Guidance for Industry

Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit 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 Steven Gitterman at 301-796-1600.

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

August 2008
Clinical Antimicrobial
Revision 1

FDA-2008-D-0419 GDL

1:4511dft.doc
07/21/08

Guidance for Industry

Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment

Additional copies are available from:

Office of Training and Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

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

August 2008
Clinical Antimicrobial
Revision 1

TABLE OF CONTENTS

I. INTRODUCTION **1**

II. BACKGROUND **2**

III. DEVELOPMENT PROGRAM **3**

A. General Considerations **3**

1. Early Phase Clinical Development Considerations *3*
2. Definition of ABECB-COPD *3*
3. Efficacy Considerations *3*
4. Safety Considerations *4*

B. Specific Efficacy Trial Considerations **5**

1. Study Design *5*
2. Study Population *6*
3. Study Inclusion Criteria *6*
a. Patient history and characteristics 7
b. Signs and symptoms 7
4. Study Exclusion Criteria *8*
5. Randomization, Stratification, and Blinding *9*
6. Dose Selection *9*
7. Choice of Comparators *9*
8. Concomitant Medications *9*
9. Efficacy Endpoints *10*
a. Evaluation of clinical response 10
b. Clinical relapse or recurrence 11
c. Adverse events or receipt of additional antibacterial therapy 12
d. Microbiological response 12
10. Study Visits and Timing of Assessments *12*
a. Entry visit 12
b. On-therapy visits 14
c. Early follow-up visit 15
d. Late follow-up assessment 16
e. Safety evaluations 16
11. Statistical Considerations *16*
a. Analysis populations 17
b. Noninferiority margins 18
c. Sample size 18
d. Missing data 18
e. Interim analyses and data and safety monitoring boards 18
f. Other analyses of interest and secondary endpoints 19
g. Statistical analysis plan 19
12. Ethical Considerations *19*

C. Other Considerations **20**

1. Animal Models *20*
2. Labeling *20*
3. Antimicrobial Resistance Claims *20*

Contains Nonbinding Recommendations
Draft — Not for Implementation

Guidance for Industry[1]
Acute Bacterial Exacerbations of Chronic Bronchitis in Patients with Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs 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

The purpose of this guidance is to assist sponsors in the clinical development of antimicrobial drugs for the treatment of acute bacterial exacerbations of chronic bronchitis in patients with chronic obstructive pulmonary disease (ABECB-COPD). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and designs of clinical trials for antimicrobial drug products to support an indication for treatment of ABECB-COPD.[2] This guidance does not address issues related to the development of drugs for other purposes such as prevention of respiratory tract infections in patients with COPD or in other populations, such as otherwise healthy persons. We expect that this guidance will serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Products, the Division of Special Pathogen and Transplant Products, and pharmaceutical sponsors, the academic community, and the public.[3] Since the science of this indication continues to evolve, this guidance may be revised as new information becomes available.

This guidance revises the draft guidance for industry *Acute Bacterial Exacerbation of Chronic Bronchitis — Developing Antimicrobial Drugs for Treatment* published in 1998. It also

[1] This guidance has been prepared by the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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

[3] In addition to consulting guidance documents, sponsors are encouraged to contact the divisions to discuss specific issues that arise during the development of antimicrobial drug products.

supersedes, with regard to the development of drugs to treat ABECB-COPD, more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective drugs (Systemic)* and *Clinical Development and Labeling of Anti-Infective Drug Products*,[4] as well as the joint FDA/Infectious Disease Society of America's *Guidelines for the Evaluation of Anti-Infective Drug Products*).[5]

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials*, *E9 Statistical Principles for Clinical Trials*, and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[6] This guidance focuses on specific drug development and trial design issues that are unique to the study of ABECB-COPD; it does not address issues regarding the development of drugs for COPD or COPD exacerbations caused by factors other than bacterial infection. Information regarding developing drugs for the treatment of COPD is available in the draft guidance for industry *Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment*.[7]

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

Since the FDA published draft guidance on the development of antimicrobial drugs for the treatment of ABECB in 1998, there have been public discussions regarding the design of clinical trials to study indications for infections involving the respiratory tract, including the indication of ABECB-COPD.[8] These discussions have focused on the appropriateness of noninferiority trial designs for ABECB-COPD and other important study design issues such as the following:

---

[4] See the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[5] Beam, TR, DN Gilbert, and CM Kunin, 1992, General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, Infectious Disease Society of America and the Food and Drug Administration, Clinical Infectious Diseases, Nov.15, Supplement 1:S5-32.

[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[7] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[8] The design of ABECB clinical trials was discussed at a meeting of the Anti-Infective Drugs Advisory Committee on February 19, 2002, and an IDSA/PhRMA/FDA workshop on November 19-20, 2002. Transcripts of these meetings are available at http://www.fda.gov/cder/audiences/acspage/antiinfectivemeetings1.htm and http://www.fda.gov/cder/present/idsaphrma/default.htm, respectively.

- Inclusion criteria
- Application of appropriate diagnostic criteria
- Use of appropriate definitions of clinical outcomes
- Timing of outcome assessments
- Use of concomitant medications
- Role of microbiological outcomes

Important changes from the 1998 draft guidance that are based on these discussions have been incorporated into the appropriate sections below.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

New drugs being studied for ABECB-COPD should have preclinical data documenting activity against the pathogens most commonly associated with ABECB-COPD (i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*).

2. Definition of ABECB-COPD

The term ABECB-COPD is used in this guidance to more accurately identify the disease that has previously been referred to as acute bacterial exacerbations of chronic bronchitis. ABECB-COPD refers to a clinical diagnosis of presumptive bacterial infection superimposed on a chronic pulmonary condition. This situation is best described pathologically as bronchial inflammation associated with the isolation of pathogenic bacteria from sputum or bronchial lavage specimens. However, it is important to note that there is some uncertainty as to the role of bacteria in causing ABECB-COPD because chronic bacterial colonization may be present in the airways of patients with COPD.

