Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Dr. Badrul A. Chowdhury at 301-796-2300.

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

May 2016
Clinical/Medical
Revision 1

Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

May 2016
Clinical/Medical
Revision 1

TABLE OF CONTENTS

Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This guidance is intended to assist the pharmaceutical industry in designing a clinical development program for new drug products[2] for the treatment of chronic obstructive pulmonary disease (COPD). The emphasis of this guidance is on the assessment of efficacy of a new molecular entity (NME) in phase 3 clinical studies of COPD.

Development of NMEs for COPD poses challenges and opportunities. This guidance outlines the Food and Drug Administration's (FDA's) current thinking on the development of various types of drugs for COPD. Not all drugs developed for COPD will fit into the types described, and the efficacy endpoints discussed in this guidance may not fit the need for all drugs. The FDA encourages pharmaceutical sponsors to develop clinical programs that fit their particular needs and to discuss their planned approach with the Division of Pulmonary, Allergy, and Rheumatology Products. For novel approaches, where warranted, outside expertise can be sought, including consultation with the Pulmonary-Allergy Drugs Advisory Committee.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. 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*

[1] 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.

[2] In this guidance, the word *drug* includes all types of therapeutic agents, such as small and large molecule drugs, and therapeutic biological products regulated within CDER.

Trials, respectively.[3] This guidance focuses on specific drug development and trial design issues that are unique to the study of COPD.

This guidance revises the draft guidance for industry *Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment* issued in November 2007. This revision includes the addition of information on the use of St. George's Respiratory Questionnaire (SGRQ) in COPD studies (see Appendix A).

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. BACKGROUND

COPD is a chronic progressive disease caused by chronic inflammation and destruction of the airways and lung parenchyma, and is usually associated with tobacco smoking or prolonged exposure to other noxious particles and gasses. The disease is characterized by progressive airflow obstruction that is sometimes partially reversible with the administration of a bronchodilator. There is heterogeneity in disease activity and in the nature of symptomatic impairment experienced by patients. The typical symptoms are cough, excess sputum production, and dyspnea. The term COPD encompasses a spectrum of pulmonary processes, with chronic bronchitis and emphysema as two clearly defined entities within that spectrum. Various consensus panels and position papers have defined and described COPD (see References).

There is pressing need to develop new drugs for COPD because the global prevalence of COPD is rising, the disease is associated with significant morbidity and mortality, and current treatment options are limited. The currently available drugs for COPD are mostly for symptomatic treatment and have not been conclusively shown to alter the underlying inflammation or to alter disease progression. The principles of development applied to COPD drugs have been generally derived from those used to develop drugs for asthma, with the primary focus aimed at demonstrating improvements in airway obstruction. With improved understanding of the pathophysiology and clinical manifestations of COPD, and the awareness of the importance of inflammation in COPD and how this inflammation differs from that occurring in asthma, this is an appropriate time to define characteristics of specific drug development programs for COPD.

[3] 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.

III. DEVELOPMENT PROGRAM

A. Overall Considerations

1. Disease Target and Indication

The clinical development program should define whether the target of the program is the whole spectrum of COPD patients or patients with only one of its clearly defined entities, such as chronic bronchitis or emphysema. Because chronic bronchitis and emphysema are histologically and clinically distinct entities, we recognize that a drug may be effective for one and not the other. Therefore, it is helpful to define early in the development program the specific indicated population the clinical development program is proposed to support.

2. Types of Drugs for COPD

There are several types of drugs that can be developed for COPD based on whether the drug is intended to improve airflow obstruction, provide symptom relief, modify or prevent exacerbations, or alter the natural progression of the disease. It is possible that a drug may affect only one aspect of the disease or that it may act on many. It is also possible that a drug may benefit COPD patients in other meaningful ways beyond these areas cited. Therefore, whereas this guidance focuses on established areas of research or intervention, the division welcomes other proposals. Novel proposals, in particular, can benefit from early discussions with the division, such as in a pre-investigational new drug application meeting.

