Guidance for Industry
Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases

DRAFT GUIDANCE

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

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Clinical/Antimicrobial

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3   **the Treatment of Serious Bacterial Diseases**

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8   This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current

9   thinking on this topic. It does not create or confer any rights for or on any person and does not operate to

10 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of

11 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA

12 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call

13 the appropriate number listed on the title page of this guidance.

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18 **I.   INTRODUCTION**

19

20 This guidance is intended to assist sponsors in the clinical development of new antibacterial drug

21 therapies.[2] Specifically, the guidance explains the FDA's current thinking about possible

22 streamlined development programs and clinical trial designs for: (1) drugs to treat serious

23 bacterial diseases in patients with unmet medical need; and (2) drugs that are *pathogen-focused*

24 antibacterial drugs (e.g., drugs that have a narrow spectrum of activity or are only active against

25 a single genus and species of bacteria) and are used for the treatment of serious bacterial diseases

26 in patients who have an unmet medical need.[3] This draft guidance is intended to serve as a focus

27 for continued discussions among the Division of Anti-Infective Products, pharmaceutical

28 sponsors, the academic community, and the public on issues related to the clinical trial design for

29 antibacterial drug products.[4] It is not intended to establish a new approval pathway or standard

30 for such drug products.

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[1] This guidance has been prepared by the Division of Anti-Infective 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 regulated in CDER unless otherwise specified.

[3] For a detailed discussion of regulatory pathways intended to streamline or expedite development (e.g., fast track, breakthrough) and their attendant criteria and definitions, see the draft guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[4] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of new antibacterial drugs.

32 This guidance does not contain discussion of the general issues of statistical analysis or clinical
33 trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*
34 *Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical*
35 *Trials*, respectively.[5]
36
37 FDA's guidance documents, including this guidance, do not establish legally enforceable
38 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
39 be viewed only as recommendations, unless specific regulatory or statutory requirements are
40 cited. The use of the word *should* in Agency guidances means that something is suggested or
41 recommended, but not required.
42
43
44 **II.   BACKGROUND**
45
46 Over the last few decades, efforts to develop new antibacterial drugs have declined substantially.
47 Over this same time period antibacterial drug resistance has become more common even in
48 settings in which attempts were made to slow the rate at which bacterial pathogens become
49 resistant, such as the prudent use of antibacterial drugs and adherence to infection control
50 procedures. As a result, an increasing number of patients are suffering from bacterial diseases
51 that do not respond to currently available antibacterial drugs, with serious consequences,
52 including increased mortality.[6]
53
54 Generally, patients hospitalized with acute serious bacterial diseases are likely to include patient
55 populations with unmet medical need. These acute bacterial diseases in hospitalized patients
56 include hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial
57 pneumonia (VABP), complicated urinary tract infection (cUTI), complicated intra-abdominal
58 infection (cIAI), community-acquired bacterial pneumonia (CABP), acute bacterial skin and skin
59 structure infection (ABSSSI), and other serious bacterial diseases. Appropriate antibacterial
60 drug therapy may not be available to these patients, and therefore they may have unmet medical
61 need, because the bacterial pathogen causing the infection is resistant to multiple antibacterial
62 drugs or is an emerging pathogen for which no antibacterial therapy has yet been developed. In
63 some cases, a patient's intolerance or allergy to available antibacterial drugs may limit available
64 therapies.
65
66 Clinical trials for antibacterial drugs can be challenging for a number of reasons, including:
67 (1) for a serious bacterial disease, there is a need to urgently initiate empiric antibacterial drug
68 therapy, which may obscure the effect of the antibacterial drug under study because patients
69 receive effective antibacterial therapy before enrolling in the trial; (2) patients with serious acute
70 bacterial diseases can be acutely ill (e.g., delirium in the setting of acute infection) and obtaining
71 informed consent and performing other trial enrollment procedures in a timely fashion may be
72 difficult; (3) there may be diagnostic uncertainty with respect to the etiology of the patients'

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[5] 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.