The acute component of ABECB-COPD is usually manifest as worsening of the same symptoms patients experience when they are not experiencing an acute infection. Accordingly, to enroll patients in studies of ABECB-COPD, clinical trials should be designed to:

- Define and document the underlying pulmonary condition in enrolled patients
- Accurately measure the symptoms of the acute episode at study entry
- Define the criteria for occurrence of an episode of ABECB-COPD (i.e., the change in symptoms that define an acute episode against the background of chronic pulmonary disease)

3. Efficacy Considerations

FDA review of previous ABECB-COPD studies has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABECB-COPD by antimicrobials (a precondition for

114 a noninferiority trial).[9] Accordingly, only superiority trials are currently recommended for
115 ABECB-COPD studies.
116
117 The goal of ABECB-COPD clinical trials should be to demonstrate an effect of antibacterial
118 therapy on the clinical course of ABECB-COPD presumptively associated with *H. influenzae*, *S.*
119 *pneumoniae*, or *M. catarrhalis*. If sponsors wish to add additional organisms to this indication,
120 they should provide data sufficient to substantiate the clinical relevance of the particular
121 organism as a pathogen in ABECB-COPD. Bacteria that may be colonizers following recent
122 antimicrobial therapy are unlikely to be pathogens in this setting.
123
124 The number of studies that should be conducted in support of an ABECB-COPD indication
125 depends on the overall development plan for the drug under consideration. If the development
126 plan for a drug has ABECB-COPD as the sole marketed indication, then at least two adequate
127 and well-controlled trials establishing safety and efficacy should be conducted.
128
129 A single randomized, double-blind study supporting the indication may be appropriate if the
130 sponsor has access to confirmatory evidence including data from other clinical studies
131 demonstrating effectiveness in other lower respiratory tract diseases and there is additional
132 supportive information such as pharmacokinetic (PK) and pharmacodynamic (PD) studies
133 demonstrating concentration of the antibacterial drug in the bronchi at a level expected to be
134 active against the common pathogens causing ABECB-COPD. For example, robust findings of
135 efficacy from well-designed community-acquired pneumonia trials with similar dosing regimens
136 may be supportive of a single superiority trial of ABECB-COPD.
137
138 Currently, there are no surrogate markers accepted by the FDA as substituting for clinical
139 outcomes in ABECB-COPD studies. Sponsors who wish to propose use of a surrogate marker
140 should discuss this with the FDA early in the drug development process.
141
142 *4. Safety Considerations*
143
144 A sufficient number of patients should be studied at the exposure (dose and duration) proposed
145 for use to draw appropriate conclusions regarding drug safety. This includes the ability to
146 evaluate the potential for relatively uncommon serious adverse events as well as commonly
147 expected adverse events. The information should be derived primarily from adequate and well-
148 controlled studies of ABECB-COPD, but also can be derived from studies of the new drug for
149 infections other than ABECB-COPD if exposure is similar to or greater than the exposure for
150 ABECB-COPD. The total number of patients needed for a drug development program that
151 includes an ABECB-COPD indication should be discussed with the FDA early in the drug
152 development process.
153
154 Antimicrobials with clinically significant toxicity may not be appropriate for study of ABECB-
155 COPD unless the treatment goal is directed at a more seriously ill patient portion of the ABECB-
156 COPD population.
157

[9] See ICH E10 (http://www.fda.gov/cder/guidance/index.htm).

158 **B. Specific Efficacy Trial Considerations**
159
160 *1. Study Design*
161
162 As previously mentioned, we recommend only superiority trials for ABECB-COPD studies.[10]
163 Superiority trials in the treatment of ABECB-COPD can consist of the following forms:
164
165 • **Placebo-controlled study with a background of *optimized* nonantimicrobial therapy**
166 — Patients in one study arm receive an experimental drug added to a standardized
167 nonantimicrobial regimen. To demonstrate efficacy, the arm receiving the test
168 antimicrobial should demonstrate superiority to a control arm of the same standardized
169 nonantimicrobial therapy plus matching placebo.
170
171 A three-arm study with the experimental treatment group, an active control arm (e.g., an
172 antibacterial drug approved for ABECB-COPD), and a placebo-controlled group permits
173 the demonstration of superiority and also can provide risk-benefit information relative to
174 an approved comparator.
175
176 • **Dose-response** — Patients in each study arm receive different antimicrobial doses (or
177 dosing regimens) together with standardized nonantimicrobial therapy. To demonstrate
178 efficacy, the arm receiving a higher dose (or more intensive therapy) should be superior
179 to the lower dose (or less intensive) regimen.
180
181 • **Delayed versus immediate therapy** — Patients in both study arms receive an active
182 therapy, but administration of the comparator treatment is delayed relative to the
183 experimental drug (i.e., one group is started on placebo but then switched to active
184 therapy after a protocol-defined interval). Both groups remain blinded to treatment
185 assignment for the entire study; to demonstrate efficacy, immediate therapy should be
186 superior to delayed therapy.
187
188 • **Superiority of the study antimicrobial to another antimicrobial** — Patients in one
189 arm receiving the test drug (with standardized background nonantimicrobial therapy) are
190 compared to patients in a control arm receiving another antimicrobial drug approved for
191 the treatment of ABECB-COPD (with standardized background nonantimicrobial
192 therapy). To demonstrate efficacy, the arm receiving the test antimicrobial should
193 demonstrate superiority to the arm receiving the control antimicrobial.
194
195 A study design can be used where patients are enrolled at days 4 to 7 and a 3-day run-in period is
196 used before randomization. Randomization of patients with symptoms that have not improved

[10] FDA review of previous ABECB-COPD studies has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABECB-COPD by antimicrobials (a precondition for a noninferiority trial). Sponsors who are considering a noninferiority trial for ABECB-COPD should justify to the FDA the proposed noninferiority margin by data that include reliable estimates of a well-defined efficacy outcome measure. Such justification should be discussed with the FDA as early as possible during protocol development and before study initiation. See also ICH E10 (http://www.fda.gov/cder/guidance/index.htm).