Each of the following targets in COPD therapy can involve different endpoints, study designs, and study duration, and can likely lead to differing explicit indications. Therefore, it is important for sponsors to develop their drugs with the appropriate drug action or actions in mind.

a. Improving airflow obstruction

Improvement in airflow obstruction historically has been the main therapeutic strategy in COPD drug development. These drugs provide benefit through relief of reversible airflow obstruction that is an important, though not universal, feature of COPD. Improvement in airflow obstruction can result from direct relaxation of the airway smooth muscles, or by other mechanisms such as reduction of airway inflammation or improved clearance of mucous in chronic bronchitis.

b. Providing symptom relief

Drugs that reduce chronic cough, excess sputum production, dyspnea, or other debilitating symptoms of COPD may provide meaningful benefit to patients. Drugs may provide symptom relief either by acting centrally or by acting within the lung. Drugs that relieve dyspnea usually accomplish this by improving airflow obstruction. It is also possible that drugs may target the sensation of dyspnea independent of effects on airflow obstruction. The division has concerns about granting a specific COPD claim for drugs that relieve dyspnea without otherwise benefiting the lung process. For instance, systemic opiates or benzodiazepines may reduce the

sensation of dyspnea, but would not otherwise specifically benefit a COPD patient and, therefore, would not be appropriate drugs for granting a specific claim of treating COPD.

c. Modifying or preventing exacerbations

COPD exacerbations can be life-threatening and have been linked to comorbid conditions. In addition, exacerbations are believed to potentially contribute to further permanent decrements in lung function. Therapeutic drugs that modify the severity or duration of COPD exacerbations or that prevent COPD exacerbations will provide meaningful benefit to patients.

d. Altering disease progression

There is ongoing research to identify therapies that modify the inflammatory processes of COPD and thereby may alter disease progression. Drugs aimed at attenuating ongoing lung damage in COPD may not yield direct discernable symptomatic benefit to patients, at least in the course of clinical studies, nor short-term improvement in lung function, but would, if effective, have longer term tangible benefits by delaying the development of COPD-related disability or death. Such drugs will provide meaningful benefit to patients with COPD.

e. Modifying lung structure

Damage of lung structure is a known feature of COPD progression. At present there are no clear strategies that can modify or regenerate damaged lung tissue, but some drugs have shown promise in animal studies. Drugs that can modify damaged lung structure and generate functional lung tissues will be of benefit to patients with COPD.

3. Drug Development Population

Because COPD represents a spectrum of pathology and manifestations, a therapy can target COPD broadly (e.g., as defined by American Thoracic Society criteria or other expert consensus statement) or specifically target subsets of the disease, such as emphysema or chronic bronchitis. This depends to a large extent on the mechanism of action of the drug being proposed. If a sponsor chooses to study a restricted subset of COPD either by specific intent or by the choice of entry criteria used, the indication would be appropriately restricted to the subset as well. Because emphysema and chronic bronchitis frequently coexist, it may be difficult to define clinical entry criteria sufficient to enroll patients with only one of these COPD subsets. Sponsors who intend to develop a drug for one subset should adequately address this issue.

4. Dose Selection

The dose or doses of drugs for definitive phase 3 efficacy and safety studies should be selected based on pharmacokinetic considerations and from earlier phase dose-ranging studies using a pharmacodynamic (PD) or clinical efficacy endpoint that is consistent with the expected benefit to be derived from the drug. The dose or doses selected for phase 3 studies should be based on benefit to risk assessment. If more than one dose is ultimately intended to be marketed, the clinical program design should produce data that allow for a comparative assessment of efficacy

and safety between the doses in addition to the usual comparison of the doses of the new drug to placebo. In circumstances where PD measures are used in phase 2 for dose identification, there is merit in considering including more than one dose level in at least one phase 3 study, even if the goal is to market a single dose. This is because even a well-validated PD endpoint may not fully predict efficacy as assessed by a clinical outcome endpoint in larger, longer term phase 3 studies, and usually will not be predictive of safety. Finally, with some treatment targets, there may be no known short-term PD or clinical endpoint that can be identified for dose-selection. This may be true, for instance, in disease modification therapies that do not affect short-term symptoms or lung function testing. In such cases, use of a range of doses in phase 3 studies is strongly encouraged.

5. Efficacy Assessment

The selection of efficacy endpoints for phase 3 studies depends on the drug's putative mechanism of action and the type of therapeutic claim sought. In the following sections, some efficacy endpoints that can be used in COPD studies are briefly discussed and grouped into broad categories of objective physiological assessments, patient- or evaluator-reported outcome measures, and biomarkers and surrogate endpoints. We recognize that not all efficacy endpoints will be appropriate for all drugs and other efficacy endpoints not discussed may be more appropriate for an NME.

a. Objective physiological assessments

The following objective physiological assessments should be considered.

- **Pulmonary function tests.** Pulmonary function testing by spirometry can be a useful way to assess airflow obstruction and, therefore, can be a useful tool to assess efficacy of a COPD treatment. Forced expiratory volume in one second (FEV1) obtained from typical spirometry is commonly used as an efficacy endpoint because FEV1 is a reflection of the extent of airway obstruction. Spirometry is also well standardized, easy to perform, and when conducted appropriately gives consistent, reproducible results across different pulmonary function laboratories. Air-trapping and hyperinflation are common features in COPD, particularly in the emphysematous-type, and are reflected in parameters of lung function testing, such as an elevation in the residual volume to total lung capacity ratio. Hyperinflation is believed to be responsible, at least in part, for the sensation of dyspnea. The division does not have a great deal of regulatory experience in the use of parameters of lung function other than spirometric measures in therapeutic approvals, but is open to considering alternative assessments. These alternatives should be discussed with the division early in drug development.

