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# Guidance for Industry Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis: Developing Drug Products for Treatment

## ***DRAFT GUIDANCE***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)**

**March 2014  
Clinical/Medical**

# **Guidance for Industry Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis: Developing Drug Products for Treatment**

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**U.S. Department of Health and Human Services  
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**Guidance for Industry<sup>1</sup>**  
**Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: Developing  
Drug Products for Treatment**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

**I. INTRODUCTION**

This guidance is intended to assist sponsors in the development of drug products for the treatment of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME).<sup>2</sup> This guidance focuses on specific drug development and trial design issues that are unique to the study of CFS/ME and on the FDA's current thinking on how effective treatments can be developed for CFS/ME. The points discussed in this guidance may not be applicable to all drug products. The FDA encourages sponsors to design clinical programs that fit their particular needs and to discuss their planned approach with the Division of Pulmonary, Allergy, and Rheumatology Products.

This guidance does not contain discussion of the general issues of statistical analysis, clinical trial design, or patient-reported outcome (PRO) instruments. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials* and the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, respectively.<sup>3</sup> This guidance does not address nomenclature considerations or nonclinical development.

<sup>1</sup> This guidance has been prepared by the Division of Pulmonary, Allergy, and Rheumatology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> In this guidance, the term *drug product* includes all types of therapeutic agents, such as small and large molecule drugs, and therapeutic biological products, regulated within CDER.

<sup>3</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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For this guidance, the terms CFS, ME, and CFS/ME are used interchangeably. The term CFS/ME is used in the singular to refer to a disease or set of diseases. The term CFS/ME is intended to be inclusive and does not infer the cause of different symptom complexes. Currently, the FDA does not recognize a particular definition or name as appropriate for use in clinical trials of drug products for CFS/ME.

FDA's guidance documents, including this guidance, 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. BACKGROUND**

CFS/ME is a complex disease that can be debilitating. The exact cause or causes of CFS/ME are unknown. Symptoms affect several body systems and may include severe fatigue or exhaustion, unrefreshing sleep, weakness, muscle and joint pain, impaired memory or mental concentration, tender lymph nodes, sore throat, headaches, and sleep dysfunction. Many patients experience post-exertional malaise, which may occur without warning and upon even minimal physical or cognitive exertion, and is associated with acute exacerbation of these symptoms. The nature and severity of symptoms vary from person to person, and diagnosis is challenging because there are no specific tests for the disease. Post-exertional malaise and cognitive impairment are symptoms that can be particularly severe and disabling.<sup>4</sup>

According to the Centers for Disease Control and Prevention (CDC), between one and four million people in the United States are afflicted with CFS.<sup>5</sup> Although CFS/ME is most common in 40- to 60-year-old women, CFS/ME affects both sexes and all racial, age, and socioeconomic groups. The disease may occur with a sudden onset, such as following an infection, or may occur with a gradual onset. Some patients improve spontaneously; however, many patients experience a prolonged course of illness with either periods of remission and exacerbation or steady decline.

CFS/ME affects patients' ability to function in daily activities of work, school, household management, and personal care. Many patients with CFS/ME are bedbound some or all of the time and experience loss of careers, decreased quality of family life, social isolation, and feelings of hopelessness.

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<sup>4</sup> The Voice of the Patient, A Series of Reports From the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative, Chronic Fatigue Syndrome and Myalgic Encephalomyelitis (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf>).

<sup>5</sup> Recognition and Management of Chronic Fatigue Syndrome: A Resource Guide for Health Care Professionals (<http://www.cdc.gov/cfs/hcp.html>)

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CFS/ME is a serious disease and there are no approved therapies indicated to treat CFS/ME. The lack of approved therapies indicated for the treatment of CFS/ME represents a public health concern.

### **III. DEVELOPMENT PROGRAM**

#### **A. General Considerations**

##### **1. Drug Development Population**

A number of different clinical diagnostic criteria are in use for CFS/ME, including the 1988 CDC criteria (Holmes, Kaplan, et al. 1988), the Fukuda Criteria (1994 Case Definition; Fukuda, Straus, et al. 1994), the International Criteria (Carruthers, van der Sande, et al. 2011), and the Canadian consensus criteria (Carruthers, Jain, et al. 2003). Currently, there is no single case definition or set of criteria that is uniformly recognized as the standard for diagnosing patients with the disease. At this time, the FDA does not recognize any particular disease definition, nomenclature, or diagnostic criteria for CFS/ME as the most appropriate for use in clinical trials of new drug products. Consequently, any case definition or criteria for CFS/ME can be used to define the patient population. Sponsors should provide justification for the chosen case definition or criteria and should provide sufficient details of the enrollment criteria (21 CFR 314.126). Regardless of the case definition or criteria used, the clinical trial should exclude patients with potentially confounding diagnoses, including, but not limited to, congestive heart failure, malignancy, and chronic hepatitis, that cause fatigue and similar symptom complexes. Drug development in CFS/ME should focus on measures of clinically relevant effects in a defined patient population.<sup>6</sup>

Sponsors should define whether the targeted patient population reflects the general CFS/ME population or a subset, such as patients with CFS/ME and postural orthostatic tachycardia syndrome (POTS). Generally, it is helpful to define the specific indicated population early in the clinical development program. Ultimately, the targeted patient population used in the definitive clinical trials should be reflected in labeling.

