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5 **Guideline on the use of pharmacokinetics and
6 pharmacodynamics in the development of antibacterial
7 medicinal products**

8 Draft

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10 This guideline replaces Points to Consider on Pharmacokinetics and Pharmacodynamics in the
11 Development of Antibacterial Medicinal Products (CHMP/EWP/2655/99)

12 Comments should be provided using this [template](#). The completed comments form should be sent to
IDWPsecretariat@ema.europa.eu

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16 **Guideline on the use of pharmacokinetics and**
17 **pharmacodynamics in the development of antibacterial**
18 **medicinal products**

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50 EXECUTIVE SUMMARY

51 This Guideline replaces the *Points to consider on pharmacokinetics and pharmacodynamics in the*
52 *development of antibacterial medicinal products* (CPMP/EWP/2655/99). The Guideline has been
53 developed to outline the regulatory expectations for application dossiers and reflects both the scientific
54 advances in the field of pharmacometrics that have implications for antimicrobial agent development
55 programmes and the regulatory experience since the adoption of CPMP/EWP/2655/99. In a field that is
56 continually advancing the Guideline does not attempt to provide detailed recommendations on issues
57 such as methodologies for modelling and simulation. In addition, the Guideline does not specifically
58 address the use of pharmacometrics to identify susceptibility testing interpretive criteria. Sponsors are
59 encouraged to discuss the use of pharmacokinetic-pharmacodynamic (PK-PD) analyses to support the
60 development of new antimicrobial agents and when planning to add to or amend the dose
61 recommendations for licensed agents with EU Regulators.

62 Before embarking on PK-PD analyses it is essential that adequate microbiological data have been
63 accumulated. In particular, data should be generated to describe the range of MICs of the test agent
64 against individual species, genera or organism groups (e.g. enterobacteria) relevant to the proposed
65 indications. Additionally, time-kill studies should be conducted to provide preliminary insight into the
66 relationship between test agent concentration and antimicrobial activity.

67 PK-PD indices may be identified from in-vitro and/or in-vivo PD models, leading to establishment of
68 nonclinical PD targets (PDTs) for the most important pathogens relevant to the intended clinical uses.
69 The determination of the probability of target attainment (PTA) using simulations to support dose
70 regimen selection requires adequate clinical PK data and the use of population PK (POPPK) models.
71 Initially these PK data will come from healthy volunteers. Since there may be important differences in
72 PK of the test agent between healthy volunteers and patients with acute infections the simulations
73 used for preliminary assessments of PTA may need to be adjusted to anticipate the possible effects of
74 infection-related systemic disturbances on PK. The PTA should be re-assessed when PK data have been
75 obtained from patients with ongoing infectious processes. Other factors to take into account in
76 simulations include test agent concentrations in body fluids (such as lung epithelial lining fluid) and the
77 effects of other interventions such as positive pressure ventilation.

78 The evaluation of clinical exposure-response (E-R) relationships and their use to derive clinical PDTs is
79 an evolving field. There are several reasons why clear conclusions may not always be reached.
80 Nevertheless, it is recommended that sponsors plan to obtain sufficient PK data from patients enrolled
81 in studies of clinical efficacy to support these analyses.

82 The identification of beta-lactamase inhibitor dose regimens has also emerged as an important area for
83 use of PK-PD analyses. As for antimicrobial agents the PK-PD index and PDT should be identified for
84 each inhibitor and simulations should be conducted that take into account the variability in PK of the
85 inhibitor and the partner beta-lactam agent.

86 The use of PK-PD analyses to identify potentially efficacious dose regimens has reduced or, in some
87 cases, replaced the need for clinical dose-finding studies during the clinical development of new
88 antimicrobial agents, allowing more rapid progress to pivotal efficacy studies. For reasons of lack of
89 feasibility and/or as part of abbreviated clinical development programmes of test agents with a
90 potential to address an unmet need there may be very limited clinical efficacy data generated to
91 support application dossiers. In these cases it is essential that there are very robust PK-PD analyses to
92 support the likely adequacy of the dose regimen and any dose adjustments that may be needed for
93 special populations. Since the PK-PD index and PDTs do not change in the presence of bacterial

94 mechanisms of resistance that may have some impact on the MIC of the test agent, the PTA can be
95 used to predict whether or not a test agent is likely to have useful clinical activity against specific
96 multidrug-resistant organisms. This is especially important when such organisms are rare so that very
97 few are likely to have been treated in pre-licensure clinical studies and it may be very difficult to
98 interpret the clinical outcome data.