- **Exercise capacity.** Reduced capacity for exercise is a typical consequence of airflow obstruction in COPD patients, particularly because of dynamic hyperinflation occurring during exercise. Assessment of exercise capacity by treadmill or cycle ergometry combined with lung volume assessment potentially can be a tool to assess efficacy of a drug. Alternate assessments of exercise capacity, such as the Six Minute Walk or Shuttle Walk, also can be used. However, all these assessments have limitations. For instance,

the Six Minute Walk test reflects not only physiological capacity for exercise, but also psychological motivation. Some of these assessments are not rigorously precise and may prove difficult in standardizing and garnering consistent results over time. These factors may limit the sensitivity of these measures and, therefore, limit their utility as efficacy endpoints, because true, but small, clinical benefits may be obscured by measurement *noise*.

b. Patient- or evaluator-reported outcome measures

The following outcome measures should be considered.

- **Symptom scores.** Symptom scores determined by asking patients to evaluate specific symptoms on a categorical, visual, or numerical scale can be a simple way to assess efficacy of a drug based on the patient's own assessment of health status. Symptom scores can be valuable for assessing efficacy of a drug specifically aimed at relieving a symptom. In clinical programs aimed at other aspects of COPD, patient-reported symptom scores can be useful in assessing secondary effects of the therapy and may provide important additional evidence of efficacy. Symptom scores as the sole measure or primary measure of efficacy in COPD are discouraged because of their subjective nature, precision issues, and lack of standardization. If a symptom score is used, particularly a novel scoring, the issue of validation of the scoring should be addressed.

- **Activity scales.** Activity scales such as the Medical Research Council dyspnea score, the Borg Scale, and the Mahler Baseline Dyspnea Index/Transitional Dyspnea Index can be used as supportive of efficacy. These scales are relatively simple to administer, but they have limitations that make them unsuitable for use as the sole or primary evidence of efficacy and for supporting specific labeling claims. These scales were not specifically developed for use in clinical studies of drugs and their attributes in longitudinal interventional settings may not be fully elucidated. Also, the results can be difficult to interpret in terms of levels of clinical significance, because for some of these scales the minimal important difference has not been identified and validated. Scales that are third-party rated (e.g., Mahler's dyspnea indices) may prove less compelling than validated patient-rated instruments, because third-party assessments have been shown in some circumstances to be less reflective of patient status than first-party assessments. In addition, scales that require patients to recall prior symptoms (e.g., how do you feel now compared to baseline?) are problematic, because patients' memories may fade over time, particularly in studies lasting several months.

- **Health-related quality-of-life instruments.** Health-related quality-of-life instruments, such as the SGRQ and the Chronic Respiratory Questionnaire, are designed to systematically assess many different aspects of the effect of COPD on a patient's life. These instruments can be used to assess efficacy of a drug, but they have some limitations. These instruments are multidimensional and assess various effects of the disease on a patient's life and health status. Therefore, these instruments may be insufficient to determine a treatment effect in cases of a drug narrowly targeted to a specific, but clinically meaningful, aspect of COPD. When they are used to assess

efficacy in the setting of multinational trials, the instruments should be validated for all languages and cultures in which the studies are conducted (see Appendix A for additional information on the use of SGRQ in COPD studies).

c. Biomarkers and surrogate endpoints

With the exception of lung function tests, there are no well-validated biomarkers or surrogate endpoints that can be used to establish efficacy of a drug for COPD. For a nonbronchodilator drug, the use of lung function test parameters, such as FEV1, as a marker of disease status has become *validated* as a surrogate endpoint through years of clinical and regulatory experience, and is commonly used and accepted as an endpoint to support efficacy.

There are many biomarkers that can be considered for use in clinical studies. Some of these biomarkers include sensitive radiological evaluation of lung tissue structure (such as high-resolution chest computed tomography (CT)), concentration of certain gases in exhaled air or breath condensate, inflammatory mediators or cells in relevant biological fluids, and sensitive measures of airflow based on imaging of radiolabeled gases. With the possible exception of the high-resolution CT, none of these biomarkers are sufficiently validated to date for use as the primary evidence of efficacy or for supporting specific labeling claims. Some of the biomarkers may be technically challenging to perform or present important additional considerations (e.g., total X-ray dose exposure in patients subjected to multiple serial CT scans). These biomarkers and surrogates can be considered as supportive of the drug's putative mechanism of action. If proposed as primary assessments of efficacy, discussions with the division early on in development would be useful to allow for earlier phase studies to not only test the drug, but help establish validity of the measure itself. A single study should not be used to establish both the validity of a novel primary endpoint and the efficacy of the drug in question.

