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Food and Drug Administration
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Comments on Assessment of Pressor Effects of Drugs Guidance for Industry (Draft) Docket No. FDA–2018–D–1636

Public Citizen, a consumer organization with more than 500,000 members and supporters nationwide, along with Robert P. Blankfield, M.D., M.S and Sonal Singh, M.D., M.P.H., submits these comments in response to the request for comment on the Food and Drug Administration's (FDA's) draft guidance titled "Assessment of Pressor Effects of Drugs: Guidance for Industry."

The draft guidance is laudable in concept. Nonetheless, the guidance, as proposed, is vague and will thereby fail to effectively identify the cardiovascular risk of drugs that have hypertensive effects.

Before discussing our proposed revisions to the draft guidance, we first would like to express our strong support for the agency's recommendation to use ambulatory blood pressure monitoring (ABPM) during premarket clinical trials for drugs. We agree with the five detailed reasons the agency gave for why ABPM has significant advantages over cuff blood pressure measurements.

Limitations of the draft guidance

For drugs that are intended for long-term use, the draft guidance states that "small, sustained increases in blood pressure (2 to 3 millimeters of mercury [mm Hg]) chronically" would be expected to correlate with a long-term increased risk of cardiovascular adverse events. However, the guidance fails to specify whether the 2 to 3 mm Hg increase in blood pressure refers to systolic blood pressure (SBP), diastolic blood pressure (DBP), or mean arterial pressure (MAP). It is critically important that the guidance distinguish between SBP, DBP, and MAP. Furthermore, the guidance fails to specify whether the threshold for an increase in blood pressure that would raise concern for a long-term increased risk of adverse cardiovascular events will be 2 mm Hg or 3 mm Hg.

The draft guidance states that "[t]here is little concern about a drug indicated for short-term use that has, at most, small effects on blood pressure," while stating that "[l]arge blood pressure-increasing effects are of concern, however, even with drugs intended for short-term use." Curiously, the draft guidance fails to specify (a) a time interval that distinguishes short-term use from long-term use and (b) what constitutes a large blood pressure increase for drugs intended for short term use.

Recommended revisions to the draft guidance

We strongly recommend that the draft guidance be revised to specify (a) a time interval that distinguishes short-term drug use from long-term use and (b) what constitutes a large blood pressure increase for drugs intended for short-term use. We propose 30 days as the upper limit of duration for defining drugs intended for short-term use.

We also strongly recommend that the guidance be revised to specify that for drugs intended for long-term use, the FDA should require premarket cardiovascular safety data for drugs that raise SBP more than 2 mm Hg or that raise DBP more than 1 mm Hg compared with a placebo. This recommendation is based upon a thorough review of the medical and pharmacological research literature concerning the cardiovascular consequences of changes in blood pressure.

For drugs intended for short-term use, less stringent guidance is appropriate. For these drugs, we suggest that the guidance be revised to require sponsors to obtain premarket cardiovascular safety data for drugs that raise SBP more than 5 mm Hg or that raise DBP more than 2.5 mm Hg compared with a placebo.

Previous FDA guidance regarding the pressor effect of drugs

For decades, the FDA has used antiquated and inconsistent guidelines to determine whether drugs raise blood pressure, and when drugs demonstrably have been shown to raise blood pressure, the FDA has failed to act.

In 1997, one FDA medical reviewer indicated that in order to be considered clinically significant, FDA guidelines required that a medication needed to raise SBP to a level greater than 179 mm Hg or raise SBP more than 19 mm Hg above baseline, or raise DBP to a level greater than 104 mm Hg or raise DBP more than 14 mm Hg above baseline.[1] Another FDA reviewer wrote in 1999 that a clinically significant increase in blood pressure meant that the drug raised SBP to a level greater than 140 mm Hg and increased

[1] Food and Drug Administration. Approval package for Meridia capsules. November 22, 1997. https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_apltr_thr_%20mor.pdf. Accessed July 30, 2018. PDF page 175.