99 **1. Introduction(background)**

100 The *Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial*
101 *medicinal products* (CPMP/EWP/2655/99) was developed at a time when the use of pharmacokinetic
102 (PK) and pharmacodynamic (PD) indices to select potentially effective dose regimens for antibacterial
103 agents was gaining importance. In the years elapsed since the adoption of CPMP/EWP/2655/99 there
104 have been considerable advances in the field of pharmacometrics. Meanwhile regulatory experience
105 has been gained from provision of scientific advice and from review of application dossiers in which
106 dose regimens have been based primarily on identification of PK-PD indices and targets (PDTs) and the
107 application of modelling and simulation to determine the probability of target attainment (PTA).

108 Since CPMP/EWP/2655/99 was issued the role of PK-PD analyses in dose regimen selection has gained
109 increasing importance. For example, in-vitro PD models and PK-PD analyses have minimised or
110 replaced clinical dose-finding studies and have emerged to be of great assistance in identifying dose
111 regimens for beta-lactamase inhibitors. In the case of antibacterial agents that can address an unmet
112 need, PK-PD analyses play a central role in dose regimen selection. Moreover, increasing reliance has
113 been placed on the use of PK-PD analyses to select dose regimens for special populations (including
114 children and those with renal impairment) and to assess the potential clinical importance of the effects
115 of intrinsic and extrinsic factors on PK.

116 Other developments include the use of PK-PD analyses to select regimens that may minimise the risk
117 of selecting for resistant organisms, which is gaining acceptance as experience grows in this field.
118 Furthermore, several application dossiers have demonstrated how analyses of exposure-response (E-
119 R) relationships can provide further support for dose regimens and dose adjustments in specific patient
120 populations as well as having other potential uses.

121 When developing new antimicrobial agents and when planning to add or modify dose regimens for
122 approved agents sponsors either have and/or obtain external expertise when performing analyses of
123 PK-PD relationships. Nevertheless, there are some crucial aspects of the data, analyses and
124 interpretation of the findings that deserve attention in a regulatory guidance document. This Guideline
125 has been developed to outline the regulatory expectations for application dossiers and reflects both the
126 scientific advances and the regulatory experience. In a field that is continually advancing the Guideline
127 does not attempt to provide detailed guidance on issues such as methodologies for modelling and
128 simulation.

129 **2. Scope**

130 This Guideline is intended to be applicable to antibacterial agents, including antimycobacterial agents,
131 as well as antifungal agents. The focus is on the use of PK-PD analyses to identify potentially
132 efficacious dose regimens. The conduct of PK-PD analyses to explore the relationship between PK of
133 the test antimicrobial agent and selected safety parameters is not addressed.

134 The Guideline addresses the following:

- 135 a. The microbiological data that should be accumulated to support PK-PD analyses, including
136 descriptions of MIC distributions and the conduct of time-kill studies to obtain preliminary
137 information on the relationship between drug concentrations and antimicrobial effects.
- 138 b. The identification of PK-PD indices and PK-PD targets (PDTs) from nonclinical data,
139 including the use of in-vitro and/or in-vivo PD models.
- 140 c. The clinical PK data needed to support PK-PD analyses at various stages of the clinical
141 development programme.
- 142 d. The determination of the probability of target attainment (PTA) using simulations to support
143 dose regimen selection.
- 144 e. The evaluation of clinical exposure-response (E-R) relationships using data that are
145 collected during clinical studies that assess clinical and microbiological outcomes in patients.
- 146 f. Identification of beta-lactamase inhibitor dose regimens.
- 147 g. The extent to which the results of PK-PD analyses may support or replace clinical data.

