Treatment for Heart Failure: Endpoints for Drug Development

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Norman Stockbridge at 301-796-2240 or (CBER) Office of Communication, Outreach, and Development at 240-402-8010.

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

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Clinical

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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 This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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.

12
13
14 **I.   INTRODUCTION**
15
16   This guidance has two purposes: 1) to make it clear that an effect on symptoms or physical
17   function, without a favorable effect on survival or risk of hospitalization, can be a basis for
18   approving drugs[2] to treat heart failure; and 2) to provide recommendations to sponsors on the
19   need to assess mortality effects of drugs under development to treat heart failure.[3]
20
21   This guidance reflects the Food and Drug Administration's (FDA's) current thinking about
22   developing drugs to treat heart failure. Areas of uncertainty (highlighted in boxes in this
23   guidance) remain, and FDA welcomes discussion and alternative approaches.
24
25   This guidance pertains primarily to treating chronic heart failure. Development of drugs to treat
26   acute heart failure and pediatric considerations are discussed briefly. This guidance applies to
27   both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved
28   ejection fraction (HFpEF).
29
30   In general, FDA's guidance documents do not establish legally enforceable responsibilities.
31   Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
32   as recommendations, unless specific regulatory or statutory requirements are cited. The use of
33   the word *should* in Agency guidances means that something is suggested or recommended, but
34   not required.
35

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[1] This guidance has been prepared by the Division of Cardiovascular and Renal Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and biological products unless otherwise specified.

[3] For purposes of this guidance, unless otherwise specified, references to "drugs" and "drug products" include drugs submitted for approval or approved under section 505(b) or (j) of the FD&C Act and biological products licensed under section 351 of the PHS Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

36 **II.   BACKGROUND**
37
38   Heart failure afflicts approximately 6.5 million patients in the United States and 26 million
39   patients worldwide. As the U.S. population ages, the prevalence of heart failure is increasing,
40   with approximately 550,000 new cases diagnosed annually.
41
42   Heart failure causes substantial mortality and morbidity and has major effects on physical
43   function and quality of life. The annual mortality rate of patients with heart failure is
44   approximately 10%. Hospitalization is common, with approximately 30% of heart failure
45   patients hospitalized annually. Despite optimal management, most patients with heart failure
46   have troublesome symptoms, including dyspnea and fatigue.
47
48   Drugs of several pharmacologic classes (angiotensin-converting enzyme (ACE) inhibitors,
49   angiotensin receptor blockers (ARBs), beta blockers, mineralocorticoid receptor antagonists
50   (MRAs)) that have been approved in the past 2 decades significantly improve heart failure
51   outcomes, including physical function, risk of hospitalization, and survival, in patients with
52   reduced ejection fraction. Despite these therapies, the disease continues to shorten lives and
53   cause significant disability and symptoms. Diuretics, both thiazides and loop diuretics, are also
54   widely used to reduce signs and symptoms of heart failure, although their outcome effects (death
55   and risk of hospitalization) have not been evaluated. These facts point to a need for new drugs to
56   treat heart failure. In addition, there are no effective treatments for HFpEF, which represents
57   approximately 50% of heart failure cases.
58
59   Unfortunately, some drugs (e.g., milrinone and flosequinan) intended to treat heart failure were
60   found to have favorable effects on exercise capacity and symptoms but were subsequently found
61   to increase mortality. This experience led FDA to ask sponsors to assess the mortality effects of
62   such drugs, usually prior to approval. The intent was not to require demonstration of improved
63   survival—although that would be an important outcome—but rather to provide reasonable
64   assurance that the drug did not increase mortality.
65
66   Subsequently, some sponsors and other stakeholders reported a belief that favorable effects on
67   mortality and morbidity (specifically, hospitalization for heart failure) were required to approve
68   drugs to treat heart failure. The approvals of ACE inhibitors, ARBs, beta blockers, and
69   sacubitril-valsartan may have contributed to this impression, as their approvals were based on
70   these endpoints. In fact, although important, favorable effects on survival and hospitalization
71   rates are not required for FDA approval.
72
73   A drug that improves symptoms or function when added to standard of care would be valuable
74   even if it did not improve survival or hospitalization. Moreover, it is possible that if a drug
75   provided substantial and persistent improvement in symptoms or function, especially for patients
76   with New York Heart Association Class III or IV heart failure, some decrease in survival would
77   be acceptable.
78
79   The type of evidence of effectiveness needed to support the approval of drugs to treat heart
80   failure does not differ from the evidence needed to support the approval of drugs intended to