[6] See the Bibliography at the end of this guidance.

73 underlying disease, including identifying a bacterial etiology; and (4) there may be a need for
74 concomitant antibacterial drug therapy with a spectrum of activity that may overlap with the
75 antibacterial drug being studied.
76
77 A decreased rate of antibacterial drug development poses a significant public health concern. As
78 bacteria continue to develop resistance because of selection pressures from empiric and/or
79 inappropriate use of currently available antibacterial therapies, increased numbers of patients will
80 have unmet medical need related to effective antibacterial drug therapy. Therefore, it is
81 important for the public health that new antibacterial drugs be developed while also considering
82 how best to ensure appropriate use.
83
84 To foster development of new antibacterial therapies for the treatment of serious bacterial
85 diseases, we are exploring approaches that may help streamline development programs for
86 antibacterial drugs, especially for drugs that could address an unmet medical need. As
87 recognized in FDA regulations for the evaluation of drugs intended to treat life-threatening and
88 severely debilitating illnesses:
89
90　　*"The Food and Drug Administration (FDA) has determined that it is appropriate to*
91　　*exercise the broadest flexibility in applying the statutory standards, while preserving*
92　　*appropriate guarantees for safety and effectiveness. These procedures reflect the*
93　　*recognition that physicians and patients are generally willing to accept greater risks or*
94　　*side effects from drugs that treat life-threatening and severely-debilitating illnesses, than*
95　　*they would accept from drugs that treat less serious illnesses. These procedures also*
96　　*reflect the recognition that the benefits of the drug need to be evaluated in light of the*
97　　*severity of the disease being treated."*[7]
98
99
100 **III.　QUESTIONS AND ANSWERS**
101
102 The following questions and answers are provided to explain the FDA's current thinking on
103 streamlined approaches and clinical trial designs that may be appropriate for development of
104 antibacterial drugs to treat serious bacterial diseases in patients with unmet medical need.
105
106　　**1.　What types of antibacterial drugs may be appropriate for a streamlined**
107　　　　**development program?**
108
109 Possible candidates for a streamlined development program are antibacterial drugs intended to
110 treat serious bacterial infections in patients who have unmet medical need.[8] Because these drugs
111 will be developed to treat infections in patients who have few or no treatment options, they are
112 likely to be drugs that: (1) act via new mechanisms of action; (2) have an added inhibitor that
113 neutralizes a mechanism of resistance; or (3) have an alteration in the structure of the molecule

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[7] See 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses.

[8] For a more general discussion of the concepts of *unmet medical need* and *serious conditions*, see the draft guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic.

114 that makes the drug no longer susceptible to the mechanism of resistance to existing drugs. Due
115 to the paucity of available therapies for many patients with bacterial infections, antibacterial
116 drugs that are intended to treat patients with intolerance or allergy to currently available drugs
117 are also likely to be considered to address an unmet medical need. In contrast, a drug that has
118 slightly greater potency (e.g., more active by a 2 to 3 dilutions in vitro testing) generally would
119 not be considered a drug that addresses an unmet need and should undergo a traditional
120 development program.
121
122 A drug that treats a single genus and species of bacteria causing a serious bacterial disease also is
123 a possible candidate for a streamlined development program, particularly when intended to treat
124 patients with unmet medical need. For an antibacterial drug active against only a single genus
125 and species, the clinical trial design should be discussed with the FDA (e.g., pathogen-focused
126 antibacterial drug development). Sponsors should consider the following factors:
127
128 • The frequency with which the genus and species of interest causes serious infections
129
130 • The ability to identify patients with the bacterial pathogen of interest; standard culture
131 and in vitro susceptibility testing often take 2 days or more to identify the bacterial
132 pathogen of interest
133
134 • The potential of rapid diagnostic tests to identify patients with the bacterial pathogen of
135 interest for prompt enrollment into a clinical trial of a pathogen-focused antibacterial
136 drug
137
138 • The availability of rapid diagnostics to detect the genus and species of interest, which
139 could be essential to the study of the drug for the demonstration of clinical benefit
140
141 **2. What are possible approaches to a streamlined development program for an**
142 **antibacterial drug for the treatment of patients with serious bacterial diseases and**
143 **unmet medical need?**
144
145 Different approaches can be used to evaluate an antibacterial drug for the treatment of a serious
146 bacterial disease in patients with unmet medical need. The four approaches outlined below are
147 provided as examples of streamlined development programs that sponsors may consider using.
148 These four approaches are not intended to be mutually exclusive; in some cases combining
149 elements from across these approaches may be appropriate. Sponsors are encouraged to discuss
150 their specific proposed development programs with the FDA before commencing clinical trials.
151
152 In each of the approaches discussed below the development program provides important
153 nonclinical information on:
154
155 • The in vitro activity of the investigational drug
156
157 • The mechanism of action of the drug and whether mechanisms of resistance to other
158 drugs affect the investigational drug's activity
159