148 The same PK-PD analyses used to identify and confirm potentially efficacious dose regimens are at the
149 cornerstone of setting interpretive criteria for susceptibility testing. This Guideline does not specifically
150 address the use of pharmacometrics to identify susceptibility testing interpretive criteria. Nevertheless,
151 the Guideline takes into account the data requirements and PK-PD analyses recommended by EUCAST
152 [19] and the CLSI [6] for the purpose of setting interpretive criteria.

153 **3. LEGAL BASIS**

154 This Guideline has to be read in conjunction with the introduction and general principles of the Annex I
155 to Directive 2001/83 as amended as well as other pertinent EU and ICG guidelines and regulations,
156 especially the following:

157 Guidance on evaluation of medicinal products indicated for the treatment of bacterial infections
158 (CPMP/EWP/558/95 Rev 2)

159 Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial
160 infections (EMA/CHMP/351889/2013)

161 Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1)

162 Dose-Response Information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4)

163 Clinical Investigation of Medicinal Products in the Paediatric Population - CPMP/ICH/2711/99 (ICH E11)

164 Note for Guidance on population exposure: The Extent of Population Exposure to Assess Clinical Safety
165 for Drugs - CPMP/ICH/375/95 (ICH E1A)

166 Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric
167 population (EMEA/CHMP/EWP/147013/2004)

168 Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired
169 hepatic function (CPMP/EWP/2339/02)

170 Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with
171 impaired renal function (CHMP/EWP/225/02)

- 172 Guideline on reporting the results of population pharmacokinetic analyses
173 (EMEA/CHMP/EWP/185990/2006)
- 174 Note for Guidance on General Considerations for Clinical Trials (ICH E8, CPMP/ICH/291/95)
- 175 Note for Guidance on Guideline for Good Clinical Practice (ICH E6, CPMP/ICH/135/95)

176 **4. Main guideline text**

177 **4.1. Microbiological data**

178 Section 4.1.1 of the *Guideline on the evaluation of medicinal products indicated for treatment of*
179 *bacterial infections* (CPMP/EWP/558/95 Rev 2) outlines the microbiological data that should be
180 collected to support an application dossier for a new antibacterial agent. The guidance provided is also
181 applicable to the accumulation of sufficient in-vitro microbiological data to underpin the identification of
182 potentially efficacious dose regimens. In particular:

- 183 • To describe the spectrum of activity of the test agent
184 • To identify from the spectrum the types of infections that may be treatable and
185 • To describe the MIC distributions for the most important pathogens relevant to the indications
186 likely to be pursued

187 The guidance is also applicable when sponsors wish to add new indications involving different
188 pathogens that may require alternative dose regimens compared to the approved indications.

189 In addition, for the purposes of supporting PK-PD analyses the following investigations may be of
190 particular importance whenever appropriate to the test agent and the intended clinical uses:

- 191 • A description of MIC distributions based on clinical isolates obtained from patients with types of
192 infections that fall within the intended range of indications for the test agent
193 • Time-kill studies
194 • Assessment of any post-antibiotic effect [7]
195 • Evaluation of intracellular antimicrobial activity
196 • Evaluation of MICs of the test agent in the presence of a range of resistance mechanisms and,
197 applicable, against any target species that demonstrate hetero-resistance
198 • Identification of organism subtypes (e.g. genotypes or serotypes) that have higher or lower
199 rates of resistance, which may be mechanism-specific, compared to other subtypes

200 The MIC data generated should be presented for entire populations by species, genus or organism
201 grouping (e.g. enterobacteria or beta-haemolytic streptococci of groups A, B, C and G) and also
202 separately for subsets with and without acquired resistance. The latter display may not be applicable
203 for a new agent of a new class against which pre-existing resistance is not detected amongst large
204 collections of recent clinical isolates.

205 The data should suffice to identify appropriate MICs of the test agent to be used in analyses to
206 describe the PTA (see section 4.4). That is, having derived PK-PD indices and PDTs as described in
207 section 4.2, to assess the PTA at selected MICs of the test agent when using specific dose regimens to
208 treat relevant pathogens. Consideration should be given to selecting the MICs from the distributions

209 for isolates obtained from patients with the types of infection targeted by the test agent. If the test
210 antimicrobial agent is proposed to have useful activity against organisms that are resistant to other
211 agents in the same class the typical MICs of the test agent for this subgroup should be at or below the
212 highest MIC at which PTA is assessed.