197 over the 3-day run-in period may enrich the study population for patients with ABECB-COPD
198 rather than a nonbacterial etiology for worsening of symptoms.
199
200 ABECB-COPD trials should be parallel group designs because crossover designs may be subject
201 to carryover and period effects.
202
203 *2. Study Population*
204
205 ABECB-COPD clinical trials should enroll males and females 35 years old and older because
206 COPD occurs primarily in older individuals; a diagnosis in younger individuals may reflect
207 misclassification. We anticipate that most patients in ABECB-COPD clinical trials will be older
208 than 50 years of age.
209
210 We recognize that it is not appropriate for patients with severe COPD (i.e., patients who are
211 mechanically ventilated) to be enrolled in placebo-controlled studies of a new antibacterial for
212 ABECB-COPD. We strongly encourage discussion with the appropriate review division if study
213 of patients with severe COPD is being considered.[11] It is essential that in any proposed trials,
214 adequate provisions are in place so that human subjects are not exposed to an unreasonable and
215 significant risk of illness or injury (21 CFR 312.42).
216
217 *3. Study Inclusion Criteria*
218
219 The diagnosis of ABECB-COPD can be challenging. Both a diagnosis of COPD and an acute
220 change superimposed against the background of chronic symptoms are needed for study
221 enrollment.
222
223 Traditionally, COPD has been defined as containing aspects of chronic bronchitis and
224 emphysema. A diagnosis of chronic bronchitis is made clinically based on the presence of
225 symptoms of cough and sputum production on most days of 3 consecutive months in at least 2
226 consecutive years. Although useful for clinical practice, this definition lacks specificity for
227 clinical trials because there is no standardized definition of the number of days that constitutes
228 *most* days of 3 months out of the year or quantification of degree of sputum and cough.
229
230 Because of the overlap of symptoms in patients with chronic bronchitis and/or emphysema and
231 the limitations of the definition of chronic bronchitis, it is more appropriate to use the term
232 COPD to describe the underlying disease in this patient population. The definition and severity
233 of underlying obstructive pulmonary disease is based on the results from spirometry testing
234 compared to predicted normative values as follows:
235
236 - Mild COPD = FEV1/FVC < 70% and FEV1 ≥ 80% predicted
237 - Moderate COPD = FEV1/FVC < 70% and 50% ≤ FEV1 < 80%
238 - Severe COPD = FEV1/FVC < 70% and 30% ≤ FEV1 < 50%
239 - Very severe COPD = FEV1/FVC < 70%, and FEV1 < 30% predicted or FEV1 < 50%
240 plus chronic respiratory failure

[11] See section III.B.12., Ethical Considerations.

241
242 Spirometry may be difficult to perform at the time of an acute bacterial exacerbation of chronic
243 bronchitis as these tests are effort dependent. Spirometry data used for enrollment should be
244 obtained from recent medical records; patients without spirometry-documented COPD should
245 not be enrolled in studies of ABECB-COPD. Spirometry data obtained at the time an episode of
246 ABECB-COPD is diagnosed have not been demonstrated to be predictive of severity or outcome.
247
248 The diagnosis of an acute exacerbation presents additional concerns. A diagnosis of ABECB-
249 COPD reflects a change in patient symptoms from their usual baseline; for a trial to demonstrate
250 efficacy of antimicrobial therapy to be effective, patients who have a true change in symptoms
251 should be selected.
252
253 The specificity of sputum cultures for selecting patients with bacterial disease is unknown in
254 ABECB-COPD since sputum is not normally sterile between exacerbations in these patients, and
255 the etiologic role of bacteria in ABECB-COPD is uncertain. However, if there is a pathogenic
256 role for bacteria in this disease, a negative sputum culture may reduce the chance of
257 demonstrating a significant benefit from an antibacterial drug. Sponsors may wish to restrict
258 enrollment in trials to patients with a positive sputum culture at baseline for any one of the three
259 most common bacteria implicated as a cause of ABECB-COPD (i.e., *S. pneumoniae*, *H.*
260 *influenzae*, and *M. catarrhalis*).[12]
261
262 The following inclusion criteria should be used for patient enrollment in studies conducted for
263 the treatment of ABECB-COPD.
264
265 a. Patient history and characteristics
266
267 The following patient demographic characteristics should be used for a better chance of selecting
268 patients more likely to have ABECB-COPD:
269
270 • Male and female patients 35 years old and older
271 • History of at least mild COPD previously defined by the spirometry criteria above
272 • History of more than two previous episodes of acute bronchitis (acute exacerbations) in
273 the previous year
274 • History of tobacco use consistent with a diagnosis of COPD
275
276 b. Signs and symptoms
277
278 Signs and symptoms that can be present in patients with ABECB-COPD include the following:
279
280 • Dyspnea or breathlessness
281 • Cough
282 • Chest tightness or discomfort

[12] This situation can be addressed by use of a run-in period, when patients with a negative culture at baseline are excluded before beginning study therapy or during analysis by analyzing patients with a positive culture at baseline separately. This is discussed further in sections III.B.10, Study Visits and Timing of Assessments, and III.B.11, Statistical Considerations.

283 • Sleep disturbances (i.e., insomnia or sleepiness)
284 • Decrease in exercise tolerance or limitation of usual activities
285 • Increase in sputum volume and/or sputum purulence
286 • Wheezing
287 • New or worsening crackles on auscultation of lung fields
288
289 Generalized signs and symptoms that are consistent with a diagnosis of ABECB-COPD (but are
290 otherwise nonspecific) include:
291
292 • Fever (temperature greater than 38.5 degrees Centigrade)
293 • Malaise or fatigue
294 • Confusion or change in mental status
295
296 All signs and symptoms that may be present in patients with ABECB-COPD should be captured
297 on the case report form, as should current tobacco use.[13]
298
299 *4. Study Exclusion Criteria*
300
301 The following patients should be excluded from trials for the treatment of ABECB-COPD:
302
303 • Patients with pneumonia documented by chest X ray at the time of initial screening. All
304 patients should receive a screening chest X ray before or at enrollment.
305 • Patients with asthma (i.e., reversible obstruction of airflow with administration of
306 bronchodilators by pulmonary function testing or a history of asthma).
307 • Patients with any concomitant illness that may confound the interpretation of the effect of
308 study medications (e.g., pulmonary malignancy, congestive heart failure, bronchiectasis,
309 pneumothorax).
310 • Immunocompromised patients; however, patients receiving systemic corticosteroids at
311 baseline for treatment of COPD can be enrolled.
312 • Patients who are allergic to any of the study medications.
313
314 Sponsors may wish to exclude patients with a negative sputum culture at baseline; however, if
315 these patients are included, stratification for this baseline characteristic should be included and
316 the statistical analysis plan should include testing for the potential effect of a positive baseline
317 culture. Depending on the trial design, sponsors also may wish to exclude patients who have
318 received antimicrobial therapy for the current episode of ABECB-COPD, or alternatively, permit
319 enrollment of patients with prior antimicrobial use only if there is a positive sputum culture
320 despite therapy. If patients who have received prior antimicrobial therapy are included, prior
321 antibacterial drug therapy should be included as a stratification factor before enrollment.
322