160 • The evaluation of pharmacokinetic/pharmacodynamic (PK/PD) relationships from animal
161   models of infection
162
163 • Activity of the investigational drug in animal models of infection; these studies may
164   provide important information evaluating the activity of an investigational antibacterial
165   drug at particular body sites (e.g., pneumonia)
166
167   **a. Prospective active-controlled clinical trials in patients with serious bacterial**
168   **diseases and unmet medical need**
169
170 An investigational drug can be compared to the best-available active-control therapy in a
171 randomized controlled trial, with the intent of showing superiority of the investigational drug,
172 because the best-available therapy may be suboptimal. Such a trial can be conducted in a patient
173 population enriched for an unmet need; for example at trial sites that have a high frequency of
174 infections caused by bacterial pathogens associated with unmet medical need. The trial could
175 study a single infection site (e.g., cIAI), but it also could enroll patients with bacterial disease at
176 any one of several different body sites; the prespecified endpoints for these trials should be
177 discussed with the FDA.
178
179 A finding of superiority based on a randomized comparison and a well-defined and reliable
180 clinical endpoint is readily interpretable evidence of effectiveness. Sample size estimates for a
181 trial intended to show substantial superiority generally are smaller than those for a noninferiority
182 trial, depending on the noninferiority margin. For example, approximately 97 patients per arm
183 would be an adequate sample size estimate (90 percent power and two-sided type I error of 0.05)
184 for a study in which the active-control group is expected to have a 65 percent success rate and
185 the investigational drug group is expected to have an 85 percent success rate.[9] Such a result
186 could occur only if the population studied had a high rate of patients with serious bacterial
187 diseases and unmet medical need (e.g., a high rate of patients with bacterial pathogens resistant
188 to most antibacterial drugs). The sample size also could be reduced by allowing for a different
189 significance level; for example a one-sided type I error of 0.05 rather than a two-sided
190 significance level.
191
192 For trials in patients with unmet medical need, it often may be the case that few patients are
193 enrolled at each clinical center. In this case, consideration could be given to randomizing centers
194 rather than individual patients, with appropriate adjustments to the statistical analysis plan to
195 accommodate cluster randomization. This strategy, with appropriate informed consent
196 procedures, could facilitate trial conduct by allowing for streamlined enrollment procedures and
197 possibly minimizing the need to administer antibacterial drug therapy to patients before
198 randomization. Patients enrolled at sites randomized to the standard-of-care arm would be
199 treated no differently than is usual practice at that site, while patients enrolled at sites
200 randomized to the investigational drug arm would be treated with the investigational drug.
201

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[9] The sample sizes were calculated using the software nQuery Advisor 7.0.

202 Innovative design and analysis strategies (including randomization of clinical trial centers,
203 adaptive design clinical trials, Bayesian design and analysis strategies, or other approaches) can
204 be employed in prospective, active-controlled trials, with an opportunity to stop the trial early for
205 efficacy or futility.[10] For example, the adaptive design might result in a shorter overall duration
206 of the trial based on modification of sample size as a result of observed rates of patients enrolled
207 who have unmet medical need. As another example, Frequentist (e.g., logistic regression
208 models) or Bayesian modeling approaches for assessing subgroup-specific treatment effects may
209 be useful in trials designed to enroll patients with infections at any one of several different body
210 sites, where the infection site defines a subgroup of interest.