6. Recommended Primary and Secondary Efficacy Endpoints

For phase 3 studies, the primary and secondary efficacy endpoints should be chosen based on the drug's putative mechanism of action and the proposed indication. It is not possible to categorically state in all cases what the primary and secondary efficacy endpoints should be. Some common efficacy endpoints that may be suitable for use in the clinical studies of different types of drugs for COPD are mentioned in the following sections.

a. Primary efficacy endpoints

The following primary efficacy endpoints should be considered for the respective indications.

- **Improving airflow obstruction.** The primary efficacy endpoint should be change in post-dose FEV1 for a bronchodilator (e.g., a new beta-adrenergic agent or a new anticholinergic agent) and change in pre-dose FEV1 for a nonbronchodilator. A bronchodilator drug may improve the FEV1 from a direct effect on the airway smooth muscle, and a nonbronchodilator drug may improve the FEV1 by other mechanisms such as reduction of airway inflammation. For a bronchodilator drug, serial post-dose FEV1 assessments should be performed to characterize a time profile curve that will help in the

estimation of time to effect and duration of effect. Assessments of post-dose FEV1 for a bronchodilator drug and pre-dose FEV1 for a nonbronchodilator drug should be performed periodically over the duration of the study to ensure that the beneficial effect is sustained over time.

- **Providing symptom relief.** The primary efficacy endpoint should reflect the claimed clinical benefit (e.g., a drug intended to reduce cough should show that effect through assessments of coughing, subjectively and/or objectively measured). The selected primary efficacy endpoint should be clinically meaningful, and the magnitude of improvement that is proposed to be shown should be clinically relevant. In addition, if the action of the drug targets the underlying process, but manifests as symptom relief, secondary endpoints should assess other aspects of the drug's effects (e.g., measures of lung function, airflow, sputum production).

- **Modifying or preventing exacerbations.** The primary efficacy endpoint should be a clinically meaningful measure of exacerbations. Such measures can include the duration of exacerbations, severity of exacerbations, delay in the occurrence of an exacerbation, or reduction in the frequency of exacerbations. If one of these measures is chosen as the primary efficacy endpoint, the others also should be assessed to ensure that some other measure has not worsened. For instance, a delay in occurrence of a first exacerbation would not be clinically meaningful if the end result were more frequent exacerbations over a longer period of assessment. The protocol should define exacerbations in a way that is clinically meaningful, and specify criteria to determine when worsening of symptoms become an exacerbation. Criteria to consider in defining exacerbation include worsening of shortness of breath, increased sputum volume, increased purulence of sputum, worsening in symptoms requiring changes in treatment, or worsening of symptoms requiring urgent treatment or hospitalization. Because exacerbations are often associated with precipitous falls in airflow, the rapidity of recovery of a pulmonary function measure, such as FEV1, following an exacerbation to pre-exacerbation status also can be considered a reasonable primary efficacy endpoint.

- **Altering disease progression.** A preferred primary efficacy endpoint is the serial measurement of FEV1 over time, with the expectation that the FEV1 decline slopes will diverge in favor of active treatment (i.e., airflow is preserved relative to the comparator). When the claim is alteration of disease progression, such divergence should exclude the possibility of parallel declines in FEV1 with the active treatment offset by an initial and sustained bronchodilator effect. This latter circumstance may still be one in which a drug approval is possible (e.g., for a bronchodilation claim), but would not be appropriate for supporting a claim of altering disease progression.

- **Modifying lung structure.** The primary efficacy endpoint can be a sensitive radiological assessment of lung structure with supportive evidence that the regenerated lung tissue is functional and that the treatment provides clinically meaningful benefit to patients.

b. Secondary efficacy endpoints

Secondary efficacy endpoints can provide useful information on the effect of the treatment and should be selected to provide support to the primary efficacy endpoint. Secondary efficacy endpoints also can explore other effects of the drug on the disease. Commonly used secondary efficacy endpoints include various measures of lung function, exercise capacity, symptom scores, activity scales, and health-related quality-of-life instruments. Biomarkers can, in some cases, also provide support of efficacy. For some efficacy measures, such as symptom scores, activity scales, and disease-specific, health-related quality-of-life instruments, the threshold that defines a clinically meaningful improvement may not be well defined for use in clinical studies that test new drugs. Having such a *benchmark* of effect would be important in interpreting the meaning of differences shown in the clinical trials. Therefore, the protocol should define minimal clinically important difference with appropriate reasoning and justification. Consideration also should be given to the added complexity of the use of these measures in clinical studies for drugs, such as comparisons to baseline, comparisons to placebo, multiplicity, missing data, and the effect of study duration (e.g., recall of baseline status over time).