213 The MIC values used for PTA analyses usually encompass values across the range observed. The MICs
214 should always include values at the upper end of the MIC distribution and would usually include the
215 MIC₉₀ for each pathogen or group of pathogens of interest and/or the epidemiological cut-off values
216 (ECVs) for each species of interest. If ECVs are used they should be derived from an adequate
217 collection of isolates within a single species and the methodology used to ECV identification should be
218 described (e.g. simple visualisation of histograms or a mathematical approach [31]).

219 Section 4.1.2 of CPMP/EWP/558/95 Rev 2 addresses the microbiological data that should be collected
220 during clinical efficacy studies. These data can be used to further substantiate the MIC distribution
221 curves for individual organisms and are necessary for the evaluation of clinical exposure-response (E-
222 R) analyses in which relationships between documented or predicted PK parameters and MICs of the
223 agent against pathogens in individual patients are explored (see section 4.5).

224 **4.2. Determining PK-PD indices and PK-PD targets**

225 **4.2.1. Introduction**

226 The pharmacokinetic-pharmacodynamic index (PK-PD index) represents the quantitative relationship
227 between a pharmacokinetic measure of exposure to the test agent (such as AUC) and a microbiologic
228 measure of bacterial susceptibility (such as MIC) [8, 20].

229 It has been shown that PK-PD index values derived from studies in animals and those obtained by
230 Classification and Regression Tree (CART) analysis of clinical exposure-response data are very similar
231 [19]. Potentially a PK-PD target (PDT; a magnitude for a PK-PD index at which a desired level of
232 predicted response is achieved) can be derived from nonclinical and/or clinical studies.

233 During development programmes for new antimicrobial agents the PDT is derived (at least initially)
234 from nonclinical rather than clinical studies (see also section 4.5). These may include nonclinical in-
235 vivo studies in animal models and/or in-vitro PD models (e.g. chemostat and hollow fibre infection
236 models). Before proceeding to conduct studies using these models the microbiological data described
237 in section 4.1, including time-kill studies, commonly provide initial insight into PK-PD index or indices
238 most likely to be associated with efficacy. For example:

- 239 • When a concentration-dependent pattern of bactericidal activity is observed in time-kill studies,
240 the AUC₀₋₂₄:MIC ratio and/or the C_{max}:MIC ratio is/are usually found to be predictive of efficacy
241 in PK-PD model systems.
- 242 • When a time-dependent pattern of bactericidal activity is observed in time-kill studies the
243 %Time>MIC and/or the AUC₀₋₂₄:MIC ratio is/are usually found to be predictive of efficacy in
244 PK-PD model systems.

245 For most antimicrobial agents it should be possible to identify specific nonclinical PK-PD index values
246 (PDTs) for each pathogen or group of pathogens of interest that result in:

- 247 - A net static effect, i.e. no log₁₀ drop in colony forming units (CFU)
- 248 - A 1 log₁₀ drop in CFU

249 - A 2 log₁₀ drop in CFU

250 **4.2.2. Nonclinical PK-PD studies**

251 The PK-PD index or indices most closely related with efficacy of an antimicrobial agent should be
252 identified from nonclinical PK-PD infection models, which may be conducted *in vitro* and/or in
253 appropriate animal models. In general, the use of *in-vitro* models is recommended initially so that i)
254 there is no restriction on the number of organisms that can be tested ii) any studies that are
255 conducted in animal models can be kept to a minimum iii) animal models can be used to answer
256 specific questions that are not adequately addressed by *in-vitro* models.

257 The organisms used in the models should be representative of those most relevant to the intended
258 clinical uses and should exhibit MICs of the test agent that include values at the upper end of the wild-
259 type distribution (see section 4.1). It is recommended that a core set of organisms should be used in
260 all the nonclinical models, to which others may be added in specific models. Generally it is suggested
261 that ~4-5 organisms of the major target species or organism groups should be tested but fewer may
262 be tested in *in-vivo* models and others tested in *in-vitro* models.