212 Another approach is a nested, active-controlled, noninferiority/superiority trial design in which
213 patients are randomized to investigational drug or control drug at the beginning of therapy before
214 the availability of the results of antibacterial drug susceptibility testing. Patients subsequently
215 confirmed to be infected with the relevant pathogen associated with an unmet medical need on
216 the basis of the results of in vitro susceptibility testing would be examined as a distinct subgroup
217 for superiority.[11] Patients confirmed to be infected with standard pathogens (i.e., not a pathogen
218 associated with an unmet medical need) would be examined in a distinct noninferiority analysis
219 that evaluates the ability of the drug to treat the infection under consideration with a
220 noninferiority margin that reflects the recognition that the benefits of the drug need to be
221 evaluated in light of the severity of the unmet medical need.[12] The noninferiority component of
222 the study would demonstrate the antibacterial activity of the drug while the smaller subset of
223 patients with the pathogen associated with an unmet medical need should demonstrate a greater
224 effect in that population.

226 **b. External control or historical control clinical trial in patients with serious**
227 **bacterial diseases who have unmet medical need**

229 A clinical trial design that relies on a historical or external control may be acceptable to evaluate
230 efficacy in a patient population with an unmet need, in particular a patient population in which
231 standard-of-care therapy is suboptimal and the investigational drug shows activity in nonclinical
232 and early clinical development such that withholding the investigational drug may be considered
233 unethical. This trial design type generally is acceptable when the untreated morbidity is high and
234 does not vary widely in the patient population enrolled in the trial, and the effect of the
235 investigational drug is expected, based upon early clinical or nonclinical data, to be large
236 compared to historical experience. The outcomes among patients with unmet medical need who
237 received the investigational drug should be compared to the outcomes in an external control
238 group, and should be expected to show a large treatment benefit for the investigational drug,
239 because of concerns regarding potential bias from cross-study comparisons. The information

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[10] Clinical trial designs with adaptive features may enhance the efficiency of the trial; sponsors who are considering an adaptive design are encouraged to consult the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic.

[11] Infectious Diseases Society of America, 2012, White Paper: Recommendations on the Conduct of Superiority and Organism-Specific Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by Drug-Resistant Bacterial Pathogens, Clin Infect Dis, 55(8):1031-1046.

[12] See 21 CFR part 312, subpart E.

240 needed to evaluate the historical control response rate is fairly similar to what is needed to
241 support a noninferiority margin in an active-controlled trial, although the goal of the trial is
242 different. In a noninferiority trial, one is seeking similarity to the best-available therapy (i.e,
243 ruling out an unacceptable difference). In the case of the historical control trial, one is seeking
244 an advantage over what is essentially no treatment.
245
246 Sponsors considering a trial design that relies on a historical control based on a retrospective
247 review should characterize the proportion of patients with the clinical outcome of interest when
248 given no therapy or inadequate therapy. Current antibacterial drug development guidances
249 contain information on retrospective reviews of outcomes when patients were given no therapy
250 or inadequate therapy in specific disease conditions. These guidances may be helpful to
251 sponsors interested in using historical controls and provide examples of approaches that have
252 been used in developing noninferiority margins.[13]
253
254 For an externally controlled trial, the control patients should be as similar as possible to the
255 population expected to receive the investigational drug in the trial, and they should have been
256 treated in a similar setting and in a similar manner, except with respect to the investigational
257 drug therapy.[14] Currency of the historical control group also should be considered, so that the
258 comparison between the investigational drug and control group is based on the most recent
259 relevant experience with the control drug as is available.
260
261 For externally controlled trials or historical controlled trials in which the primary statistical
262 comparison is between the investigational drug and the external or historical control, sponsors
263 should consider the possibility of randomizing at least a small number of patients to the active
264 control in the trial (e.g., through disproportionate randomization of 3:1, 4:1, among others), if
265 feasible, based on an active control considered to be the best-available therapy. Both Frequentist
266 and Bayesian statistical methods can then be used to incorporate historical or external control
267 data with data from the patients randomized to the active control in assessing treatment group
268 differences for the primary comparison. Data external to the trial can be down-weighted relative
269 to the concurrent control data to reflect lesser comparability, as needed.
270