In studies where an objective measure is used as an endpoint, such as FEV1, use of subjective measures as important secondary assessments may be particularly useful in judging the value of mean changes in the primary endpoint. Similarly, in treatments intended to affect subjective perceptions of the disease through an effect on the underlying pathophysiology of COPD, secondary objective measures also can provide useful additional assessments to support the efficacy of the drug.

7. Study Duration

The duration of active treatment in the phase 3 studies that will support efficacy depends on the type of drug being developed, because different types of drugs will need different periods to show clinically meaningful effect. Differing claims also will demand differing durations of assessments.

- **Improving airflow obstruction:** the duration of treatment should be at least 3 months for a bronchodilator drug and at least 6 months for a nonbronchodilator drug. This is both to establish durable efficacy and to assess safety.

- **Symptom relief:** the duration of treatment should be at least 6 months.

- **Modifying or preventing exacerbations:** the duration of treatment may need to be at least 1 year. In studies for this type of claim, the timing of study treatment may prove important (e.g., capturing winter *cold* season in the majority of patients).

- **Altering disease progression:** the duration of treatment normally should be at least 3 years.

- **Modifying lung structure:** the duration of treatment will vary depending on the expected magnitude of clinically meaningful benefit, but likely will be several years in duration.

The durations of treatment described here refer to the portion of the clinical study intended to support efficacy. Longer durations of treatment may be needed to adequately assess safety.

8. Number of Studies

The number of studies that will support efficacy depends on the type of drug that is being developed. Generally, two confirmatory phase 3 studies should be conducted to establish efficacy for a drug being developed to improve airflow obstruction, provide symptom relief, or modify or prevent exacerbations. The two studies should provide replicated evidence of efficacy, but need not be identical in design. For a drug being developed to alter disease progression or modify lung structure, a single confirmatory study may be appropriate, provided the study is reasonably large, the endpoint is well validated, the findings are robust and clinically persuasive, and there is sufficient weight of evidence from prior data to suggest a clear benefit of the treatment.

9. Considerations Regarding Demonstration of Efficacy

For most drugs, phase 3 studies that use a single primary efficacy endpoint with supportive secondary efficacy endpoints will be adequate to establish efficacy, provided the efficacy findings are robust and clinically meaningful. Such a program should support an indication derived from the effect assessed by the primary efficacy endpoint used and the drug type.

It is possible that some drugs may have relatively small, but statistically significant, effects on a single measure of the disease that is made more clinically convincing through corroboration in other areas of the disease. This may be because of the mechanism of action of the drug or the inherent complexity and heterogeneity of COPD. In such a situation, two efficacy endpoints may need to be declared as primary endpoints in phase 3 studies to support efficacy. An example of using two primary efficacy endpoints would be measurement of lung function, such as FEV1, plus a measure of a patient-reported outcome, such as a validated symptom score, activity scale, or disease-specific, health-related quality-of-life instrument. The indication granted would reflect this broader assessment. When choosing multiple variables as primary endpoints, sponsors should consider issues of effect size and of multiplicity.

10. Considerations Regarding Demonstration of Safety

Treatment of COPD is usually prolonged; therefore, long-term data on safety evaluation should be collected. The extent of the safety database should be consistent with 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*. Sponsors should consider whether the drug is designed for intermittent or continuous use. Sponsors also should consider other concomitant diseases that COPD patients are likely to have and other concomitant drugs that these patients are likely to take. Finally, the intended use (i.e., treatment versus preventive)

may further inform the size and duration of safety assessments. In cases where efficacy studies are substantially less than 1 year, or if the drug is to be chronically administered, separate long-term safety studies should be conducted. Because the goal should be to rule out long-term effects on the disease characteristics, sponsors should consider including a control arm and assessing efficacy over time as well. In some cases, specific safety hypotheses should be tested, depending on if safety signals are identified during nonclinical studies or early clinical studies.