[13] Use of a patient-reported outcome (PRO) instrument is recommended for capturing clinical response. PROs are discussed further in section III.B.9., Efficacy Endpoints.

323 *5. Randomization, Stratification, and Blinding*
324
325 Patients should be randomized for receipt of study drugs at enrollment. All studies should be
326 double-blinded for study therapy.
327
328 *6. Dose Selection*
329
330 Data from phase 1 and phase 2 studies and dose-ranging PK/PD studies (including information
331 regarding bronchial/lung penetration of the drug) can be integral to selecting an appropriate dose
332 for phase 3 clinical trials.
333
334 *7. Choice of Comparators*
335
336 As previously mentioned, only superiority trials for ABECB-COPD studies are recommended.[14]
337 The control arm for these superiority studies can be placebo or another antibacterial drug.
338
339 *8. Concomitant Medications*
340
341 All patients should receive (or be receiving) bronchodilator and/or systemic corticosteroid
342 therapy at the time of enrollment. Lack of standardization of concomitant medications can
343 introduce an important source of confounding in clinical trials if there are imbalances in receipt
344 of nonantimicrobial therapy between trial groups. Such confounding may occur even if the
345 number of patients receiving concomitant medications is similar between study groups but the
346 reasons for administering concomitant medications differ. Confounding also may occur when
347 the patients in one group who receive concomitant medications differ in baseline characteristics
348 from those patients who do not receive concomitant medications. Therefore, sponsors should
349 make every attempt to control for potential confounders such as concomitant medications during
350 the study. This can be accomplished through a protocol-specified nonantimicrobial background
351 regimen with the dose and frequency of use similar for all patients in the trial (e.g.,
352 bronchodilator treatment or protocol-specified rules for the addition of nonantimicrobial therapy
353 such as corticosteroids). At a minimum, the protocol should specify appropriate options for
354 nonantimicrobial therapies during the study.
355
356 We anticipate that changes in the use of the following medications will be monitored or specified
357 in an ABECB-COPD study:
358
359 • Changes in the frequency or dose of beta-agonist therapy, or the addition of new beta-
360 agonist therapy (long- or short-acting therapy)
361 • Changes in the frequency or dose of anticholinergic therapy or the addition of an
362 anticholinergic therapy
363 • Addition of methylxanthine therapy
364 • Changes or the addition of systemic corticosteroids; systemic corticosteroids should be
365 administered in a standardized way to all patients with a pre-enrollment FEV1 of < 50%
366 of predicted FEV1

[14] See note 9, supra.

367
368 Assessment of the need for concomitant medications as an endpoint may not be an accurate
369 surrogate for persistent patient signs or symptoms; the presence of such signs or symptoms
370 should be confirmed by a patient-reported outcome (PRO) instrument that shows continued signs
371 or symptoms at the time of administration of the concomitant medication. Efforts should be
372 made to capture all concomitant medication use on a PRO instrument and to relate this
373 information to patient signs or symptoms.
374
375 *9. Efficacy Endpoints*
376
377 a. Evaluation of clinical response
378
379 The primary emphasis of the study should be the effect of the antimicrobial drug on outcomes
380 that are clinically important to patients. A well-defined and reliable method of assessing patient
381 symptoms should be used for ABECB-COPD studies; accordingly, only use of a reliable PRO
382 instrument is recommended as the primary outcome measure.[15] The PRO also should be used at
383 baseline to define enrollment criteria; there should be a sufficient *score* on the PRO instrument
384 such that a clinically meaningful response (i.e., change on the PRO instrument) can be observed.
385 The amount of improvement determined to be clinically meaningful (and therefore appropriate
386 for regulatory decisions) should be determined during instrument development and should be
387 discussed with the FDA before study initiation. Statistically significant differences between
388 comparator regimens may not be sufficient for demonstrating benefit if response to treatment has
389 not been confirmed to be clinically meaningful. For example, signs or symptoms used to
390 diagnose ABECB-COPD that may be important to a clinician, such as the color of sputum, may
391 not be an important outcome to patients and therefore would not be appropriate as part of the
392 response instrument scale score.
393
394 If an adequate instrument is not available for studying ABECB-COPD, we recommend that the
395 new instrument development process begin well in advance of phase 3 clinical trials so that the
396 instrument can be ready for incorporation into the phase 3 protocol. If the plan is to enroll
397 patients with very severe COPD or acute exacerbations, use of a caregiver-reported outcome
398 instrument may be necessary when patients cannot respond themselves.
399
400 Assessment of clinical response at each time point should not be limited solely to symptoms
401 identified at enrollment but should also capture symptoms that occur after study entry. A
402 combined endpoint, including symptom assessment by a PRO instrument and other significant
403 events (e.g., respiratory failure), is most appropriate in ABECB-COPD, with the expectation that
404 the overall study result will be driven primarily by outcomes related to patient symptoms.
405

[15] The use of a well-defined and reliable PRO instrument, even for a categorical response, can yield greater assurance that symptoms are being measured in a consistent manner across patients. For more information regarding the development of PRO measures, see the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