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[13] Certain infectious disease indication-specific guidances contain information on retrospective reviews of historical data (e.g., draft guidances for industry *Complicated Urinary Tract Infections: Developing Drugs for Treatment* and *Complicated Intra-Abdominal Infections: Developing Drugs for Treatment*) and can be found at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (when final, these guidances will represent the FDA's current thinking on these topics).

[14] See ICH E10.

271   **c. Noninferiority clinical trials in patients with serious bacterial diseases with**
272   **treatment options to provide evidence of efficacy supporting use for patients**
273   **with unmet medical need**
274

275   An investigational drug intended to treat serious bacterial diseases in patients with unmet
276   medical need can have efficacy established primarily on the basis of disease-specific
277   noninferiority clinical trials enrolling patients with a particular serious bacterial disease for
278   whom other treatment options are available.[15] These trials should prespecify a supportable
279   noninferiority margin based on the historical evidence of active-control treatment effect, if
280   available. If not, for severe bacterial diseases in which the magnitude of treatment effect is
281   known to be substantially large, a noninferiority margin based on other sources of information or
282   on clinical judgment could be considered. The choice of the margin should be discussed with the
283   FDA in advance of trial initiation.
284

285   The performance of the active-control drug in the current trial should be evaluated for
286   establishing a reliable and large treatment effect in the patient population of interest. Given that
287   the investigational drug would be considered only for patients who do not have other treatment
288   options and thus only where there is an unmet need, the characterization of efficacy in the
289   noninferiority disease-specific trial could be based on different assumptions about type I and
290   type II error or on the use of a larger noninferiority margin that still falls within the treatment
291   effect of the active control. The level of certainty about efficacy could have greater flexibility
292   than would be needed for a broader claim because of the recognition that the benefits of the drug
293   need to be evaluated in light of the severity of bacterial diseases in patients with unmet medical
294   need.[16] In addition to the noninferiority trial, PK/PD, safety, and outcome assessment data can
295   be described from a trial that enrolls patients with serious bacterial diseases and unmet medical
296   need who were treated with the investigational drug.
297

298   **d. Accelerated approval based on a surrogate endpoint**
299

300   Accelerated approval may be appropriate when there is a surrogate or clinical endpoint
301   reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to
302   predict clinical benefit. Sponsors interested in pursuing a clinical development program using
303   accelerated approval should discuss the choice of such an endpoint with the FDA. After
304   approval based on a surrogate endpoint, postmarketing studies are required to verify and describe
305   the clinical benefit (21 CFR 314.510, subpart H, or 21 CFR 601.41, subpart E).
306

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[15] See examples for the noninferiority clinical trial designs in the following draft guidances (when final, these guidances will represent the FDA's current thinking on these topics): *Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment*; *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*; *Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment*; *Complicated Urinary Tract Infections: Developing Drugs for Treatment*; and *Complicated Intra-Abdominal Infections: Developing Drugs for Treatment*.

[16] See 21 CFR part 312, subpart E.

