
Hypertension: Developing Fixed- Dose Combination Drugs for Treatment Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Naomi Lowy at 301-796-0692.

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

**January 2018
Clinical/Medical**

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Food and Drug Administration
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TABLE OF CONTENTS

I.	BACKGROUND AND INTRODUCTION.....	1
II.	COMBINATION RATIONALE AND DEMONSTRATING CONTRIBUTION OF COMPONENTS	2
III.	PHASE 3 TRIAL DESIGN	3

1
2
3
4
5
6
7
8
9
10
11
12
13
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. BACKGROUND AND INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of fixed-dose combination drugs for the treatment of hypertension. The 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 drugs.

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.^{2, 3} 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 to achieve adequate blood pressure control. In the past, the usual approach was to give patients the drugs sequentially, that is, titrate the first drug to its full dose, then add a second drug and titrate to its full dose, etc. More recently, physicians commonly initiate treatments with less than full doses of two drugs, with the goal of avoiding side effects but gaining most of the effect of each drug and gaining an overall effect greater than the single drugs would have at their maximum doses. The American Society of Hypertension (ASH) and the International Society of Hypertension (ISH) have jointly

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

² 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.

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

Contains Nonbinding Recommendations

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36 recommended initiating treatment with two drugs if a patient's untreated blood pressure is at
37 least 20/10 mmHg above the target blood pressure.⁴
38

39 In considering fixed combinations, FDA recognizes the interest both in: (1) developing
40 combinations of less than full doses of drugs with distinct mechanisms of action (e.g., a diuretic
41 combined with an angiotensin-converting enzyme inhibitor, an angiotensin-receptor blocker, or a
42 beta blocker) that could be used as initial therapy; and (2) providing a range of combinations that
43 allow dose titration to attain adequate blood pressure control.
44

45 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
46 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
47 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
48 the word *should* in Agency guidances means that something is suggested or recommended, but
49 not required.
50

51 **II. COMBINATION RATIONALE AND DEMONSTRATING CONTRIBUTION OF** 52 **COMPONENTS** 53 54

- 55 • In selecting drugs for use in fixed combinations, sponsors should consider previously
56 approved antihypertensive drugs with reasonably distinct mechanisms of action. Because
57 of the different mechanisms of action, the drugs' individual components used together are
58 likely to demonstrate additive blood pressure effects. In addition, if combinations include
59 doses of each drug below the maximum dose, dose-related adverse effects of the
60 components can be expected to be reduced compared to uses of single drugs at their
61 highest approved doses.
62
- 63 • For sponsors to establish safety and effectiveness of combination drugs, 21 CFR 300.50
64 (the combination rule) states that: (1) each component must make a contribution to the
65 claimed effects; and (2) the dosage of each component (amount, frequency, duration) is
66 such that the combination is safe and effective for the intended patient population. In the
67 past, sponsors satisfied the combination rule for combination antihypertensive drugs by
68 examining the overall contribution of each drug in a large factorial study using multiple
69 doses of each component (e.g., A and B) and showing that A plus B is greater than A and
70 A plus B is greater than B in an overall analysis of doses. As alternatives to conducting
71 full factorial studies of multiple doses of each component of the combination, we believe
72 a sponsor can demonstrate the independent contribution of the components in two
73 additional ways:
74
 - 75 – In a factorial study comparing A+B to A and to B at their highest-approved doses,
76 showing that each component contributes to the blood pressure effect, which shows
77 that there is not complete overlap of the mechanisms by which the drugs exert their
78 effects.

4 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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80 – Alternatively, in a factorial study comparing A+B to A and to B, *at the highest doses*
81 *planned for the fixed combination*, showing that each component contributes to the
82 blood pressure effect, provided that other evidence supports dissimilar mechanisms of
83 action and the doses in the combination are reasonably high on their dose-response
84 curves.

85
86 • Once a sponsor addresses the combination rule with a study at the highest approved doses
87 or at the highest doses proposed for use in combination, the sponsor does not need to
88 study combinations of lower approved doses to satisfy the combination rule because the
89 drugs' independent effects at lower doses can be assumed.

90
91 • Sponsors should adequately characterize pharmacokinetics of each of the components
92 when used in combination.

93
94 • The FDA encourages sponsors to market dose combinations that represent clinically
95 meaningful titration steps.

96
97

98 **III. PHASE 3 TRIAL DESIGN**

99
100 • In general, the FDA considers a single phase 3, double-blind, randomized trial to be
101 sufficient for demonstrating effectiveness of combination drugs of previously approved
102 antihypertensive drugs.

103
104 • The study intended to show an effect of both components should be carried out in a
105 population where initiating therapy with 2 drugs is appropriate; consult contemporary
106 treatment guidelines. The higher the baseline blood pressure, the easier it will be to
107 demonstrate BP effects, and the less likely there will be intolerance to blood pressure
108 reduction.

109
110 • The sponsor should prespecify the primary endpoint, but the primary endpoint can be
111 systolic, diastolic, or mean blood pressure, and it can be assessed before the next dose.
112 The effect of treatment should persist throughout the interdosing interval.

113
114 • FDA has published guidance intended to assist applicants in developing labeling for
115 cardiovascular outcome claims for drugs that are indicated to treat hypertension.⁵

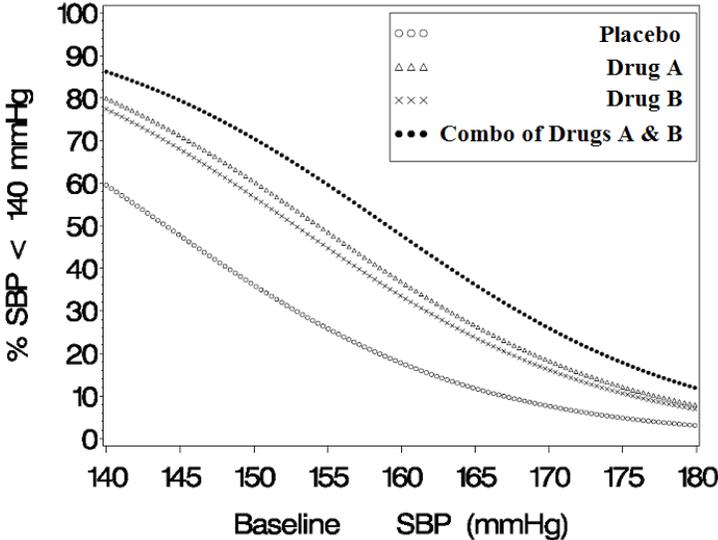
116
117 • Sponsors should consider that labeling for two-drug combinations intended for initial use
118 frequently includes model-based figures, as shown below in Figure 1, that describe the
119 likelihood of reaching blood pressure goals on individual drugs or the combination, as a
120 function of the baseline blood pressure.

⁵ 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 Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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



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