406 Patients with ABECB-COPD are unlikely to be asymptomatic at the end of study treatment, and
407 may not even return to their baseline status before the onset of the acute episode. Improvement
408 of symptoms over time as measured by a well-defined and reliable PRO measure should be the
409 primary efficacy endpoint rather than return to previous baseline.
410
411 Since exacerbations are often associated with precipitous declines in airflow, the rapidity of
412 recovery of a pulmonary function measures, such as FEV1, following an exacerbation to pre-
413 exacerbation status also can be considered as an important possible primary efficacy endpoint.
414 However, use of this endpoint involves the collection of recent pre-exacerbation FEV1
415 measurements.
416
417 A fixed time endpoint may not be as sensitive a measure of treatment effect as a time-to-
418 resolution analysis. For example, clinical outcome at greater than 3 weeks after onset of therapy
419 may not show a difference between treatment arms since many patients may have resolution of
420 the acute exacerbation by this time, regardless of the administration of antibacterial drug therapy.
421 Sponsors who choose to use response at a fixed time point as the primary outcome (i.e., as the
422 *test-of-cure* assessment) should provide evidence to support the selection of that specific time
423 point.
424
425 An outcome scale can be used for describing categorical responses (e.g., *improvement* or *failure*)
426 at each time point if the criteria for the categories are well-defined and reliable. Overall response
427 should also incorporate survival and the absence of complications of ABECB-COPD (e.g., the
428 development of pneumonia should be considered a clinical failure) as part of the overall response
429 assessment. Failure criteria should be defined *a priori* (e.g., protocol defined worsening of
430 symptoms, failure to improve at certain time points after treatment onset). Failure should likely
431 mandate a change in treatment, which would now include *active* therapy for the placebo arm.
432
433 Objective measures such as peak expiratory flow or exercise testing (e.g., a *six-minute walk*) can
434 be incorporated into a clinical protocol and should be considered secondary outcome measures.
435
436 Patients designated as clinical failures at any time point should be designated as clinical failures
437 for all subsequent follow-up visits.
438
439 Early clinical assessment for treatment failure is needed in a placebo-controlled trial so that
440 *rescue* therapy can be incorporated into the study design at the time a failure outcome is
441 assigned; this process can serve to mitigate concerns regarding inclusion of a placebo arm in an
442 ABECB-COPD trial.
443
444 b. Clinical relapse or recurrence
445
446 Since it is unlikely that patients will exhibit a complete resolution of symptoms, there should be
447 no separate categories for success or relapse. However, patients who return to baseline at the end
448 of study treatment can be assessed for the recurrence of symptoms that meet the study definition
449 of ABECB-COPD. These patients should be evaluated (clinically and microbiologically) as
450 would a new patient being entered into the study. This may be useful for studies that examine

451 recurrence as a secondary endpoint (i.e., assessment of the prolonged effect from antibacterial
452 treatment of a single episode).
453
454 c. Adverse events or receipt of additional antibacterial therapy
455
456 Patients who discontinue therapy because of an adverse event should be evaluated at the time of
457 discontinuation of the study medication. These patients should not necessarily be considered
458 withdrawn from the study in terms of overall evaluation; investigators should continue to follow
459 all such patients at scheduled study visits and continue to record information on both safety and
460 efficacy outcomes. If at the time study medication is discontinued the patient is alive, without
461 complications, and does not receive additional antimicrobial therapy, then the patient should be
462 evaluated following the protocol criteria; discontinuation of therapy because of an adverse event
463 should not automatically be considered a clinical failure.
464
465 Patients who receive another antibacterial drug while on study drug should be identified since
466 these patients generally should be considered failures in an efficacy analysis.
467
468 d. Microbiological response
469
470 Although microbiological outcome may provide useful information regarding the biological
471 activity of antimicrobials, microbiological outcome is not a direct measure of benefit to patients
472 and, therefore, should be viewed as being supportive information but not as a substitute for
473 clinical outcome in a specific trial.[16]
474
475 If follow-up specimens for culture are obtained from patients, the most useful specimens are
476 those obtained at least 72 hours after the completion of drug therapy since negative culture
477 results obtained while on therapy may represent suppression rather than elimination of
478 organisms. Any target pathogens isolated from follow-up specimens should be tested for
479 susceptibility to the antimicrobial used to treat the disease.
480
481 All target pathogens isolated from patients during clinical trials should be appropriately saved in
482 the event that there is a need to do additional studies with the bacteria.
483
484 *10. Study Visits and Timing of Assessments*
485
486 a. Entry visit
487
488 At entry, the investigator should evaluate the patient by performing an appropriate history and
489 physical examination. Information recorded on the case report form during the entry
490 examination should include the following.
491

[16] Microbiological outcomes may be valuable in phase 2 studies addressing dosing regimens (i.e., where time to no growth on culture is being used as an outcome to optimize dose and/or dosing frequency) that will be evaluated in phase 3 studies.

492 • **History and demographic characteristics**
493
494 – Date of visit.
495 – Age, sex, and weight.
496 – Underlying medical condition(s).
497 – Current medications.
498 – Number of distinct and well-documented episodes of acute bronchitis in the past,
499 including how this information is obtained (i.e., chart review or patient recall); dates,
500 treatment regimens, and outcomes should be recorded.
501 – Detailed history of COPD including results of prior pulmonary function testing. This
502 history is best obtained from objective sources (e.g., patient medical records).
503 – History of tobacco use.
504 – Recent or current use of antibacterial drugs, and the indication or reason for use.
505 – Bacteria previously isolated from sputum during previous exacerbations, with
506 antimicrobial susceptibility profile.
507
508 • **Symptoms**
509
510 A well-defined and reliable PRO instrument, as discussed in section III.B.9., Efficacy
511 Endpoints, should be used to assess symptoms at baseline.
512
513 • **Signs**
514
515 – Vital signs, including body temperature measurement
516 – Posteroanterior and lateral chest X rays[17]
517 – Electrocardiography (to rule out arrhythmia and for safety analysis)
518 – Other laboratory tests for evaluation of safety parameters (e.g., complete blood count,
519 serum chemistries)
520
521 • **Sputum sample collection**
522
523 The entry visit should include baseline sputum gram stain with submission of sputum for
524 culture and susceptibility testing. Sponsors should describe in the protocol the methods
525 of obtaining specimens, specimen processing, and culture techniques. For
526 microbiological assessment, the investigator should collect the following information:
527

[17] Patients should have a baseline chest X ray to rule out pneumonia and other confounding illnesses such as congestive heart failure, malignancy, or bronchiectasis. Spiral computed tomography and D-dimer testing may be indicated in selected patients to exclude pulmonary embolism.

