April 21, 2006

Dr. Andrew von Eschenbach
Acting Commission
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. von Eschenbach,

On April 26, 2006, the Food and Drug Administration's Cardiovascular and Renal Drugs Advisory Committee will consider the FDA's draft guidance for labeling antihypertensive drugs. Earlier this month, the Center for Drug Evaluation Research posted conflict of interest waivers for nine of the physician/scientists who will serve on this committee. While it is possible that additional scientists will be added to 12 people listed for this panel (if the FDA follows its usual custom, the full roster will not be released until the day of the meeting), it is already clear that this conflicted and unbalanced panel cannot give a full and fair hearing to the many complicated and contentious issues surrounding the appropriate labeling of antihypertensive drugs. We recommend that you postpone the meeting to allow time for the CDER staff to construct a panel comprised of experts, avoiding conflicts of interest to the greatest extent possible, who would reflect the full range of views on this topic. This balance is required under the Federal Advisory Committee Act.

Our concerns about the FDA's proposed "Guidance for Industry: Labeling for Outcome Claims for Drugs to Treat Hypertension" are threefold and underscore our protest against the makeup of this panel. First, the draft Guidance ignores the National Institute of Health's Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" (JNC 7), especially the primary role its recommendations give to lifestyle modifications. Second, the draft Guidance misrepresents the findings of JNC 7 and the government-funded Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), both of which were conducted at great taxpayer expense and, if followed, could save taxpayers billions of dollars through the recently enacted Part D of Medicare (the senior citizen prescription drug benefit), as well as Medicaid and other government programs. And third, the labeling provision of the draft Guidance permits the use of claims that have not been submitted to nor reviewed by the FDA, which, in combination with the previously mentioned flaws in the Guidance, could result in less than optimal physician prescribing patterns and less efficacious health care outcomes.

As the draft Guidance points out, labels on the more than 60 drugs in seven or more classes that lower blood pressure are "mute on the clinical benefits expected from blood pressure reduction." The FDA is considering this Guidance because it feels it would be in the best interest of physicians and patients to spell out those benefits "to encourage appropriate use of these drugs." But as the JNC 7 report points out:

Adoption of healthy lifestyles by all persons is critical for the prevention of high blood pressure and is an indispensable part of the management of those with hypertension. Major lifestyle modifications shown to lower blood pressure include weight reduction in those individuals who are overweight or obese, adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan, which is rich in potassium and calcium, dietary sodium reduction, physical activity, and moderation of alcohol consumption.[1]

Given that 65 million Americans suffer from hypertension and over half of them are already on some form of medication (at a direct cost of over $15 billion a year), the draft Guidance to industry for labeling antihypertensive drugs represents a golden opportunity for the FDA to begin educating the public about other effective ways of treating this leading cause of heart disease. Research has shown that non-drug lifestyle modifications can be as effective or almost as effective as pharmaceuticals, and those modifications are virtually free in terms of economic costs and side effects. And even when lifestyle modifications don't solve a health problem, they often allow lower doses of pharmaceuticals to be used.

The FDA could help improve public health and reduce drug costs by ensuring that patients taking (and doctors prescribing) pharmaceuticals to treat hypertension are reminded that lifestyle changes could reduce or eliminate the need for the drugs. We propose that the FDA require a "green box" on the label and patient package inserts explaining the lifestyle changes that would reduce the need for the drug. For example:

Important Notice

Please talk to your doctor about lifestyle changes that might enable you to use lower amounts of this medication that is used to treat high blood pressure.

Weight loss, diets rich in vegetables and fruits, and diets low in salt are simple ways of treating high blood pressure. Lowering your blood pressure through such changes could save you the cost and side effects of this (and possibly other) medications.

The second issue involves the draft Guidance's claim that:

[1] "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," National Institutes of Health, National Heart, Lung, and Blood Institute, December 2003, p. 7.