81 treat other conditions: substantial evidence demonstrating that the drug improves how a patient
82 feels, functions (i.e., symptomatic or functional improvement), or survives.
83
84
85 **III.   MORTALITY DATA: PURPOSE AND REQUIREMENTS**
86
87 Mortality data can serve two purposes in the context of developing drugs to treat heart failure:
88
89   1) As a **primary efficacy endpoint**, a decrease in mortality provides evidence of
90   effectiveness in heart failure trials.
91
92   2) As a **safety endpoint**, mortality data provides an assessment of the possibility of an
93   adverse effect on survival.
94
95 When approval is based on improvement of symptoms or function, FDA will consider the
96 following factors in determining whether and when (i.e., pre- or postapproval) additional
97 mortality data are needed:
98
99 • **The mortality and other safety findings of pharmacologically similar drugs**. For
100   example, the safety profiles of ACE inhibitors, ARBs, beta blockers, MRAs, and digoxin are
101   well-established. The safety of a new drug in these classes could be supported by existing
102   data, and additional information on mortality might not be needed. In general, drugs with
103   novel mechanisms of action are more likely to require mortality data.
104
105 • **Planned duration of exposure**. If the planned treatment is for short-term use (typically less
106   than 10 days), for example, treatment of acute exacerbations, there is generally no
107   requirement for long-term mortality data.
108
109 • **The mortality and other safety findings of the drug in a closely related population in**
110   **which at least a subset of the patients had heart failure or were at risk of heart failure**.
111   For example, many patients with coronary artery disease or long-standing diabetes have or
112   will develop heart failure. Results of studies in such populations could therefore support the
113   safety of the drug in a heart failure population.
114

115
116 • FDA believes there should be further discussion about whether the nature, magnitude, and clinical
117 importance of a symptomatic benefit, considered with the demonstrated risks, could justify deferral or
118 omission of outcome studies to assess mortality.
119
120 • When mortality data are needed, FDA believes it would be useful to discuss the risk of mortality that
121 should be ruled out in outcome studies and whether the acceptable upper bound should be influenced by
122 the drug's demonstrated benefits and risks.
123
124 • FDA believes there should be discussion about whether and when an increased risk in mortality could be
125 acceptable for a drug with an important symptomatic benefit.
126

127
128 When a mortality study is needed, sponsors should consider simple outcome studies (i.e., with
129 selective data collection, which are highly feasible in patients with heart failure, particularly
130 those with advanced disease, because the mortality rate is high in such patients).
131
132
133 **IV.   EFFICACY ENDPOINTS RELATED TO HOW PATIENTS FEEL AND**
134 **FUNCTION**
135
136 Evidence of effectiveness for a heart failure drug could be based on improvements in symptoms
137 (e.g., dyspnea, fatigue, edema) and/or function (e.g., walking, exercising, performing other
138 activities of daily living).
139
140 Endpoints acceptable to FDA include individual symptoms or a composite symptom score,
141 exercise capacity, functional capacity, New York Heart Association functional class, and
142 measures of activity/daily living. FDA will consider trials that use novel endpoints, including
143 other clinical outcome assessments, other measures of functional capacity, and measures of daily
144 activity (e.g., accelerometry data). For endpoints that can be influenced by expectation bias or
145 motivation (e.g., 6-minute Walk Test), blinding of investigators and subjects is critically
146 important.
147
148 Sponsors should consult with the Agency early in the drug-development process to obtain
149 agreement on proposed endpoints.
150
151 For guidance on patient-reported outcome measures, see the guidance for industry *Patient-*
152 *Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*
153 (December 2009).
154
155
156 **V.   HOSPITALIZATION AND OUTPATIENT INTERVENTION**
157
158 Hospitalization represents an important clinical outcome, reflecting worsening function and/or
159 symptoms, interruption of daily activities, and superimposed risks and inconveniences.
160

161 Hospitalization has been widely used as a measure of "morbidity" in trials of drugs for heart
162 failure, either as an independent endpoint or as a component of a composite endpoint that
163 includes mortality. Typically, these endpoints have been assessed as time-to-first events.
164
165 Acceptable approaches to quantifying hospitalization (and outpatient interventions) for use as an
166 endpoint include binary endpoints (hospitalization (yes/no)), number of hospitalizations, time-to-
167 initial hospitalization, time alive (or at home) and out of the hospital, and time to recurrent
168 hospitalizations.
169