B. Specific Efficacy Study Considerations

1. Study Design

The nature and design of phase 3 studies depends on the type of drug that is being studied and the clinical benefit to be demonstrated. In general, studies should be placebo-controlled, double-blinded, randomized, and parallel-group in design. Use of an active comparator in addition to a placebo is, while encouraged, not necessary, unless comparative efficacy or safety claims are desired, or when there is uncertainty about a novel efficacy assessment methodology and a validation of the methodology is desired. The use of a placebo control does not necessarily preclude *usual care* treatment in patients randomized to placebo (see section III.B.3., Concomitant Treatments). The appropriateness of a placebo control may change in the future when drugs become available such that use of placebo control raises ethical issues (i.e., if a drug is shown to be convincingly effective in disease modification or changes mortality). This may be more relevant for certain types of studies, such as studies for drugs that alter disease progression. However, active-controlled studies can be a viable alternative to placebo controls when the intent of the study is to show superiority.

When there is a desire to show noninferiority to an active comparator and no placebo is planned, many important design issues are raised, including assay sensitivity, the noninferiority margin, and knowledge of how the chosen endpoint performs in historical studies with the active comparator. Proposing a noninferiority design is dependent on there being a well-defined, reproducible treatment effect for the established comparator such that the effect of that treatment in further studies can be inferred. Any such proposal should be carefully considered and discussed in depth with the division before starting clinical studies using this design.

2. Study Populations

In general, it is desirable to include patients broadly representative of the spectrum of the COPD population. Patients should be diagnosed for inclusion in the study based on accepted clinical practice parameters and criteria set by consensus panels (see References). Asthma and COPD can coexist and asthma is, in many senses, a more remediable disease. Therefore, in specific COPD drug development programs, patients whose primary disease is asthma should be excluded using existing guidelines for its diagnosis supported by assessment of FEV1 reversibility with a predefined criterion of reversibility that would classify a patient as asthmatic. For drugs designed to improve airflow obstruction, FEV1 reversibility should be determined using a beta-adrenergic agonist and/or an anticholinergic agent in all patients to serve as a basis for characterizing the patient population being studied, but not necessarily as a strict entry criterion. For drugs designed to provide symptom relief, enrollment of patients with consistent

clinical evidence of the symptoms being investigated during a baseline period should be included in the study.

3. Concomitant Treatments

Patients enrolled in the study should be permitted to use concomitant treatments as needed to manage disease symptoms. Use of concomitant treatments should be recorded for each patient throughout the study. 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 interpretation of the study to the need for any *rescue* medications for acute symptoms (e.g., corticosteroids in exacerbations).

4. Handling of Tobacco Smoking

Given the etiology of COPD, a large proportion of patients enrolled in the studies will be current or past tobacco smokers, and change of smoking status during the study may influence the outcome of a patient's response to the drug. The protocol should define how smoking status will be handled, including the way in which it will be monitored throughout the study, and how patients who change their smoking status during the study will be handled and accounted for in the analyses. It may be reasonable to stratify patients according to current and previous smoking status and conduct secondary analyses to determine the potential effect of smoking status on the investigational treatment. To assess the effect of change in smoking status during the study, it may be reasonable to conduct secondary analyses excluding patients who significantly change their smoking status during the study.

To maintain appropriate standard of care of patients enrolled in the studies, sponsors should encourage active smokers to discontinue tobacco smoking and provide appropriate counseling and help. This is particularly important for long-term studies, such as studies lasting for more than 3 months.

Another consideration with regard to smoking is that there are emerging data suggesting that in asthma, inhaled corticosteroids have less efficacy in smokers than in nonsmokers. It is possible that for certain therapies in the future, the indication of drugs for smoking-related pulmonary diseases may have specific wording regarding patient smoking status (e.g., drug X is indicated for active smokers with COPD). Although it is premature to make a definitive statement in this regard, sponsors should keep in mind that if they do not wish to contemplate such a restricted indication, clinical studies may need to include active smokers, ex-smokers, and, where applicable, nonsmokers.

C. Other Considerations

1. Drugs Administered by Inhaled Route

For drugs delivered by the orally inhaled route, the delivery systems, comprising the formulation and the device, may affect safety and efficacy. The development of the delivery system should

take into consideration the characteristics of the COPD patient population. For breath-actuated devices, the inspiratory flow-rate that will be necessary to activate the device should be such that a COPD patient can easily generate that level of flow. The device should have a dose indicator or counter that informs patients of the number of doses remaining. The device should be durable and the dexterity required to use the device should be within the capability of COPD patients who may often be elderly and may have co-existent arthritides. Phase 3 studies should assess device durability in patients' hands and assess whether patients can follow the instructions to use the device effectively.