307 **3. Can the nonclinical development program associated with a streamlined clinical**
308 **program also be smaller or streamlined?**
309
310 In general, the answer is no. Information about chemistry, manufacturing, and controls and
311 nonclinical toxicology studies are expected to be included in an investigational new drug
312 application.[17] To the extent that a streamlined clinical development program involves smaller,
313 shorter, or fewer clinical trials, it is likely that less quantitative data will be generated from
314 clinical trials. Note that a sponsor developing a drug using a streamlined clinical development
315 program must still provide adequate data to demonstrate that the drug is safe and effective to
316 meet the statutory standard for approval.[18] In such programs involving antibacterial drugs, the
317 other nonclinical studies may assume an even more important role in contributing to the
318 assessment of the drug's antibacterial activity, the dose and dosing regimen to be evaluated in
319 patients, mechanisms of drug metabolism, and adequate distribution of the antibacterial drug to
320 relevant tissue sites. See other guidances for industry, which discuss in more detail these
321 important elements of nonclinical development considerations.[19]
322
323 Data from nonclinical development should support the selection of a dose and frequency of
324 administration to study in the clinical setting. In addition, the nonclinical data package should
325 provide information on the following:
326
327 • The mechanism of action of the drug and whether mechanisms of resistance to other
328 drugs affect the investigational drug's activity
329
330 • The in vitro activity of the investigational drug, including the minimum inhibitory
331 concentration (MIC) from a representative sample of target bacterial pathogens
332
333 • Dose and frequency of administration that can be evaluated in in vitro models of infection
334 using PK parameters obtained from human PK studies
335
336 • Evidence for the antibacterial drug's ability to achieve appropriate levels in relevant
337 tissue sites from nonclinical studies (e.g., from animal models of infection)
338
339 • Activity of the investigational drug in animal models of infection
340
341 • The evaluation of the PK/PD index that is associated with efficacy in a relevant animal
342 and/or in vitro model(s), based on the following:
343

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[17] See 21 CFR 312.23.

[18] 21 U.S.C. 355(d)

[19] See, for example, the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*, and the guidances for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* and *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information*.

344   –   Area under the plasma concentration time curve over the MIC

345   –   Maximum plasma concentration over the MIC

346   –   Time above MIC

347

348   •   The target value of the PK/PD index that is associated with efficacy in the animal model

349

350   **4. What is the importance of PK/PD (exposure-response) data in a streamlined**

351   **development?**

352

353   Information on the distribution of MIC for the target pathogen based on recent surveillance data,

354   the results of PK/PD (exposure-response) assessments in animals, and results from human PK

355   trials should be integrated to help identify the appropriate dose and frequency of administration

356   for evaluation in clinical trials.[20] The PK information from humans should include information

357   about the distribution of the drug to the action site (e.g., endothelial lining fluid obtained via

358   bronchio-alveolar lavage for the lungs). Comparison of human and animal exposure data should

359   include correction for any differences in plasma protein binding.

360

361   Collection of PK data in clinical trials (e.g., sparse sampling in all patients enrolled in clinical

362   trials) may help in considering potential questions about efficacy or safety that arise and help

363   describe the effects of intrinsic and extrinsic factors on pharmacokinetics and

364   pharmacodynamics. Patients with serious bacterial diseases with unmet medical need often have

365   important comorbidities, notably renal or hepatic impairment, and, therefore, an increased

366   likelihood of alterations in pharmacokinetics. An important consideration in the conduct of trials

367   is to characterize pharmacokinetics in such patients. For example, understanding the

368   pharmacokinetics of the investigational drug in patients with renal or hepatic impairment early in

369   development could facilitate enrollment in clinical trials of such patients (e.g., by providing

370   guidance on dosing).

371

372   **5. What are possible appropriate efficacy endpoints for a streamlined development**

373   **program?**

374

375   Possible endpoints include the endpoints described in the individual disease-specific guidances,

376   clinical response endpoints, or a survival endpoint for the serious bacterial disease(s) being

377   studied. Selection of appropriate endpoints depends upon the specific serious bacterial disease

378   being studied. Sponsors should discuss with the FDA the efficacy outcome assessments

379   appropriate to each specific infectious disease.

380

381   **6. What is the size of the premarketing safety database when considering streamlined**

382   **development?**

383

384   The premarketing safety database of an investigational drug should be appropriate to its potential

385   benefit. A development program for a drug intended to treat a population of patients with unmet

386   medical need generally would likely have a more limited safety database than would be expected

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[20] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration*.