170
171 The Agency encourages discussion of the pros and cons of capturing all-cause hospitalization versus
172 cause-specific hospitalization.
173

174
175 As heart failure treatment moves away from the inpatient setting, FDA will consider alternative
176 endpoints that reflect clinically important worsening symptoms leading to an intervention (e.g.,
177 treatment in an emergency department, a same-day access clinic, or an infusion center) or
178 unscheduled visits to a healthcare provider for administration of an intravenous diuretic.
179
180
181 **VI.   BIOMARKERS AND SURROGATE ENDPOINTS**
182
183 To date, no biomarkers have been validated as surrogate endpoints for clinical benefit in heart
184 failure. For patients with symptomatic heart failure, it is generally possible to assess directly
185 how individuals feel, function, and survive; therefore, biomarkers have little utility for evaluating
186 drug efficacy in this setting. Biomarkers, however, can be used to characterize risk in patients
187 with heart failure (e.g., NT pro-BNP, left ventricular ejection fraction), and such measures can be
188 useful for prognostic enrichment. Moreover, biomarkers have utility for early proof-of-concept
189 studies and, in particular, studies that serve as the basis for dose selection.
190
191 Where heart failure is a consequence of long-term myocardial damage (e.g., infiltrative
192 cardiomyopathies), disease advancement can be slow, and there is great interest in therapies that
193 may slow or prevent disease progression. For such diseases, manifestations of a clinical benefit
194 can take years to observe, and intermediate clinical endpoints and surrogate endpoints[4] could
195 support accelerated approval. For example, consider a therapy that leads to a reduction, reversal,
196 or prevention of myocardial infiltration. A biomarker that assesses myocardial damage or
197 infiltration, which is not a direct measure of clinical benefit, could be considered a reasonably
198 likely surrogate endpoint[5] to serve as the basis for accelerated approval if certain conditions are

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[4] See FDA-NIH BEST (Biomarkers, EndpointS, and other Tools) Resource for the definition of intermediate clinical endpoint and surrogate endpoint:
https://www.ncbi.nlm.nih.gov/books/NBK453485/.

[5] See FDA-NIH BEST (Biomarkers, EndpointS, and other Tools) Resource for the definition of reasonably likely surrogate endpoint:
https://www.ncbi.nlm.nih.gov/books/NBK453485/.

199 met (see the guidance for industry *Expedited Programs for Serious Conditions – Drugs and*
200 *Biologics* (September 2017)), with subsequent verification of clinical benefit.
201
202
203 **VII.   ACUTE HEART FAILURE**
204
205 Drugs developed with the intended indication of acute heart failure are generally targeted at
206 acute exacerbations of chronic heart failure. The duration of treatment is generally expected to
207 be less than 10 days.
208
209 Such drugs could be approved based on symptom relief (e.g., dyspnea, time to hospital
210 discharge, or avoidance of invasive therapies (left ventricular assist devices, dialysis)).
211
212 Safety must be assessed following drug administration (i.e., ascertainment of death and
213 rehospitalization, generally through 30 days) for drugs with a short duration of exposure.
214
215
216 **VIII.   HEART FAILURE WITH PRESERVED EJECTION FRACTION**
217
218 Although HFpEF and HFrEF are pathophysiologically distinct, the same considerations apply for
219 both.
220
221
222 **IX.   HEART FAILURE IN THE PEDIATRIC POPULATION**
223
224 Although a detailed discussion of heart failure in the pediatric population is out of scope of this
225 guidance, many of the principles enumerated above apply to pediatric populations.
226 Demonstration of clinical benefit may not be needed in pediatric patients with heart failure when
227 the disease in pediatric patients is similar to that in adults and the drug is expected to exert the
228 same effect irrespective of the underlying pathophysiology of heart failure (e.g., diuretics).
229 There may, however, be unique safety considerations when developing drugs to treat heart
230 failure in a pediatric population (e.g., effects on growth and development and hormonal
231 changes).
232
233 Guidance documents specific to pediatric drug development should be consulted for additional
234 information. They include the following guidances for industry:
235
236 • *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study*
237   *Plans and Amended Initial Pediatric Study Plans* (March 2016)
238
239 • *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December
240   2000)
241
242 • *E11(R1) Addendum Clinical Investigation of Medicinal Products in the Pediatric*
243   *Population* (April 2018)

244   • *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and*
245   *Biological Products* (December 2014)
246
247   • *Nonclinical Safety Evaluation of Pediatric Drug Products* (February 2006)