##### **2. Unmet Medical Need**

CFS/ME is a serious disease and there is unmet medical need in the treatment of CFS/ME. There are FDA programs intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the benefits of a therapy outweigh its risks. For information regarding expedited programs, including fast track designation, breakthrough therapy designation, accelerated approval, and priority review, see the draft guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics*.<sup>7</sup> This guidance includes information regarding FDA programs intended to facilitate and expedite

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<sup>6</sup> See the ICH guidance for industry *E8 General Considerations for Clinical Trials*.

<sup>7</sup> When final, this guidance will represent the FDA's current thinking on this topic.

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development and review of drugs to address unmet medical need in the treatment of serious or life-threatening conditions.

### ***3. Efficacy Considerations***

To meet the regulatory standards for approval under section 505(d) of the Federal Food, Drug, and Cosmetic Act, sponsors must provide substantial evidence of efficacy in the enrolled patient population and demonstrate an acceptable risk-benefit profile for their drug product.<sup>8</sup> This section outlines the principles of assessing efficacy of drug products for the treatment of CFS/ME.

The efficacy endpoints selected for evaluation of drug products for the treatment of CFS/ME should include patient-reported symptoms using well-defined and reliable PRO instruments. These patient-reported symptoms can include any scientifically supported and logical combination of symptoms that are common in CFS/ME. Additionally, sponsors should consider using objective measures. Several potential efficacy endpoints that may be suitable for use in clinical trials of drug products for CFS/ME are mentioned in the following sections; however, sponsors are encouraged to also propose other clinically meaningful endpoints that may better assess the efficacy of their drug products. As with all adequate and well-controlled clinical investigations, the protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response (21 CFR 314.126(b)(6)).

For most drug products, phase 3 trials that use a single primary efficacy endpoint with supportive secondary efficacy endpoints should be adequate to establish efficacy, provided the efficacy findings are robust and clinically meaningful. The wording of the indication statement should reflect the effect assessed by the primary efficacy endpoint used.

The FDA understands that there is an emerging body of research focused on understanding a range of laboratory abnormalities and biomarkers in CFS/ME. Although biomarkers can be considered as exploratory endpoints, the primary endpoints used to demonstrate efficacy should reflect the claimed clinical benefit related to how a patient feels or functions.

### **B. Specific Efficacy Trial Considerations**

#### ***1. Trial Design***

The nature and design of the definitive trials depends on the type of drug product that is being studied and the clinical benefit to be demonstrated. In general, trials should be placebo-controlled, double-blinded, randomized, and parallel-group in design. The use of a placebo control should not preclude *usual care* treatments in patients randomized to placebo (see section III.B.5., Concomitant Treatments). The appropriateness of a placebo control may change in the future when approved drug products become available such that use of placebo control raises ethical issues (i.e., if a drug product is approved for treatment of patients with CFS/ME).

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<sup>8</sup> 21 U.S.C. 355(d)

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2. *Efficacy Endpoints*

This section outlines the principles sponsors should follow to assess efficacy of drug products for the treatment of CFS/ME.

- **Establishing efficacy in key CFS/ME domains.** To support efficacy of drug products for the treatment of CFS/ME, sponsors should demonstrate substantial evidence<sup>9</sup> of efficacy in the key CFS/ME domain: symptoms.
  - *Symptoms.* The primary efficacy endpoint should reflect the claimed clinical benefit (e.g., a drug product intended to reduce fatigue associated with CFS/ME should show the effect through assessments of fatigue, subjectively measured). The selected primary efficacy endpoint should be clinically meaningful.<sup>10</sup>
    - Methods for symptom assessments. The FDA is not aware of existing PRO instruments or set of instruments optimal for measurement of fatigue or other symptoms of CFS/ME. The division will consider the use of symptom assessments that have been developed and evaluated in other conditions or novel instruments. These alternatives should be discussed with the division early in drug development.
- **Other domains.** Other domains that are important to patients can provide further characterization of the efficacy of the drug product and its utility in clinical practice. Other domains can include the following:
  - *Exercise capacity and post-exertional malaise.* CFS/ME can be associated with both reduced exercise capacity and post-exertional malaise. It is important to consider that post-exertional malaise and exercise capacity represent two different potential treatment benefits, and a drug product may act on both, or it may act on one, but not the other. The efficacy endpoints should reflect the claimed clinical benefit (e.g., a drug product intended to decrease post-exertional malaise should show the effect through objective assessments of exercise capacity and PROs).
    - Methods for exercise capacity and post-exertional malaise assessment. Assessment of exercise capacity by treadmill or cycle ergometry or PROs intended to measure post-exertional symptoms can be used to assess efficacy of a drug product. Although the FDA is not aware of existing PRO instruments for post-exertional malaise, the division will consider the use of existing or newly developed measures for this use. These assessment tools should be considered in the context of the desired trial population, because some assessment tools would not be appropriate for patients with large degrees of functional impairment.

