Treatment for Heart Failure: Endpoints for Drug Development
Guidance for Industry

DRAFT GUIDANCE

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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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Treatment for Heart Failure: Endpoints for Drug Development
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I. INTRODUCTION

This guidance has two purposes: 1) to make it clear that an effect on symptoms or physical function, without a favorable effect on survival or risk of hospitalization, can be a basis for approving drugs to treat heart failure; and 2) to provide recommendations to sponsors on the need to assess mortality effects of drugs under development to treat heart failure.

This guidance reflects the Food and Drug Administration’s (FDA’s) current thinking about developing drugs to treat heart failure. Areas of uncertainty (highlighted in boxes in this guidance) remain, and FDA welcomes discussion and alternative approaches.

This guidance pertains primarily to treating chronic heart failure. Development of drugs to treat acute heart failure and pediatric considerations are discussed briefly. This guidance applies to both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

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.

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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)).
II. BACKGROUND

Heart failure afflicts approximately 6.5 million patients in the United States and 26 million patients worldwide. As the U.S. population ages, the prevalence of heart failure is increasing, with approximately 550,000 new cases diagnosed annually.

Heart failure causes substantial mortality and morbidity and has major effects on physical function and quality of life. The annual mortality rate of patients with heart failure is approximately 10%. Hospitalization is common, with approximately 30% of heart failure patients hospitalized annually. Despite optimal management, most patients with heart failure have troublesome symptoms, including dyspnea and fatigue.

Drugs of several pharmacologic classes (angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, mineralocorticoid receptor antagonists (MRAs)) that have been approved in the past 2 decades significantly improve heart failure outcomes, including physical function, risk of hospitalization, and survival, in patients with reduced ejection fraction. Despite these therapies, the disease continues to shorten lives and cause significant disability and symptoms. Diuretics, both thiazides and loop diuretics, are also widely used to reduce signs and symptoms of heart failure, although their outcome effects (death and risk of hospitalization) have not been evaluated. These facts point to a need for new drugs to treat heart failure. In addition, there are no effective treatments for HFpEF, which represents approximately 50% of heart failure cases.

Unfortunately, some drugs (e.g., milrinone and flosequinan) intended to treat heart failure were found to have favorable effects on exercise capacity and symptoms but were subsequently found to increase mortality. This experience led FDA to ask sponsors to assess the mortality effects of such drugs, usually prior to approval. The intent was not to require demonstration of improved survival—although that would be an important outcome—but rather to provide reasonable assurance that the drug did not increase mortality.

Subsequently, some sponsors and other stakeholders reported a belief that favorable effects on mortality and morbidity (specifically, hospitalization for heart failure) were required to approve drugs to treat heart failure. The approvals of ACE inhibitors, ARBs, beta blockers, and sacubitril-valsartan may have contributed to this impression, as their approvals were based on these endpoints. In fact, although important, favorable effects on survival and hospitalization rates are not required for FDA approval.

A drug that improves symptoms or function when added to standard of care would be valuable even if it did not improve survival or hospitalization. Moreover, it is possible that if a drug provided substantial and persistent improvement in symptoms or function, especially for patients with New York Heart Association Class III or IV heart failure, some decrease in survival would be acceptable.

The type of evidence of effectiveness needed to support the approval of drugs to treat heart failure does not differ from the evidence needed to support the approval of drugs intended to
treat other conditions: substantial evidence demonstrating that the drug improves how a patient
feels, functions (i.e., symptomatic or functional improvement), or survives.

III. MORTALITY DATA: PURPOSE AND REQUIREMENTS

Mortality data can serve two purposes in the context of developing drugs to treat heart failure:

1) As a primary efficacy endpoint, a decrease in mortality provides evidence of
effectiveness in heart failure trials.

2) As a safety endpoint, mortality data provides an assessment of the possibility of an
adverse effect on survival.

When approval is based on improvement of symptoms or function, FDA will consider the
following factors in determining whether and when (i.e., pre- or postapproval) additional
mortality data are needed:

- **The mortality and other safety findings of pharmacologically similar drugs.** For
  example, the safety profiles of ACE inhibitors, ARBs, beta blockers, MRAs, and digoxin are
  well-established. The safety of a new drug in these classes could be supported by existing
data, and additional information on mortality might not be needed. In general, drugs with
novel mechanisms of action are more likely to require mortality data.

- **Planned duration of exposure.** If the planned treatment is for short-term use (typically less
  than 10 days), for example, treatment of acute exacerbations, there is generally no
requirement for long-term mortality data.

- **The mortality and other safety findings of the drug in a closely related population in
  which at least a subset of the patients had heart failure or were at risk of heart failure.**
For example, many patients with coronary artery disease or long-standing diabetes have or
will develop heart failure. Results of studies in such populations could therefore support the
safety of the drug in a heart failure population.
• FDA believes there should be further discussion about whether the nature, magnitude, and clinical importance of a symptomatic benefit, considered with the demonstrated risks, could justify deferral or omission of outcome studies to assess mortality.

• When mortality data are needed, FDA believes it would be useful to discuss the risk of mortality that should be ruled out in outcome studies and whether the acceptable upper bound should be influenced by the drug’s demonstrated benefits and risks.