> *Numerous single studies (e.g. ALLHAT) and pooled analyses have tested whether drugs given to achieve the same blood pressure goals have the same clinical benefits. To date such studies have not distinguished the effects of different treatments on* **the** *(emphasis added) major hypertension-related outcomes (strokes, myocardial infarction, and cardiovascular mortality).*

By limiting the primary endpoints to strokes, myocardial infarction, and cardiovascular mortality, this statement inaccurately represents the findings of ALLHAT and JNC 7. It leaves out the higher rates of congestive heart failure suffered by patients who take calcium channel blockers, one of the more popular and most expensive classes of antihypertensive drugs. The JNC 7 specifically recommends AGAINST using calcium channel blockers as first-line therapy in patients with congestive heart failure. In the new guidance, heart failure should be considered a major cause of morbidity and mortality, and the guidance should distinguish between drug classes in their effectiveness in treating this condition.

Finally, the draft Guidance's recommendation for labeling includes "many antihypertensive agents have additional effects – on angina, heart failure, or diabetic kidney disease, for example – and these considerations may guide selection of therapy." The labeling guidance further allows companies to include "a summary of placebo- or active-controlled trials showing the specific drug's outcome benefits in hypertension."

While this could be a positive thing if applied to agents that are less effective in reducing heart failure or less effective when used in certain subgroups like African-Americans, it opens the door for labeling abuse. The medical literature is filled with studies that measured the antihypertensive effects of specific agents on patient subgroups that have particular co-morbidities. While those studies may show the drugs are effective in reducing the co-morbidities as well as reducing high blood pressure, they are rarely tested against other agents to see if they were any more or less effective in reducing those co-morbidities. These trials, which are usually industry-funded and sometimes referred to as "seeding trials," are a way to broaden the use of a particular drug within a crowded field where there are other, often cheaper alternatives that may well be just as effective or more effective – not just against high blood pressure and its primary effects but the co-morbidity. To allow these trials to be included on labels (and thus fair game for mention to physicians by drug industry marketing representatives) would put the FDA imprimatur on some of the most abusive sales tactics in today's pharmaceutical marketplace. Combined with the earlier part of the Guidance that did not distinguish between drugs on a primary outcome like congestive heart failure, the net effect of this Guidance could be a huge setback for public health and the public purse.

Several of the physicians who will play key roles in the committee's deliberations have conflicts of interest that relate directly to the labeling discussion. For instance, committee chair William R. Hiatt, a professor of medicine at the University of Colorado, has conducted research for Bayer Pharmaceutical showing the benefits of controlling blood pressure in diabetics with peripheral arterial disease, a study typical of the seeding

trials discussed earlier. On the other hand, none of the 11 physicians associated with the National High Blood Pressure Education Program Coordinating Committee that wrote JNC 7 nor the physicians who conducted the ALLHAT trial was asked to serve on the committee.

In your testimony before the House Appropriations subcommittee earlier this year, you said that the FDA should not be prohibited from including scientists with conflicts of interest from serving on FDA advisory panels because they are frequently the best minds in a particular field. We do not believe that to be the case. We stand ready to help the FDA find highly qualified physicians and scientists without ties to industry to serve on this panel.

Just as importantly, the Federal Advisory Committee Act requires that outside panels be comprised of scientists that reflect a careful balancing of diverse points of view. This refers not only to the expertise needed to carry out the mission of the committee, but to the scientists' opinions and perspectives, especially when there is controversy in a field.

Anyone even remotely familiar with the field of antihypertension research can see that this panel is extraordinarily imbalanced. It does not include researchers familiar with the benefits of dietary and lifestyle changes in lowering blood pressure and how those strategies can be coordinated with drug therapy. It does not include any scientists who were involved in the conduct of the most far-reaching trial of antihypertensive medicines in recent American history. And it does not include any scientists involved in writing the government's own clinical practice guidelines for this crucial public health field. Indeed, it is fair to conclude from the proposed makeup of this panel that the FDA is biased against choosing scientists without conflicts of interest or who have engaged in government-funded research (even when they have also conducted industry-funded research).

We think the public's faith in the integrity of the FDA's scientific advisory process will best be served at this point if you step in and insist that CDER correct the flaws in this committee before proceeding to consider the draft antihypertensive drugs labeling Guidance.

Sincerely,