528 – A description of how the sample was obtained (e.g., expectoration, induced sputum,
529 aspiration), processed, and transported to the laboratory.
530 – The adequacy of the specimen in terms of numbers of polymorphonuclear cells and
531 epithelial cells present.[18]
532 – Identification of bacterial isolates.[19]
533 – In vitro susceptibility (preferably minimum inhibitory concentration) testing of the
534 isolates to both the study and control drugs. In vitro susceptibility testing should be
535 performed by using standardized methods, such as the Clinical and Laboratory
536 Standards Institute methods, unless otherwise justified.
537
538 Microbiological information that is not part of the entry criteria (e.g., susceptibility
539 results) should remain blinded to investigators.
540
541 If a positive sputum culture is used as one of the entry criteria for a clinical trial,[20] then
542 no growth of pathogens on culture may allow exclusion of a significant number of
543 patients whose exacerbation may be caused by factors other than bacterial infection (e.g.,
544 viruses, pollutants, allergens, cigarette smoke). Previous studies have shown that patients
545 with the following characteristics may be more likely to have bacteria isolated by sputum
546 culture at baseline:
547
548 – Purulent sputum
549 – Patients with more than two episodes of acute bronchitis per year
550 – Patients with a positive baseline sputum gram stain
551
552 Sputum culture data for *S. pneumoniae*, *M. catarrhalis*, and *H. influenzae* should be
553 correlated with clinical outcome.
554
555 b. On-therapy visits
556
557 Each patient should have daily on-therapy assessments of signs and symptoms using a well-
558 defined and reliable PRO instrument. Regardless of how the assessment is conducted (e.g.,
559 interview, interactive voice response via telephone, diary), the questioning of patients should be
560 performed in a reproducible and structured way so that any potential biases in the method of

[18] Investigators should evaluate the adequacy of sputum samples by ensuring that the specimen is most likely from lower respiratory secretions by use of the following criteria: greater than 25 white blood cells per field at 100x magnification (low power, 10x objective) confirming the impression of *sputum purulence* and less than 10 squamous epithelial cells at 100x magnification (low power 10x objective).

[19] This information should remain blinded while the patient is receiving study medication.

[20] If it is believed that treatment should not be given unless patients are bacteriologically confirmed, then enrollment and treatment should be delayed until positive culture results return. If that is not the case, then an alternative is to enroll all patients at the time of presentation with screening by sputum gram stain, then analyze patients in the modified intent-to-treat (MITT) population. This situation is discussed further in section III.B.11., Statistical Considerations. We strongly recommend that patients enrolled at the time of screening continue to be followed per protocol, regardless of whether sputum culture is subsequently positive or not.

561 questioning do not affect study outcome.[21] The ability to detect differences between study
562 therapies for a time-to-resolution endpoint may be increased if assessments are done more often
563 (e.g., twice daily). Therapy should be continued as described in the study protocol regardless of
564 whether symptoms have improved. Investigators should attempt to allow a minimum of 72
565 hours on therapy with the study medication before classifying a patient as a clinical failure;
566 accordingly, investigators may wish to include a 48- to 72-hour visit to ensure there is not
567 substantial clinical worsening at this time.
568
569 Assigning an outcome of clinical failure and permitting use of rescue antibacterial therapy
570 should be reserved for patients who are worsening on their assigned treatment arm; specific
571 criteria to identify these patients should be included in the protocol. It is important that
572 investigators distinguish patients who are worsening (i.e., where rescue therapy is appropriate)
573 from patients who are slow to improve but may still remain on assigned therapy. The protocol
574 should also specify a failure endpoint if symptoms have not improved by a certain day on study,
575 even if the symptoms are not clearly clinically worsening at that time; this may be most objective
576 if defined as a score remaining above a certain threshold for a PRO instrument. In general,
577 patients should not be unblinded if a criterion for rescue therapy is met.
578
579 In the case of clinical failure, therapy should be changed to include initiation of antimicrobial
580 therapy (or alternative antimicrobial therapy if appropriate) and/or other appropriate therapeutic
581 modifications as necessary. If failure is assigned, the investigator should attempt to obtain a
582 repeat sputum culture and the sample should be sent for culture and susceptibility testing.
583 Patients who meet study criteria for clinical failure should continue to have the identical
584 protocol-specified assessments as patients who continue to receive their originally assigned
585 treatment.
586
587 Investigators should document findings from on-therapy office visits (e.g., history, physical
588 examination, and laboratory test results) on the case report form. If the investigator contacts the
589 patient by telephone or by another interactive technology, documentation of the specific
590 questions asked, how they were asked, and the responses given should be captured on the case
591 report form. If a well-defined and reliable diary is used to capture patient symptoms during this
592 study visit, this information also should be recorded on the case report form.
593
594 c. Early follow-up visit
595
596 The early follow-up visit should occur after completion of all study medication at a time when
597 the drug is expected to be clear from the infection site (usually at least 5 half-lives). For
598 example, if a study drug with a short half-life is administered for 10 days, this study visit can
599 occur on days 0 to 4 after completion of therapy; this study visit should occur later for drugs with
600 a longer half-life. At this visit, the investigator should perform a directed medical history and
601 physical examination, as well as appropriate laboratory measurements. The investigator also

[21] When interviews are used they should be standardized; in addition, symptoms recorded from the patient should be recorded without interpretation by the interviewer. (See the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.* When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.)

