
Hypertension: Developing Fixed-Combination Drug Products for Treatment Guidance for Industry

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

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I. BACKGROUND AND INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of fixed-combination drug products² for the treatment of hypertension. This guidance focuses on development of two-drug combinations of previously approved drugs, although the general approach is readily applicable to three or more drugs in combination. This guidance does not address combinations that include unapproved drug products.

Hypertension is the most common chronic cardiovascular condition dealt with by primary care physicians and other health care practitioners. Hypertension increases the risk of stroke, coronary artery disease, heart failure, atrial fibrillation, and peripheral vascular disease.^{3, 4} Effective control of blood pressure has been shown to reduce the rate of these adverse outcomes.

In general, most patients will require more than one drug product to achieve adequate blood pressure control. In the past, the usual approach was to give patients the drug products sequentially, that is, titrate the first drug product to its full dose, then add a second drug product and titrate to its full dose, etc. More recently, physicians commonly initiate treatments with less

¹ This guidance has been prepared by the Division of Cardiovascular and Renal Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

² For purposes of this guidance, a fixed-combination drug product is one in which two or more active ingredients are combined at a fixed dosage in a single dosage form.

³ Rapsomaniki E, Timmis A, George J, et al., 2014, Blood Pressure and Incidence of Twelve Cardiovascular Diseases: Lifetime Risks, Healthy Life-Years Lost, and Age-Specific Associations in 1·25 Million People, *Lancet*, 383:1899–1911.

⁴ Angeli F, Reboldi G, and Verdecchia P, 2014, Hypertension, Inflammation and Atrial Fibrillation, *J Hypertens*, 32(3):480–483.

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than full doses of two drug products, with the goal of avoiding side effects but gaining most of the effect of each drug product and gaining an overall effect greater than the single drug products would have at their maximum doses. The American Society of Hypertension and the International Society of Hypertension have jointly recommended initiating treatment with two drug products if a patient's untreated blood pressure is at least 20/10 millimeters of mercury (mmHg) above the target blood pressure.⁵

In considering fixed-combination drug products, FDA recognizes the interest both in (1) developing combinations of less than full doses of drug products with distinct mechanisms of action (e.g., a diuretic combined with an angiotensin-converting enzyme inhibitor, an angiotensin-receptor blocker, or a beta blocker) that could be used as initial therapy; and (2) providing a range of combinations that allow dose titration to attain adequate blood pressure control.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. COMBINATION RATIONALE AND DEMONSTRATING CONTRIBUTION OF COMPONENTS

- In selecting drug products for use in fixed-combination drug products, sponsors should consider previously approved antihypertensive drug products with reasonably distinct mechanisms of action. Because of the different mechanisms of action, the drug products' individual components used together are likely to demonstrate additive blood pressure effects. In addition, if combinations include doses of each drug product below the maximum dose, dose-related adverse effects of the components can be expected to be reduced compared to uses of single drug products at their highest approved doses.
- For sponsors to establish safety and effectiveness of combination drug products, 21 CFR 300.50 (the combination rule) states that (1) each component must make a contribution to the claimed effects; and (2) the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for the intended patient population. In the past, sponsors satisfied the combination rule for combination antihypertensive drug products by examining the overall contribution of each drug in a large factorial study using multiple doses of each component (e.g., A and B) and showing that A plus B is greater than A and that A plus B is greater than B in an overall analysis of doses. Alternatively to conducting full factorial studies of multiple doses of each component of the combination, we believe a sponsor can demonstrate the independent contribution of the components in two additional ways:

⁵ Weber MA, Schiffrin EL, White WB, et al., 2014, Clinical Practice Guidelines for the Management of Hypertension in the Community: A Statement by the American Society of Hypertension and the International Society of Hypertension, *J Hypertens*, 32(1):3–15.

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- In a factorial study comparing A plus B to A and to B at their highest approved doses, showing that each component contributes to the blood pressure effect, which shows that there is a difference between the mechanisms by which the drug products exert their effects.
- Alternatively, in a factorial study comparing A plus B to A and to B, *at the highest doses planned for the fixed-combination drug product (i.e., not necessarily the highest approved doses)*, showing that each component contributes to the blood pressure effect, provided that other evidence supports dissimilar mechanisms of action and the doses in the combination are reasonably high on their dose-response curves.
- Once a sponsor addresses the combination rule with a study at the highest approved doses or at the highest doses proposed for use in combination, the sponsor does not need to study combinations of lower approved doses to satisfy the combination rule because the drug products' independent effects at lower doses can be assumed.
- Sponsors should adequately characterize the pharmacokinetics of each of the components when used in combination.
- Sponsors that intend to market multiple dose combinations should pay attention to avoid marketing excessive numbers of combinations whose components exert similar blood pressure effects (e.g., a 5 mg/10 mg combination and a 7.5 mg/12.5 mg combination that both produce similar decreases in blood pressure).

III. PHASE 3 TRIAL DESIGN AND LABELING CONSIDERATIONS

- In general, the FDA considers a single phase 3, double-blind, randomized trial to be sufficient for demonstrating effectiveness of combination drug products of previously approved antihypertensive drug products.
- The study intended to show an effect of both components should be carried out in a population where initiating therapy with two drugs is appropriate. Sponsors should consult contemporary treatment guidelines. The higher the baseline blood pressure, the easier it will be to demonstrate blood pressure effects of the components, and the less likely it is that there will be intolerance to blood pressure reduction.
- It is expected that significant effects are observed on both systolic and diastolic blood pressures. The effects should be assessed at the end of the dosing interval.
- Sponsors should consider guidance intended to assist applicants in developing labeling for cardiovascular outcome claims for drugs that are indicated to treat hypertension.⁶

⁶ See the guidance for industry *Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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- Sponsors should consider that labeling for two-drug combinations intended for initial use frequently includes model-based figures, as shown below in Figure 1, that describe the likelihood of reaching blood pressure goals on individual drug products or the combination, as a function of the baseline blood pressure.

Figure 1: Probability of Achieving Systolic Blood Pressure Less Than 140 mmHg

