race or ethnicity is not an accurate means of determining genetic factors that may influence a drug’s activity in individuals. The GAO report does not fully address this fundamental medical fact, nor does it acknowledge that there is a lot already known from studies in adults about how drugs affect minority groups, and that this knowledge is used to make decisions about the inclusion of minority children in studies for pediatric exclusivity in ways that limit the overall number of children that are exposed to experimental drugs in clinical trials.

FDA believes it has ensured representation of racial and ethnic groups in diseases where these groups are disproportionately affected by the disease. FDA does ask for increased representation of ethnic and racial minority populations in studies of treatments for these diseases where, based on scientific knowledge and, often, adult experience with the drug, specific populations are disproportionately affected either by the disease or by safety concerns with the drug. However, FDA believes it is scientifically unjustified to specify that specific percentages of certain ethnic or racial groups be included in studies when the disease being treated or safety concerns with

the test product do not affect any particular ethnic or racial population differently from the general population.

FDA believes that the effort to enroll specific populations in a trial needs to be a careful decision made on a drug-by-drug basis, and should be based on current knowledge of the drug and/or disease. This practice should be preserved because it constitutes good science, good medicine, and good ethics.

4. High Level of Reporting Even Before BCPA Enacted: FDA would like to point out that sometimes the summary of the report fails to reflect much of the substance of the more detailed text, especially the fact that all of the drug studies that GAO evaluated were based on Written Requests issued prior to the passage of the BCPA. GAO does note, however, that 86 percent of study participants were identified by race or ethnicity in these studies even before BCPA was enacted. FDA notes that in the studies of the 23 drugs reviewed by, FDA calculated that 90 percent of study participants were identified by race or ethnicity, and that the race or ethnicity of only 10 percent of study participants was unknown, even though this was not yet a requirement. This was based on a total number of 7002 participants, of which race or ethnicity was not identified for 723 participants.

5. Comment on GAO Recommendation: GAO recommended that FDA require drug sponsors to use the standard racial and ethnic group definitions described in FDA's January 2003 draft guidance to identify study participants. FDA's guidance documents do not establish legally enforceable rights or responsibilities and do not bind the public or FDA. However, if FDA believes that the use of the categories in reporting pediatric study results provides information necessary to adequately label the drug for pediatric use, it can, in the written request or in the written agreement, describe the racial and ethnic categories the sponsor must use in data collection and presentation to the agency.

In fact, as a result of the mandate in the BCPA to "take into account adequate representation of children of ethnic and racial minorities," FDA began including a standard statement in all written requests issued after April 2002. The statement reads as follows: "In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities." After the issuance of draft guidance for industry, *Collection of Race and Ethnicity Data in Clinical Trials*, and as of August 2003 FDA began including the following statement in all written requests: "In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study (s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native American, Native Hawaiian or Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino."

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Martin T. Gahart, (202) 512-3596

Acknowledgments

Gloria E. Taylor, Sharif Idris, George Bogart, and Elizabeth T. Morrison also made major contributions to this report.

GAO's Mission

The General Accounting Office, the audit, evaluation and investigative arm of Congress, exists to support Congress in meeting its constitutional responsibilities and to help improve the performance and accountability of the federal government for the American people. GAO examines the use of public funds; evaluates federal programs and policies; and provides analyses, recommendations, and other assistance to help Congress make informed oversight, policy, and funding decisions. GAO's commitment to good government is reflected in its core values of accountability, integrity, and reliability.

Obtaining Copies of GAO Reports and Testimony

The fastest and easiest way to obtain copies of GAO documents at no cost is through the Internet. GAO's Web site (www.gao.gov) contains abstracts and full-text files of current reports and testimony and an expanding archive of older products. The Web site features a search engine to help you locate documents using key words and phrases. You can print these documents in their entirety, including charts and other graphics.

Each day, GAO issues a list of newly released reports, testimony, and correspondence. GAO posts this list, known as "Today's Reports," on its Web site daily. The list contains links to the full-text document files. To have GAO e-mail this list to you every afternoon, go to www.gao.gov and select "Subscribe to e-mail alerts" under the "Order GAO Products" heading.

Order by Mail or Phone

The first copy of each printed report is free. Additional copies are \$2 each. A check or money order should be made out to the Superintendent of Documents. GAO also accepts VISA and Mastercard. Orders for 100 or more copies mailed to a single address are discounted 25 percent. Orders should be sent to:

U.S. General Accounting Office
441 G Street NW, Room LM
Washington, D.C. 20548

To order by Phone: Voice: (202) 512-6000
 TDD: (202) 512-2537
 Fax: (202) 512-6061

To Report Fraud, Waste, and Abuse in Federal Programs

Contact:

Web site: www.gao.gov/fraudnet/fraudnet.htm

E-mail: fraudnet@gao.gov

Automated answering system: (800) 424-5454 or (202) 512-7470

Public Affairs

Jeff Nelligan, Managing Director, NelliganJ@gao.gov (202) 512-4800
U.S. General Accounting Office, 441 G Street NW, Room 7149
Washington, D.C. 20548