602 should inquire about adverse events. Depending on the study design, follow-up sputum culture
603 may be appropriate at this visit.
604
605 d. Late follow-up assessment
606
607 The late follow-up assessment should occur 10 to 14 days after the completion of all study
608 medication (e.g., if study drug is administered for 10 days, this assessment can occur on days 20
609 to 25 after initiation of therapy (unless a drug with a long $t_{1/2}$ has been studied)). For patients
610 with adverse events occurring at or after the early follow-up assessment, investigators should
611 perform an assessment that includes a medical history, a physical examination, appropriate
612 laboratory evaluations, identification of any new adverse events, and follow-up on unresolved
613 adverse events. All adverse events should be followed to resolution.
614
615 e. Safety evaluations
616
617 The protocol should clearly specify the methods to be used to obtain safety data during the
618 course of the study. Both adverse event information and safety laboratory data should be
619 collected during the study. Age- and sex-appropriate normal laboratory values should be
620 included with clinical measurements when reporting laboratory data. Additional safety
621 evaluations also may be needed because of the preclinical and clinical profile of the specific drug
622 under study (e.g., additional electrocardiogram measurements). Longer-term assessment of
623 adverse events after discontinuation or completion of the antibacterial drug therapy also can be
624 considered depending on the specific drug being studied.
625
626 All patients should be evaluated for safety at the time of each study visit or assessment,
627 regardless of whether the test drug has been discontinued.[22] All adverse events should be
628 followed until resolution, even if time on study would otherwise have been completed.
629
630 *11. Statistical Considerations*
631
632 Sponsors should designate the hypotheses to be tested before initiation of the trial. These
633 hypotheses should be clearly stated in the protocol or statistical analysis plan, and the trial should
634 be powered to detect differences between study arms if group differences exist. If sponsors
635 choose to test multiple hypotheses, they should address issues related to the potential increase in
636 obtaining false positive results (type I error) because of multiple comparisons, either by adjusting
637 the type I error or using a stepwise, closed testing strategy for hypothesis testing. If sponsors use
638 a closed testing hypothesis strategy, they should specify the order of hypothesis testing before
639 initiation of the trial and the method for controlling the overall type I error rate. These issues
640 should be discussed with the FDA in advance of enrollment in the trial, and should be
641 incorporated into the statistical analysis plan as appropriate.
642

[22] For specific safety reporting recommendations during clinical trials, see the ICH guideline for industry *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (http://www.fda.gov/cder/guidance/index.htm).

643 a. Analysis populations
644
645 The following definitions apply to various populations for analyses in ABECB-COPD clinical
646 trials:
647
648 • **Safety population** — All patients who receive at least one dose of assigned therapy
649 during the study.
650
651 • **Intent-to-treat (ITT) population** — All patients who are randomized.
652
653 • **Modified intent-to-treat (MITT) population (also sometimes referred to as**
654 **microbiological intent-to-treat population)** — All patients who are randomized and
655 who have a pathogen associated with ABECB-COPD isolated at baseline. Patients
656 should not be excluded from this population based upon events that are measured post-
657 randomization (e.g., loss to follow-up). If a positive culture is required for study entry,
658 this population is identical to the ITT population.[23]
659
660 • **Per-protocol populations (also referred to as the *clinically evaluable* or**
661 ***microbiologically evaluable* populations)** — The population of patients who meet the
662 definition for the primary analysis population (ITT or MITT population) and who follow
663 important components of the protocol as specified (e.g., administration of a specified
664 minimum amount of study medication). Traditionally, adequacy of therapy for a per-
665 protocol analysis population has been defined as patients who have received greater than
666 80 percent (or within 80 to 120 percent) of the prescribed dose amount and/or dosing
667 regimen. Sponsors should document compliance with dosing (e.g., daily assessment,
668 patient diary, urine testing, or MEMS caps).
669
670 To ensure consistency of results, the ITT and/or MITT populations in the study should be
671 evaluated as well as the population of patients who follow important aspects of the protocol (i.e.,
672 the per-protocol populations). However, it is also important to note that the per-protocol
673 population analyses are subgroup analyses since they exclude patients based upon events that
674 occur after randomization. Patients in such subgroup analyses may differ by important factors
675 (both measured and unmeasured) other than the drug received; because of this, analyses based on
676 the ITT (or MITT) population should be considered the primary study analyses, with analyses
677 based on a per-protocol population reviewed for consistency of results. Results in both
678 populations should provide evidence of effectiveness.
679
680 The primary and secondary analyses should be defined in the protocol before starting the study.
681 Depending on the exact hypothesis being tested, sponsors may prefer to specify either the ITT or
682 MITT population as the primary population for analysis; for example, if patients are enrolled
683 before results of the sputum culture return but the primary hypothesis is that an effect is most
684 likely to be seen in patients with *S. pneumoniae* or other likely pathogens isolated, then the study
685 should be powered for the MITT population and this should be the primary analysis. If it is
686 expected that the treatment arm will be superior to the placebo arm for all patients enrolled, even

[23] The culture results (i.e., the specific bacterial organisms) that define whether a patient should be included in the MITT population should be stated in the protocol.

687 including patients who did not have a pathogen isolated, then an ITT population would be the
688 most appropriate primary analysis population. The choice of population (i.e., MITT or ITT) for
689 the primary analysis may guide the details of product labeling if the drug is approved.
690
691 b. Noninferiority margins
692
693 As mentioned, FDA review of previous ABECB-COPD studies has not been able to establish a
694 reliable estimate of the magnitude of benefit for treatment of ABECB-COPD with antibacterial
695 drug therapy; because of this, noninferiority trials currently are not considered adequate to
696 establish evidence of effectiveness for regulatory approval of a new indication for ABECB-
697 COPD. For additional information regarding noninferiority studies in general and in
698 antibacterial trials, see ICH E10 and the draft guidance for industry *Antibacterial Drug Products:*
699 *Use of Noninferiority Studies to Support Approval.*[24]
700
701 c. Sample size
702
703 The appropriate sample size for a clinical trial should be based upon the number of patients
704 needed to answer the research question posed by the study. The sample size is influenced by
705 several factors including the prespecified type I and type II error rates, the expected success rate,
706 and the noninferiority margin (for a noninferiority trial), or the amount by which the study drug
707 is expected to be superior to the control in a superiority trial. Sample size should be based upon
708 the number of patients needed to draw conclusions in the ITT or MITT analysis population.
709
710 d. Missing data
711
712 There is no single optimal way to deal with missing data from clinical trials. Sponsors should
713 make every attempt to limit loss of patients from the trial. Analyses that exclude patients are
714 subgroup analyses, and patients who do not complete the trial may differ substantially from
715 patients who remain in the trial in both measured and unmeasured ways. Therefore, sponsors
716 should prespecify in the protocol the method of how missing data will be addressed in the
717 analysis of trial results. Sponsors also should present sensitivity analyses in the final study report
718 such as including all missing patients as failures, including all missing patients as successes, and
719 including all missing data as successes or failures in each study group respectively.
720
721 Different rates of missing data or differences in the reasons for missing data across treatment
722 arms can be a cause for concern in the interpretation of a clinical trial. If this occurs, it should be
723 addressed in the study report.
724
725 e. Interim analyses and data and safety monitoring boards
726
727 If interim (or futility) analyses will be performed, they should be specified in the analysis plan.
728 The purpose of the interim analysis should be clearly stated in the analysis; it is important that
729 the interim analysis does not affect study conduct and thereby compromise study results. Study
730 data also should be examined at the time of interim analysis for any emerging safety signals. We