It is likely that early phase clinical studies will be conducted using a prototype device and the device may undergo design changes as more information about it is gathered from in vitro studies and from early clinical studies. Depending on the design changes, in vitro and clinical data may be necessary to link the various versions of the device. Changes in the formulation, excipients, drug flow path, or device components that affect the drug delivery characteristics are critical and will likely affect the clinical performance of the drug product. Because most inhaled drugs do not have short-term PD endpoints suitable for establishing relative bioavailability (i.e., delivery to the site of action in the lungs, not systemic exposure), clinical studies may be needed to demonstrate clinical acceptability of such changes. To avoid having to conduct clinical bridging studies, critical clinical studies, such as definitive dose-finding studies and phase 3 efficacy and safety studies, should be conducted with the to-be-marketed formulation and device whenever possible.

2. Combination Drug Products

Given the complexity of COPD, it is possible that a single new 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. A combination drug product also can be for convenience where more than one singly active drug is formulated as one product. In most situations, the individual drugs are likely to have been previously evaluated and approved for use in humans. It is possible that one or more of the individual drugs may not be previously evaluated and approved for use in humans.

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 (21 CFR 300.50, combination rule). 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 clinical study to demonstrate that the combination drug product provides clinical benefit that is superior to each of its constituents. Because the pharmacological action of the two components may be disparate, the efficacy endpoint selected to show superiority of the combination drug product to one component may be different than the efficacy endpoint selected to show superiority to another component (i.e., two primary endpoints may be assessed, one for drug A versus combination drug AB and another for drug B versus combination drug AB). In these cases, the study should show separate superiority on both endpoints to meet the combination rule.

REFERENCES

American Thoracic Society, 1995, Standards for the Diagnosis and Care of Patients With Chronic Obstructive Pulmonary Disease, *Am. J. Respir. Crit. Care Med.*, 152:S77-S120.

British Thoracic Society Guidelines for COPD, 1997, *Thorax.*, 52 (Suppl 5):S1-S28.

Global Initiative for Chronic Obstructive Lung Disease (GOLD), updated December 2015, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease (http://www.goldcopd.com).

National Institute for Clinical Excellence, 2004, Clinical Guideline 12: Chronic Obstructive Pulmonary Disease, *Thorax.*, 59 (Suppl 1):1-232.

Siafakas, NM, P Vermeire, NB Pride, P Paoletti, J Gibson, P Howard, JC Yernault, M Decramer, T Higenbottam, DS Postma, et al., 1995, Optimal Assessment and Management of Chronic Obstructive Pulmonary Disease (COPD), The European Respiratory Society Task Force, *Eur Respir J.*, Aug. 8(8):1398-420.

APPENDIX A: ST. GEORGE'S RESPIRATORY QUESTIONNAIRE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE STUDIES[4]

Introduction

This appendix provides information on the St. George's Respiratory Questionnaire (SGRQ), as a patient-reported outcome (PRO) assessment in interventional clinical trials in patients with chronic obstructive pulmonary disease (COPD). There are several versions of the SGRQ; up-to-date information, versions, translations, and manuals for each version can be found on the developer's instrument Web site.[5] The original SGRQ is a 50-item questionnaire with 76 weighted responses. There are several versions of the 50-item instrument, each with a different recall period: 1 year, 3 months, or 4 weeks. As of March 2016, only the 3-month and 4-week recall versions were available from the developer.[6] The shorter 40-item COPD-specific version, SGRQ-C, does not have a defined recall period. Not all versions have equivalent validation information. Throughout this appendix, the term *SGRQ* refers to the 50-item, 3-month or 4-week recall version, or the 40-item SGRQ-C version, unless otherwise specified.

Administration and Scoring of SGRQ

The SGRQ is self-administered and should be administered and scored in accordance with current manuals, as appropriate. Versions in languages other than English should undergo linguistic and cultural validation for all languages and cultures in which the studies are conducted. The SGRQ can be administered using a paper or electronic platform, provided the latter development has followed accepted procedures (Coons, Gwaltney, et al. 2009).

The SGRQ total score is made up of three components: (1) Symptoms — frequency and severity of symptoms; (2) Activity — effect of disease on common daily physical activities; and (3) Impacts — psycho-social effects of the disease. Only the total score should be used in the context of this guidance. Use of one or more individual domains, as a measure in clinical trials, should be discussed with the division.

The minimum clinically important difference for the total score between patients and within-patient has been determined to be at least 4 units on the SGRQ scale (Jones 2002; Jones 2005). There is no evidence to support the use of other values.

Method of Analysis of SGRQ

Responder analysis is the preferred primary method for reporting results from SGRQ data. This analysis compares those who improve with those who deteriorate or do not change. Responder

[4] The references for Appendix A are listed in Appendix B.

[5] See the St. George's University of London Health Status Research Web site at http://www.healthstatus.sgul.ac.uk/.

[6] Ibid.

analyses may be presented as the responder rate for each arm and the difference in the responder rates, or the Odds Ratio. Other analyses may be appropriate and should be discussed with the division.