263 Evidence to date indicates that the PK-PD index for a specific antimicrobial agent and pathogen is not
264 affected by the presence of mechanisms of resistance that result in MICs of the test agent far above
265 the upper end of the wild-type distribution. In addition, the PK-PD index should not be affected by
266 mechanisms that confer resistance to other agents in the same class or those that have a similar
267 spectrum of activity as the test agent, with or without any impact on MICs of the test agent.
268 Nevertheless, sponsors may wish to select the organisms to be tested in the models on the basis of
269 specific phenotypes in order to confirm these expectations.

270 If the test agent is of a known class it may be useful to include an active comparator from the same
271 class as an internal control at least in *in-vitro* models.

272 In-vitro models

273 In-vitro models have several advantages over animal models. In particular, in-vitro models make it
274 possible to:

- 275 • Derive PK-PD indices based on larger numbers of representative organisms and a wider range
276 of inocula than is possible and justifiable in animal models
- 277 • Assess the effects of multiple different PK profiles. Initial studies can be conducted before there
278 are any clinical PK data available to derive nonclinical PK-PD indices and PDTs. Once clinical PK
279 data have been generated the models can be used to simulate typical plasma/serum profiles
280 expected in infected patients (which may be based on POPPK model predictions of typical PK
281 profiles) and assess the effect on organism numbers to provide further support for the PDTs
282 [15].
- 283 • Study the relationships between rates of emergent resistance, drug exposure and duration of
284 therapy [10, 11, 17]
- 285 • Compare the test agent with other agents of the same class or, at least, other agents with a
286 similar spectrum of activity

287 The most widely used in-vitro models have been the chemostat and hollow fibre models. Other models
288 may be acceptable subject to provision of adequate data to describe assay performance and
289 sensitivity.

290 **Animal models**

291 Most animal models involve mice. In the commonly used neutropenic mouse thigh and lung infection
292 models [1, 9] mice are rendered neutropenic and then infected with an estimated inoculum of colony
293 forming units (CFU; confirmed retrospectively from plating the inoculum and determination of colony
294 counts) in the thigh or lung that is known to be sufficient for assay sensitivity (i.e. to be able to detect
295 differences between untreated control groups and groups given the test agent if such a difference
296 exists). Treatment is initiated and blood sampling for determination of test agent concentrations (or
297 test agents if combinations are under evaluation) is conducted at appropriate intervals based on prior
298 PK studies and total bacterial counts are determined for designated tissues/organs at pre-determined
299 time points. Plasma/serum exposures using different doses and/or dose intervals are plotted against
300 CFU.

301 Other nonclinical models (e.g. using non-neutropenic mice or using other species) may be used if
302 supported by adequate data, such as a demonstration of the correlation of the results with neutropenic
303 mice. Additional specialised models may be used if the test agent is proposed to treat infections at
304 sites where plasma/serum levels may not be predictive of compartmental levels, such as in meningitis
305 and in infections involving intracellular organisms (such as *M. tuberculosis* and *L. monocytogenes*).

306 **4.2.3. Analyses of PK-PD relationships**

307 Sponsors should provide details of the analysis methods used with the model parameters and
308 goodness of fit. For example, in the common case that a Hill-type function is fit to PK-PD data the
309 report should include the E_0 , EC_{50} , E_{max} and Hill's constant.

310 PK-PD indices should be expressed as a function of free drug concentrations or there must be a
311 justification why total drug is used.

312 As a minimum the analyses should report the magnitude of the PK-PD indices (i.e. PDTs) necessary to
313 achieve net bacterial stasis, 1- and 2- \log_{10} reductions in bacterial densities for each pathogen or group
314 of pathogens of interest, taking into account that not all agents will achieve 2- \log_{10} reductions or, at
315 least, not for all pathogens. Section 4.4.2 considers factors to be taken into account when selecting
316 PDTs for use in analyses of PTA.

317 Sponsors may propose an extrapolation of PDTs that are based on actual data with specific organisms
318 to other organisms that commonly behave similarly, i.e. have been shown to have the same PK-PD
319 indices and similar PDTs for antimicrobial agents closely related to the test agent.