387 for a drug with broader use to the extent it involves smaller, shorter, or fewer clinical trials. In
388 general, a safety database for a drug that is the subject of a streamlined development program
389 should include approximately 300 patients at the dose and duration of therapy proposed for
390 marketing.[21] This safety database may include patients with the same proposed bacterial disease,
391 but who do not have an unmet need (i.e., do not have an infection caused by a resistant form of
392 the pathogen or who are not allergic or intolerant to currently available therapies).[22]
393
394 **7. Will the FDA accept greater uncertainty about adverse effects?**
395
396 With all drugs, adverse effects may become apparent only after a drug is marketed and used
397 more widely. To the extent a clinical development program involves smaller, shorter, or fewer
398 clinical trials, there likely will be greater uncertainty about the safety of the drug. Nonclinical
399 and early clinical development data may be helpful in predicting such risks. Postmarketing
400 monitoring (e.g., postmarketing requirements) or, in some circumstances, continued development
401 of the drug by the applicant, will help to further define the drug's safety profile.
402
403 It is also possible that some drugs with risks that would be unacceptable for a broad population
404 could be acceptable for patient populations that do not have other treatment options. As stated
405 previously, balancing greater uncertainty or higher risk with an unmet need is an appropriate
406 approach to benefit and risk assessment.[23]
407
408 **8. Why is it important for the FDA and for sponsors to emphasize to the health care**
409 **community the risks and benefits of drugs developed under a streamlined**
410 **development program for the treatment of serious bacterial diseases in patients with**
411 **unmet medical need?**
412
413 To obtain approval, a drug sponsor must demonstrate that its drug is safe and effective for use
414 under the conditions prescribed, recommended, or suggested in its labeling. Therefore, a drug's
415 labeling should include the limitations of the approved use, including any limitations on the
416 approved patient population and any limitations on the available data for drugs developed under
417 such programs. Furthermore, it is important to emphasize the following points:
418

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[21] Ruling out serious and unexpected adverse events that occur at a rate of fewer than 1 in 100 patients exposed may be a reasonable expectation for a premarketing safety database for a new drug for treatment of patients with serious bacterial infections for which there are limited therapeutic options. See the guidance for industry *Premarketing Risk Assessment* for further discussion on sizes of premarketing safety databases. For example, when there are no serious and unexpected adverse events in approximately 300 patients using the Clopper-Pearson method of the estimate of the upper bound of the two-sided 95 percent confidence interval of an adverse event rate, a true rate of serious and unexpected adverse events is likely to be fewer than 1 in 100 (Clopper CJ and E Pearson, 1934, The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial, Biometrika, 26:404-413).

[22] Nonclinical data and early safety data can be informative for the type and amount of the premarketing safety database; see, for example, ICH guidances for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* and *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs — Questions and Answers (R1)*.

[23] See 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses.

419   •   Product labeling for such drugs should include not only the known risks and benefits of
420   the drug but also a description of the limitations of the available information that
421   supported approval
422
423   •   It is important for the health care community to be informed on how to use the drug
424   appropriately (i.e., make clear the approved patient population for which the FDA has
425   determined the benefits of the drug outweigh the risks)
426
427   •   Postmarketing monitoring (or, in some cases, continued development of the drug by the
428   applicant) can help to further define the drug's safety and efficacy profile
429
430 For all drugs, but particularly for drugs supported by smaller, shorter, or fewer clinical trials,
431 important findings regarding safety or new limitations of efficacy may first become apparent in
432 the postmarketing period. Adequate steps to identify such important safety or efficacy findings
433 early, and appropriately address the risks they pose, will be important for streamlined
434 development programs.
435
436   **9. Is the animal rule an appropriate consideration for a streamlined development**
437   **program?**
438
439 No, because human clinical effectiveness trials can be conducted, drugs that are the subject of
440 this guidance are not eligible for approval under the animal rule, as set forth in 21 CFR part 314,
441 subpart I, Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible.
442
443   **10. What is the role of a rapid diagnostic in streamlined antibacterial drug development**
444   **programs?**
445
446 The use of bacterial detection methods, other than culture, may help define the population
447 identified to have a bacterial pathogen. Examples of nonculture detection of bacterial pathogens
448 include urinary antigen tests, serology, and polymerase chain reaction.
449
450 The clinical trial for a candidate antibacterial drug may provide an opportunity to contribute to
451 the development and evaluation of a new diagnostic test.[24] Sponsors are encouraged to discuss
452 these approaches with the Division of Anti-Infective Products and the appropriate review
453 division in the Center for Devices and Radiological Health.
454
455 The development and use of rapid detection methods should be helpful in identifying patients
456 with the particular pathogen for drugs that have a narrow spectrum of activity (e.g., drugs only
457 active against a single genus and species).
458