• FDA believes there should be discussion about whether and when an increased risk in mortality could be acceptable for a drug with an important symptomatic benefit.

When a mortality study is needed, sponsors should consider simple outcome studies (i.e., with selective data collection, which are highly feasible in patients with heart failure, particularly those with advanced disease, because the mortality rate is high in such patients).

IV. EFFICACY ENDPOINTS RELATED TO HOW PATIENTS FEEL AND FUNCTION

Evidence of effectiveness for a heart failure drug could be based on improvements in symptoms (e.g., dyspnea, fatigue, edema) and/or function (e.g., walking, exercising, performing other activities of daily living).

Endpoints acceptable to FDA include individual symptoms or a composite symptom score, exercise capacity, functional capacity, New York Heart Association functional class, and measures of activity/daily living. FDA will consider trials that use novel endpoints, including other clinical outcome assessments, other measures of functional capacity, and measures of daily activity (e.g., accelerometry data). For endpoints that can be influenced by expectation bias or motivation (e.g., 6-minute Walk Test), blinding of investigators and subjects is critically important.

Sponsors should consult with the Agency early in the drug-development process to obtain agreement on proposed endpoints.

For guidance on patient-reported outcome measures, see the guidance for industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (December 2009).

V. HOSPITALIZATION AND OUTPATIENT INTERVENTION

Hospitalization represents an important clinical outcome, reflecting worsening function and/or symptoms, interruption of daily activities, and superimposed risks and inconveniences.
Hospitalization has been widely used as a measure of “morbidity” in trials of drugs for heart failure, either as an independent endpoint or as a component of a composite endpoint that includes mortality. Typically, these endpoints have been assessed as time-to-first events.

Acceptable approaches to quantifying hospitalization (and outpatient interventions) for use as an endpoint include binary endpoints (hospitalization (yes/no)), number of hospitalizations, time-to-initial hospitalization, time alive (or at home) and out of the hospital, and time to recurrent hospitalizations.

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

As heart failure treatment moves away from the inpatient setting, FDA will consider alternative endpoints that reflect clinically important worsening symptoms leading to an intervention (e.g., treatment in an emergency department, a same-day access clinic, or an infusion center) or unscheduled visits to a healthcare provider for administration of an intravenous diuretic.

VI. BIOMARKERS AND SURROGATE ENDPOINTS

To date, no biomarkers have been validated as surrogate endpoints for clinical benefit in heart failure. For patients with symptomatic heart failure, it is generally possible to assess directly how individuals feel, function, and survive; therefore, biomarkers have little utility for evaluating drug efficacy in this setting. Biomarkers, however, can be used to characterize risk in patients with heart failure (e.g., NT pro-BNP, left ventricular ejection fraction), and such measures can be useful for prognostic enrichment. Moreover, biomarkers have utility for early proof-of-concept studies and, in particular, studies that serve as the basis for dose selection.

Where heart failure is a consequence of long-term myocardial damage (e.g., infiltrative cardiomyopathies), disease advancement can be slow, and there is great interest in therapies that may slow or prevent disease progression. For such diseases, manifestations of a clinical benefit can take years to observe, and intermediate clinical endpoints and surrogate endpoints could support accelerated approval. For example, consider a therapy that leads to a reduction, reversal, or prevention of myocardial infiltration. A biomarker that assesses myocardial damage or infiltration, which is not a direct measure of clinical benefit, could be considered a reasonably likely surrogate endpoint 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/.

met (see the guidance for industry Expedited Programs for Serious Conditions – Drugs and Biologics (September 2017)), with subsequent verification of clinical benefit.

VII. ACUTE HEART FAILURE

Drugs developed with the intended indication of acute heart failure are generally targeted at acute exacerbations of chronic heart failure. The duration of treatment is generally expected to be less than 10 days.

Such drugs could be approved based on symptom relief (e.g., dyspnea, time to hospital discharge, or avoidance of invasive therapies (left ventricular assist devices, dialysis)).

Safety must be assessed following drug administration (i.e., ascertainment of death and rehospitalization, generally through 30 days) for drugs with a short duration of exposure.

VIII. HEART FAILURE WITH PRESERVED EJECTION FRACTION

Although HFpEF and HFrEF are pathophysiologically distinct, the same considerations apply for both.

IX. HEART FAILURE IN THE PEDIATRIC POPULATION

Although a detailed discussion of heart failure in the pediatric population is out of scope of this guidance, many of the principles enumerated above apply to pediatric populations. Demonstration of clinical benefit may not be needed in pediatric patients with heart failure when the disease in pediatric patients is similar to that in adults and the drug is expected to exert the same effect irrespective of the underlying pathophysiology of heart failure (e.g., diuretics). There may, however, be unique safety considerations when developing drugs to treat heart failure in a pediatric population (e.g., effects on growth and development and hormonal changes).

Guidance documents specific to pediatric drug development should be consulted for additional information. They include the following guidances for industry:

- Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans (March 2016)
- E11 Clinical Investigation of Medicinal Products in the Pediatric Population (December 2000)
- E11(R1) Addendum Clinical Investigation of Medicinal Products in the Pediatric Population (April 2018)
Contains Nonbinding Recommendations
Draft — Not for Implementation

- General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (December 2014)
- Nonclinical Safety Evaluation of Pediatric Drug Products (February 2006)