320 **4.3. Clinical pharmacokinetic data to support PK-PD analyses**

321 Human PK data are critical for selection of potentially effective dose regimens. Population PK (POPPK)
322 models should be developed in accordance with CHMP guidance in order to predict human exposures to
323 the test agent (see section 4.4) and for analyses exploring exposure-response (E-R) relationships in
324 the target patient population (see section 4.5).

325 **4.3.1. PK data from uninfected subjects**

326 The initial PK data will come from healthy volunteers in whom intensive PK sampling is possible after
327 single and multiple doses. These data should be sufficient to describe the PK properties of the test
328 antimicrobial agent, including plasma/serum profiles and routes of metabolism and elimination. As

329 appropriate, the effects of renal and/or hepatic impairment may need to be assessed. An initial POPPK
330 model may be based solely on data from healthy subjects and can be used for the preliminary
331 assessment of potentially efficacious doses for use in patients.

332

333 **4.3.2. PK data from infected patients**

334 The PK profile of a test antimicrobial agent in the infected target patient population may demonstrate
335 several important differences compared to healthy volunteers. For example, some oncology patients
336 and some intensive care unit patients, with or without ongoing infections, have been found to be in a
337 state of renal hyperfiltration, whereby doses or dose frequencies of renally excreted agents may need
338 to be adjusted to achieve the desired PTA. Another example is that active infection may alter the
339 volume of distribution of the test agent and so impact on plasma/serum levels. On occasion the
340 mean/median values for PK parameters may be similar between healthy volunteers and patients but
341 inter-individual variability is considerably greater in the patients even in the absence of significant
342 organ dysfunction and/or changes in plasma proteins. In addition, covariates that have a significant
343 effect on PK in infected patients may not impact on PK in healthy volunteers.

344 In initial studies with a test antimicrobial agent in infected patients or when an established agent is to
345 be used in a new indication it is recommended that intensive PK data are obtained from a subset and
346 sparse sampling PK data are obtained from the total study population assigned to the test agent. The
347 PK data obtained from patients typical of the intended target population in terms of site of infection
348 and severity of infection (but regardless of pathogen susceptibility) should be used to update the
349 POPPK model. The updated model can then support repeat PK-PD analyses to confirm or reject the
350 likely sufficiency of the dose regimen before proceeding to larger studies in patients.

351 In order to support analyses of clinical E-R relationships (see section 4.5) it is recommended that
352 sponsors plan for sparse sampling of all patients in pivotal clinical efficacy studies.

353 **4.3.3. Other relevant data**

354 The degree of binding of the test agent to human plasma proteins in the presence of clinically relevant
355 concentrations should be assessed. Initially this may be evaluated *in vitro* by spiking human plasma
356 with different concentrations of the test agent to determine whether there is concentration-dependent
357 binding. Further estimates should be obtained during a study with radiolabelled test agent (if
358 conducted) or from samples collected during clinical PK studies. The data collected from infected
359 patients should suffice support a robust estimation of unbound (free) concentrations of the test agent
360 that can be used for PK-PD analyses.

361 As relevant to the test agent and its intended clinical uses, total and free test agent concentration-time data
362 should be presented for specific body fluids and ~~eompared~~ related to plasma/serum levels using
363 compartmental PK modelling. At the present time it is considered important to provide data on the
364 following:

- 365 • Urinary concentrations when a significant amount of the test agent is excreted unchanged in
366 urine and it is intended for treatment of urinary tract infections.
- 367 • Epithelial lining fluid (ELF) free drug concentrations when the test agent is to be used to treat
368 pneumonia. Typically, these studies are conducted in uninfected patients each of whom is

369 assigned to receive a single dose of the test agent at a specific time prior to a scheduled
370 bronchoscopy.

- 371 • Cerebrospinal fluid (CSF) concentrations whenever the test agent is intended to treat
372 meningitis. The approach is similar to that used to obtain ELF data.

373 If supported by emerging scientific data, it may be appropriate to assess total and free concentrations
374 in non-homogenate tissues [24].