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[24] See the draft guidance for industry and Food and Drug Administration staff *In Vitro Companion Diagnostic Devices*. When final, this guidance will represent the FDA's current thinking on this topic.

459　　　**11. Can an antibacterial drug be developed using a streamlined approach for patients**
460　　　　　　**with an unmet medical need and subsequently for other indications?**
461
462　　Yes, a sponsor can use the streamlined development approach to obtain approval of an indication
463　　that addresses an unmet medical need, and subsequently develop the drug for other indications.
464
465　　　**12. Does the approval of one drug for the treatment of a serious bacterial disease in**
466　　　　　　**patients with unmet medical need preclude approval of another drug for the same**
467　　　　　　**indication using a streamlined development program?**
468
469　　No. The approval of an antibacterial drug for the treatment of serious bacterial diseases in
470　　patients with unmet medical need does not necessarily preclude the development of a subsequent
471　　drug for the same or similar indication using a streamlined development program. For example,
472　　a drug with a different mechanism of action, an alteration in its structure that makes the drug no
473　　longer susceptible to mechanisms of resistance, or use of the drug with an inhibitor that
474　　neutralizes a mechanism of resistance, may provide options for patients with certain infections
475　　either in the present or in the future as resistance develops, and would be considered to address
476　　an unmet medical need. In addition, under the following circumstances, an antibacterial drug
477　　may be considered to address an unmet medical need when there is an already approved
478　　treatment for the same indication:
479
480　　　• 　The first drug approved is found to have serious adverse effects in the postmarketing
481　　　　　period that significantly affect its assessment of risk and benefit.
482
483　　　• 　The adverse effects of the first drug could affect its utility in certain subpopulations (e.g.,
484　　　　　a drug with the potential to cause nephrotoxicity would be a less than ideal choice in a
485　　　　　patient with impaired renal function). A subsequent drug with a different adverse effect
486　　　　　profile could provide a treatment option for these patients.
487
488　　　• 　The approval of more than one therapy addresses an emerging or anticipated public
489　　　　　health need, such as a drug shortage or the development of antimicrobial resistance.
490
491　　　**13. Are there special considerations for the INDICATIONS AND USAGE section of**
492　　　　　　**product labeling?**
493
494　　The labeled indication for drugs approved under a streamlined development program should
495　　reflect the patient population for which the drug is approved (i.e., the patient population with
496　　serious infections caused by a bacterial pathogen for which the unmet medical need exists). The
497　　INDICATIONS AND USAGE section should also summarize the limitations of available data
498　　that supported the approval (e.g., limited safety data).
499
500　　The example below represents wording for an indication whose approval was based on a
501　　streamlined development program for patients with serious infections with unmet medical need.
502

503   *Drug X is indicated, in [approved patient population], for the treatment of [HABP/VABP,*
504   *cIAI, ABSSSI, CABP, cUTI (include as appropriate)] caused by the following susceptible*
505   *microorganism(s): [list the genus and species of the bacterial pathogen(s)]. Drug X has*
506   *been approved for use in patients with [HABP/VABP, cIAI, ABSSSI, CABP, cUTI*
507   *(include as appropriate)] where limited or no alternative therapies are available. The*
508   *safety and effectiveness of Drug X have not been established beyond this patient*
509   *population. This indication is based on (summarize the limitations of available data that*
510   *supported the approval).*

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