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<sup>9</sup> 21 U.S.C. 355(d)

<sup>10</sup> See ICH E8.

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- *Improving health-related quality of life.* Health-related quality of life (HRQL) is a multidomain concept that represents the patient’s general perception of the effect of illness and treatment on physical, psychological, and social aspects of life. Improvement in HRQL is an important aspect of CFS/ME treatment.
- Methods for assessing HRQL. The FDA is not aware of existing HRQL instruments that are designed to systematically assess different aspects of the effect of CFS/ME on a patient’s life. However, the division will consider the use of HRQL instruments that have been developed in other populations or novel instruments for the purposes of assessment of efficacy in CFS/ME. The FDA often suggests that specific domains of health status and HRQL that are most relevant to the disease of interest (e.g., disease-related symptoms or disease-related effect on physical functioning or cognitive functioning) be specified as primary or secondary endpoints to assess treatment benefit in clinical trials, while broader measures of overall HRQL be used as exploratory outcome measures in clinical trials.

For example, CFS/ME impairs the degree to which patients can perform successfully tasks and roles required for everyday living (e.g., patients’ ability to function in daily activities of work, school, household management, and personal care). Direct evidence of treatment benefit can be supported by demonstration of the effect of treatment on the patient’s performance of activities of value in his or her daily life. The choice of the specific assessment tool depends on the context of the targeted trial population.

### ***3. Trial Duration***

The duration of controlled clinical trials may be influenced by data from earlier trials, so this should be discussed with the FDA during protocol development. In general, sponsors should use data from 24-week placebo-controlled clinical trial(s) to provide evidence of efficacy in symptom relief domains. Assessment of efficacy in some other domains may need long-term controlled clinical trial data. Longer durations of treatment may be needed to adequately assess safety.

### ***4. Number of Trials***

Generally, support from two definitive trials should establish efficacy for a drug product being developed to provide symptom relief for CFS/ME. The trials should provide independent substantiation of the evidence of efficacy, but need not be identical in design.

### ***5. Concomitant Treatments***

In general, patients enrolled in the trial should be permitted to use concomitant treatments as needed to manage disease symptoms. An appropriate analysis plan should be defined in the protocol to account for possible imbalance of concomitant treatment use between treatment groups. For some treatments, consideration should be given in the design, conduct, and

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interpretation of the trial to the need for any medications for acute symptoms (e.g., analgesics for pain exacerbations).

**C. Safety Considerations**

Treatment of CFS/ME is usually prolonged; therefore, sponsors should collect long-term safety data. The size of the safety database should be consistent with the recommendations outlined in the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*. Consideration should be given to whether the drug is designed for intermittent or continuous use. Consideration also should be given to other concomitant drugs that CFS/ME patients are likely to take. In cases where efficacy trials are substantially less than 1 year, or if the drug product is to be chronically administered, separate long-term safety trials should be conducted with consideration of including a control arm to facilitate interpretation of these data. Additional safety data may be needed depending on the safety profile observed for the drug product and the specific situation.<sup>11</sup> Sponsors are encouraged to discuss their plans for specific safety monitoring with the FDA during the early stages of drug product development.

**D. Other Considerations**

**1. Combination Drug Products**

Given the complexity of CFS/ME, it is possible that a single drug may not possess all necessary pharmacological activity to result in a desired therapeutic effect. Therefore, a new drug product can be a combination of two or more individual drugs. Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect and the dosing of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy (21 CFR 300.50, Fixed-combination prescription drugs for humans). A reasonable way to support the efficacy of a combination drug product would be to compare the combination drug product to each of its constituents in the same placebo-controlled clinical trial to demonstrate that the combination drug product provides clinical benefit that is superior to each of its constituents (see section III.B.1., Trial Design).

**2. Drug-Device Combination Product Considerations**

Therapies developed for the treatment of CFS/ME can include drug products that require parenteral administration and the use of an accessory delivery unit (e.g., an injector device). In these cases, the manufacturer of the drug product should ensure that the accessory delivery unit is approved or cleared for marketing through the device regulatory process (e.g., 510(k) process or premarket approval) by the Center for Devices and Radiological Health. If the accessory delivery unit is not already approved or cleared for marketing, then it should be approved or cleared at least concurrently with the drug product approval. Generally, each drug-device combination product should have a complete chemistry, manufacturing, and controls database; device design and development; and a substantially complete clinical development program to support efficacy and safety of the entire combination product. Sponsors are encouraged to

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<sup>11</sup> See ICH E1A.

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295     contact the Office of Combination Products and the division early in the development stage to  
296     seek guidance for their drug-device combination product.

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**REFERENCES**

**Guidances**

Draft guidance for industry *Expedited Programs for Serious Conditions—Drugs and Biologics*

Guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*

ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*

ICH guidance for industry *E8 General Considerations for Clinical Trials*

**Other**

The Voice of the Patient, A Series of Reports From the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative, Chronic Fatigue Syndrome and Myalgic Encephalomyelitis (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf>)

Recognition and Management of Chronic Fatigue Syndrome: A Resource Guide for Health Care Professionals (<http://www.cdc.gov/cfs/hcp.html>)

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