375 For test agents that will be used to treat patients receiving positive pressure ventilation (PPV) the
376 potential for this to affect PK of the test agent should be considered before commencing studies in
377 infected patients. If an effect of PPV on PK cannot be ruled out based on the physicochemical
378 properties of the test agent it is important that the issue is evaluated either in a dedicated study or in
379 an initial cohort of infected patients within a larger study.

380 **4.4. Determination of the probability of target attainment (PTA)**

381 **4.4.1. Use of simulations**

382 When a specific PK-PD index value has been identified for use as a PDT to predict the probability of
383 successful treatment of a specific pathogen or group of pathogens as described in section 4.2 it is
384 necessary to assess whether this applies across a typical patient population, taking into account that
385 there will be some degree of inter-individual variation in PK. Actual data may not be available from
386 patients when these simulations are first attempted and, even when available, patient data may be
387 limited to relatively small numbers when dose regimens are selected for pivotal studies. Therefore a
388 statistical approach is taken to simulate individual patient PK profiles for which the inputs include
389 measures of central tendency statistics for PK parameters and their associated variance.

390 The statistical method most often used is Monte Carlo Simulations (MCS) but other methods may be
391 used if adequately justified by sponsors [21].

392 The total number of simulated patients (which is commonly around 5,000) should be justified based on
393 the variability of the data and the complexity of the model. The sponsor should describe the underlying
394 population distributions (e.g. normal, log normal) and/or should justify any assumptions used for the
395 various inputs to the simulations.

396 In the majority of cases, the simulations are based on the nonclinical-derived PK-PD indices and PDTs,
397 i.e. they are based on free test agent concentrations. Unless otherwise justified, adjustments should
398 be made for the degree of human plasma protein binding.

399 Whenever possible the PK inputs for simulations should be based on a POPPK model built from or
400 including PK data from infected patients. As described in section 4.3.2, the patient PK dataset should
401 provide a point estimate and variance for the main PK parameters and an assessment of the effect of
402 covariates.

403 If only healthy volunteer PK data are available the POPPK model should be adjusted so that the
404 simulation results reflect the potential degree of inter-individual variability in the target patient
405 population and any changes in the PK covariates and PK parameters. The most common adjustment
406 involves inflation of variability around the point estimate of drug clearance based on an assumption of
407 the variability to be expected in infected patients with severe systemic upset. It is also necessary to
408 include a distribution for creatinine clearance that is usually found in the target patient population.

409 The simulations should be performed using the same PK model from which the PK parameter and
410 dispersion estimates were obtained. Exceptions are model adjustments, as previously described,
411 intended to better estimate PK and associated variability in the target patient population.

412 **4.4.2. Probability of target attainment (PTA)**

413 Using simulations it is possible to estimate the probability of attaining the PDT (i.e. the PTA) when
414 MICs of the test agent are within a range observed for the major pathogens relevant to the intended
415 clinical uses. The simulation results should be presented for each species, genus or organism group(s)
416 of relevance:

- 417 • By selected MIC values of the test agent (see section 4.1)
- 418 • By PDT associated with stasis, 1-log₁₀ kill and 2-log₁₀ kill (see section 4.2.3) [25, 26, 27]

419 The following should be taken into account when selecting PDTs for use in analyses of PTA when the
420 aim is primarily to achieve clinical and microbiological response rates expected to be at least as good
421 as those associated with best available standard of care:

- 422 • For potentially life-threatening infections that usually involve high organism burdens (e.g.
423 hospital or ventilator-acquired pneumonia [HAP/VAP]) and low spontaneous resolution rates
424 the PDT associated with ≥ 1 log₁₀ reduction in CFU is generally recommended.
- 425 • For infections that may be associated with lower organism burdens and/or may be treated with
426 antimicrobial therapy in conjunction with other types of therapeutic intervention (such as some
427 types of acute bacterial skin and skin structure infections and intra-abdominal infections in
428 which surgical intervention is often used) the PDT associated with at least net stasis may be
429 considered sufficient.