Because the time course of SGRQ responses may provide useful information, frequent measurements (e.g., once a month[7]) during a clinical trial are appropriate. Because treatment effect may be slow in onset, in shorter trials (such as those of 6 months or less), an average estimate over the study period may underestimate the benefit with chronic therapy; end-of-treatment measurements may provide a more accurate estimate of the benefit from chronic use therapies. In longer studies, taking an average over the latter part of the study period, such as over the last 3 months, may be appropriate.

Missing data should be considered at the study design stage, and plans for dealing with it should be adequately addressed in the analysis, because an absent SGRQ caused by patient withdrawal may not be missing at random. Methods of addressing missing data should be discussed with the division during the protocol development phase.

Use of SGRQ

SGRQ is designed to measure health status in patients with obstructive airway diseases such as COPD. In patients with COPD, scores from the SGRQ may be obtained either through the use of the SGRQ or through the shorter COPD-specific version, SGRQ-C. Both versions are acceptable in COPD trials. However, within the same drug development program, or at least within the same trial, only one version should be used (i.e., either one of the two SGRQ versions or the SGRQ-C).

The SGRQ can be used as a PRO assessment of efficacy in submissions to investigational new drug applications, new drug applications, and biologics license applications. Use of the SGRQ for stratification or enrichment purposes should be discussed with the division early during the protocol development phase. Development of the SGRQ has been described for the COPD population in the literature (Jones, Quirk, et al. 1992; Meguro, Barley, et al. 2007).

SGRQ can be used as a co-primary endpoint,[8] or as a secondary endpoint providing supporting evidence of efficacy in a clinical trial. For example, use of SGRQ can be considered as a co-primary endpoint, along with another measure of efficacy (such as measure of lung function), for a drug that has a relatively small effect on a single outcome measure (such as lung function), which can be made more clinically convincing through corroboration by SGRQ data. In general, SGRQ information is considered clinically important, and the data obtained in clinical trials should be reported irrespective of the direction of the results.

[7] Applicable to SGRQ-C, which does not have a specific recall period, or the version of the SGRQ with a 4-week recall period, but not applicable to the version of the SGRQ that has a 3-month recall.

[8] Multiple primary endpoints become co-primary endpoints when it is necessary to demonstrate an effect on each of the endpoints to conclude that a drug is effective.

APPENDIX B: REFERENCES FOR ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

Cazzola, M, NA Hanania, W MacNee, K Rüdell, C Hackford, and N Tamimi, 2015, A Review of the Most Common Patient-Reported Outcomes in COPD — Revisiting Current Knowledge and Estimating Future Challenges, *International Journal of COPD*, 10:725-738.

Coons, SJ, CJ Gwaltney, RD Hays, JJ Lundy, JA Sloan, DA Revidki, WR Lenderking, D Cella, E Basch, and ISPOR ePRO Task Force, 2009, Recommendations on Evidence Needed to Support Measurement Equivalence Between Electronic and Paper-Based Patient-Reported Outcome (PRO) Measures: ISPOR ePRO Good Research Practice Task Force Report, *Value Health*, 12(4):419-9.

Glaab, T, C Vogelmeier, and R Buhl, 2010, Outcome Measures in Chronic Obstructive Pulmonary Disease (COPD): Strengths and Limitations, *Respiratory Research*.

Jones, PW, 2002, Interpreting Thresholds for a Clinically Significant Change in Health Status in Asthma and COPD, *European Respiratory Journal*, 19:398-404.

Jones, PW, 2005, St George's Respiratory Questionnaire: MCID, *Journal of COPD*, 2:75-9.

Jones, PW, FH Quirk, CM Baveystock, and P Littlejohns, 1992, A Self-Complete Measure of Health Status for Chronic Airflow Limitation, *American Review of Respiratory Disease*, 145:1321-1327.

Martinez, FJ, JF Donohue, and SI Rennard, 2011, The Future of Chronic Obstructive Pulmonary Disease Treatment — Difficulties of and Barriers to Drug Development, *Lancet*, 376:1027-1037.

Meguro, M, EA Barley, S Spencer, and PW Jones, 2007, Development and Validation of an Improved, COPD-Specific Version of the St. George Respiratory Questionnaire, *Chest*, 132:456-463.

Schünemann, HJ, L Griffith, R Jaeschke, R Goldstein, D Stubbing, and GH Guyatt, 2003, Evaluation of the Minimal Important Difference for the Feeling Thermometer and the St. George's Respiratory Questionnaire in Patients With Chronic Airflow Obstruction, *Journal of Clinical Epidemiology*, 56:1170-1176.