SBP greater than 20 mm Hg, or raised DBP to a level greater than 90 mm Hg and increased DBP by greater than 10 mm Hg above baseline.[2]

Other FDA reviewers compared the difference in mean change in BP between drug and placebo. When those differences were in the 1 to 4 mm Hg range, FDA reviewers concluded that the differences were clinically irrelevant.[3]

Notably, rofecoxib (Vioxx) was approved despite the FDA being aware that it raised blood pressure to a clinically significant degree,[4] and valdecoxib (Bextra) also was approved despite the FDA being aware that it significantly raises blood pressure.[5] We are aware of no instances in which a manufacturer has been required to obtain premarket cardiovascular safety data due to a hypertensive effect of a drug.

Data regarding blood pressure changes and cardiovascular risk

There is a continuous relationship between blood pressure and adverse cardiovascular outcomes for SBP ranging from 115 to 180 mm Hg and for DBP ranging from 75 to 105 mm Hg.[6] Consequently, even small changes in BP can be significant. For instance, in middle-aged individuals, a 2 mm Hg increase in SBP or a 1 mm Hg increase in DBP increased the risk of heart attack by 10 percent and increased the risk of stroke by 7 percent.

Data from the Framingham heart study showed that compared with normal blood pressure (defined as SBP 120 to 129 and DBP 80 to 84), high normal blood pressure (defined as SBP 130 to 139 and DBP 85 to 89) was associated with a risk-factor-adjusted hazard ratio for cardiovascular disease of 2.5 (95 percent confidence interval, 1.6 to 4.1) in women and 1.6 (95 percent confidence interval, 1.1 to 2.2) in men.[7]

Additional data from several hypertension clinical trials further support our proposed revisions to the draft guidance. The findings of the Antihypertensive and Lipid-Lowering

[2] Food and Drug Administration. Medical review for rofecoxib, part 5. May 17, 1999. https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/021042_52_vioxx_medr_P5.pdf. Accessed July 30, 2018. PDF page 8.
[3] Food and Drug Administration. Medical review #3 for NDA 21-427, Cymbalta (duloxetine). August 16, 2002. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021427_s000_Cymbalta_Medr_P2.pdf. Accessed July 30, 2018. PDF page 45.
[4] Food and Drug Administration. Medical review for rofecoxib, part 5. May 17, 1999. https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/021042_52_vioxx_medr_P5.pdf. Accessed July 30, 2018. PDF page 8.
[5] Food and Drug Administration. Medical review for valdecoxib. November 7, 2001. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-341_Bextra_medr_P3.pdf. Accessed July 30, 2018.
[6] Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360(9349):1903-1913.
[7] Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Eng J Med*. 2001;345(18):1291-1297.

Treatment to Prevent Heart Attack Trial (ALLHAT),[8,9] the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial,[10] and the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial[11] are consistent with the notion that a greater than 2 mm Hg SBP difference or a greater than 1 mm Hg DBP difference results in significantly different rates of adverse cardiovascular outcomes. On the other hand, the Nordic Diltiazem (NORDIL) study found that a 3 mm Hg SBP difference did not significantly influence cardiovascular events,[12] and the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial found that a 1.3 mm Hg DBP difference did not significantly alter cardiac morbidity and mortality.[13] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, neither a SBP difference of 14 mm Hg nor a DBP difference of 6 mm Hg resulted in any difference in major cardiovascular events.[14]

The regulatory experience with valdecoxib and sibutramine (Meridia) provides a major justification for our recommendation that for drugs intended for long-term use, the FDA should require premarket cardiovascular safety data for drugs that raise SBP more than 2 mm Hg or that raise DBP more than 1 mm Hg compared with a placebo. After being approved by the FDA, valdecoxib and sibutramine were subsequently taken off the market due to cardiovascular safety concerns. Prior to the approval of valdecoxib, data submitted to the FDA demonstrated that, depending upon the dose, valdecoxib increased SBP by 0.8-2.9 mm Hg while simultaneously increasing DBP by 1.2 mm Hg. [15,16] Likewise, prior to the approval of sibutramine, data submitted to the FDA demonstrated