[24] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

731 encourage sponsors to discuss their plans with the review division before initiation of the trial to
732 ensure that the overall study significance tests properly address the effect of interim testing.
733
734 Use of a data and safety monitoring board (DSMB) may be appropriate depending on the design
735 of the proposed phase 3 trial and the patient population that the trial will enroll. If a DSMB is
736 used, a detailed charter with the composition of the committee members and the operational
737 details should be provided for review.[25]
738
739 f. Other analyses of interest and secondary endpoints
740
741 Analyses of secondary and additional endpoints should be considered exploratory since a trial
742 usually is not designed to address the questions raised by these analyses, either because of
743 multiple comparisons and/or concerns with subgroup analyses. However, the conclusions of
744 such analyses can be strengthened if hypotheses related to these endpoints are prespecified in the
745 protocol, if adjustments for multiple comparisons (maintenance of type I error) are outlined in
746 the protocol, and if the trial is appropriately powered to determine differences between groups
747 related to these variables. Analyses of secondary and additional endpoints can be most helpful
748 for identifying areas for study in future trials.
749
750 g. Statistical analysis plan
751
752 If a statistical analysis plan is developed to expand on the details of the analysis from that in the
753 protocol, the sponsor should submit the analysis plan for any phase 3 ABECB-COPD study to
754 the FDA before initiation of the trial.[26]
755
756 Clinical and microbiological outcomes from blinded studies also can be used for assessing the
757 accuracy of an established or tentative microbiological breakpoint for the treatment under study.
758
759 *12. Ethical Considerations*
760
761 Review of previous placebo-controlled studies of the treatment of ABECB-COPD has shown
762 variable results, with several placebo-controlled studies showing no effect for antimicrobial
763 treatment of exacerbations. Accordingly, for patients with mild to moderate disease, studies
764 have not shown a risk to placebo-treated patients that make future placebo-controlled trials
765 unethical; the risk from placebo treatment may be similar to that associated with antibacterial
766 therapy since low-frequency severe events (e.g., pseudomembranous colitis or serious allergic
767 reactions) have been observed with almost all antibacterial drugs. The occurrence of common
768 but less-severe adverse events (e.g., diarrhea) from antibacterial drugs also can be relevant in
769 assessing the risk-benefit to patients in a placebo-controlled trial where the expected treatment
770 effect may be small. Rescue therapy can be incorporated into the study design so that individual

[25] For more detailed information, see the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (http://www.fda.gov/cder/guidance/index.htm).

[26] For more detailed information, see the draft guidance for industry *Developing Antimicrobial Drugs — General Considerations for Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

771 patients are treated at the time a failure outcome is assigned; this addition may serve to mitigate
772 concerns regarding inclusion of a placebo arm in an ABECB-COPD trial. All study designs
773 should provide appropriate provisions for patient safety.
774
775 Although study results have been varied, some prior studies of ABECB-COPD have shown
776 clinically significant benefit in severely ill patients. We strongly encourage discussion with the
777 appropriate review division regarding design of placebo-controlled studies if enrollment will
778 include patients with clinically severe disease (e.g., patients requiring hospitalization or at
779 immediate risk of respiratory failure).
780
781 **C. Other Considerations**
782
783 *1. Animal Models*
784
785 Currently, there are no animal models for ABECB-COPD. However, animal models for other
786 upper and lower bacterial infections by the same microorganisms implicated as a cause of
787 ABECB-COPD may be useful in determining antimicrobial candidates for further study in the
788 treatment of ABECB-COPD.
789
790 *2. Labeling*
791
792 The following is an example of a labeled indication for the treatment of ABECB-COPD:
793
794 *"[Drug] is indicated in the treatment of acute exacerbations of chronic bronchitis in patients*
795 *with underlying chronic obstructive pulmonary disease (ABECB-COPD) due to susceptible*
796 *isolates of [relevant pathogens based on trial results]."*
797
798 *3. Antimicrobial Resistance Claims*
799
800 To date, the FDA has not granted resistance claims for ABECB-COPD caused by antimicrobial
801 resistant bacteria. To propose a claim for antimicrobial resistant pathogens in ABECB-COPD,
802 data from within the clinical trials should be presented that clearly demonstrate the adverse
803 clinical effect(s) of in vitro resistance and the ability of the study antimicrobial to significantly
804 reduce or eliminate the adverse clinical effect(s). If resistance is mediated by different
805 mechanisms within the same class of resistance (e.g., extended-spectrum beta-lactamases), the
806 effect of the study drug to eliminate bacteria with the various different mechanisms of resistance
807 should be demonstrated clinically. Resistance claims should be relevant to ABECB-COPD (e.g.,
808 amoxicillin resistance is more clinically relevant than penicillin resistance since the latter is
809 rarely prescribed for ABECB-COPD). Sponsors seeking resistance claims should contact the
810 review division before initiating clinical trials to discuss appropriate study designs that may be
811 suitable to achieve the desired resistance claims.
812