[8] The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2000;283(15):1967-1975.
[9] The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288(23):2981-2997.
[10] Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359(23):2417-2428.
[11] Black HR, Elliott WJ, Grandits G. Prinicipal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. *JAMA*. 2003;289(16):2073-2082.
[12] Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and ß-blockers on cardiovascular morbitity and mortality in hypertension: The Nordic Dilitiazem (NORDIL) study. *Lancet*. 2000;356(9227):359-365.
[13] Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: The VALUE randomised trial. *Lancet*. 2004;363(9426): 2022-2031.
[14] The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabets mellitus. *N Engl J Med*. 2010;362(17):1575-1585
[15] Food and Drug Administration. Medical review for valdecoxib. November 7, 2001. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-341_Bextra_medr_P3.pdf. Accessed July 30, 2018.
[16] Blankfield RP, Iftikhar IH. FDA regulation of drugs that raise blood pressure. *J Cardiovasc Pharmacol Ther*. 2015;20(1):5-8.

that, depending upon the dose, sibutramine increased SBP by 0.7-4.7 mm Hg.[17,18] The same data demonstrated that some doses of sibutramine lowered DBP by 0.5 mm Hg, but most doses increased DBP by 2.0-3.7 mm Hg. Given the demonstrated pressor effects, it would have been appropriate for the FDA to have required appropriately designed premarket cardiovascular safety trials for both drugs prior to making an approval decision.

Conclusions

The history of the regulatory actions taken for valdecoxib and sibutramine should provide a lasting lesson that translates into guidance recommendations based on the best available scientific evidence. The draft guidance should be revised to specify the of the threshold increases in SBP and DBP that would lead the agency to request cardiovascular safety data prior to drug approval.

A previously published 2013 "White Paper" on this topic, authored by academic cardiovascular experts, FDA representatives, and representatives from the pharmaceutical industry, failed to include specific recommended thresholds for SBP or DBP increases that would be sufficient to trigger a mandatory pre-approval cardiovascular safety trials.[19] However, unlike the White Paper — which appropriately noted that the current thinking and suggestions in the document "do not represent regulatory guidance" or "regulatory policy" — it is imperative that the FDA guidance include a requirement for premarket cardiovascular safety trials for drugs intended for chronic use that raise SBP by more than 2 mm Hg or that raise DBP by more than 1 mm Hg. If such guidance had been in effect at the time that valdecoxib and sibutramine were be considered for approval, premarket cardiovascular safety data for both drugs would have been required, and it is likely that neither drug would have been approved. We cannot emphasize enough that less stringent guidance would not have triggered a requirement for cardiovascular safety data for either drug.

For drugs intended for short-term use that have pressor effects, the criteria for requiring cardiovascular safety trials need not be as stringent as the criteria for drugs intended for long-term use that have pressor effects. We propose a threshold for drugs intended for short-use term use that is 2.5 times our proposed threshold for drugs intended for long-term use. We propose that for drugs intended for short-term use, the guidance should be revised to include a requirement for premarket cardiovascular safety trials for drugs that raise SBP by more than 5 mm Hg or that raise DBP by more than 2.5 mm Hg. We

[17] Food and Drug Administration. Approval package for Meridia capsules. November 22, 1997. https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020632a_apltr_thr_%20mor.pdf. Accessed July 30, 2018. PDF page 175.
[18] Blankfield RP, Iftikhar IH. FDA regulation of drugs that raise blood pressure. *J Cardiovasc Pharmacol Ther*. 2015;20(1):5-8.
[19] Sager P, Heilbraun J, Turner JR, et al. Assessment of drug-induced increases in blood pressure during drug development: Report from the Cardiac Safety Research Consortium. *Am Heart J*. 2013;165(4):477-488.

strongly suggest 30 days as the upper limit of duration for drugs intended for short-term use.

The overwhelming evidence for the serious dangers of drug-induced hypertension mandates that the FDA be much more specific in its guidance, in ways including the above suggested revisions.

Thank you for considering our comments regarding this important public health issue.

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