430 Sponsors may consider several other aims of therapy when selecting PDT values to be used in analyses
431 of PTA, including:

- 432 • A PDT value associated with minimisation of the risk of selecting for resistance (e.g. based on
433 evidence derived from in-vitro models) [10, 18, 28]
- 434 • A PDT value associated with a rapid response to treatment
- 435 • A PDT value appropriate for a specific patient population (e.g. profoundly neutropenic)

436 It is recommended that simulation outputs are presented in both tabular and graphical form. The 95%
437 confidence intervals around the point estimate of PTA should be reported.

438 For the purpose of identifying potentially efficacious dose regimens to treat pathogens with MICs of the
439 test agent at the upper end of the wild-type distribution (e.g. including the MIC₉₀ and/or the ECV) it is
440 commonly expected that the proposed dose regimen (i.e. a specific dose, dose interval and, if
441 appropriate, duration of infusion) provides a PTA > 90% based on the selected PDT (see section 4.2.3
442 regarding the PDT selection).

443 An even higher PTA could be expected if the test agent is proposed to treat life-threatening infections
444 for which efficacious agents are already available.

445 A PTA <90% may sometimes be acceptable. For example, if the dose needed to achieve >90% PTA is
446 known to be poorly tolerated and the test agent addresses an unmet need. Otherwise, sponsors would
447 have to justify the acceptability of a PTA < 90% based on issues such as low severity of the infection

448 type or very few organisms with MICs at the upper end of the range such that PTA is >90% at MICs
449 observed for the vast majority.

450 **4.5. Clinical exposure-response (E-R) relationships**

451 **4.5.1. Potential value of E-R relationships**

452 On completion of a clinical study it is common that sponsors present the clinical and microbiological
453 outcomes according to the dose regimen administered (if the study included more than one dose
454 regimen) and according to the MICs (or the highest MIC) of the test agent for the pathogen(s)
455 obtained from the individual patient. Although these presentations of data should be provided they
456 frequently give no insight into the adequacy of the dose regimen due to several factors that may
457 include:

- 458 • Lack or rarity of pathogens with MICs of the test agent that are near to or above the upper end
459 of the wild-type distribution
- 460 • The limited range of infection types and pathogens that are treated
- 461 • Lack of certainty regarding the actual or major causative pathogen(s)
- 462 • The impact of various non-treatment-related factors on outcomes (e.g. host immune systems,
463 adjunctive treatments, surgical interventions)
- 464 • The dose regimen(s) studied will have been chosen based on PK-PD analyses with the aim of
465 achieving high PTA in the patient population as a whole. Thus, a simple analysis of outcomes
466 by dose regimen will not identify those patients who may have failed due to inadequate
467 exposures.

468 Analyses of clinical E-R relationships can be used to describe the interplay between MIC(s) of the test
469 agent for the pathogen(s), PK of the test agent (derived from application of POPPK models to sparse
470 sampling data) and the outcome of treatment. An understanding of the E-R relationship can identify
471 clinical PK-PD indices and clinical PDTs to provide further support for the adequacy of dose regimens
472 initially selected from the nonclinical PK-PD indices and PDTs.

473 It is recommended that sponsors plan to collect sufficient data to describe the E-R relationship for all
474 new antimicrobial agents. Nevertheless, it may not be feasible to describe the E-R relationship when
475 one or more of the following apply:

- 476 • The clinical programme included very limited numbers of patients (e.g. as may sometimes
477 apply to new antimicrobial agents with potential to address an unmet need)
- 478 • High clinical success rates were observed in conjunction with a dose regimen that resulted in
479 the majority of patients having plasma/serum exposures that were very high relative to MICs
480 of the test agent for their pathogens (i.e. there were insufficient clinical failures to support
481 identification of a clinical PDT).
- 482 • Most or all patients received the test agent in conjunction with another antimicrobial agent
483 active against the responsible pathogens.
- 484 • Clinical outcomes are heavily confounded by underlying diseases and/or surgical interventions.
- 485 • The exact identity of the infecting pathogen(s) is debatable.

486 For antimicrobial agents that are already licensed it is unlikely that analyses of E-R relationships can
487 be used to assist in assessment of the adequacy of approved dose regimens and to support changes to
488 dose regimens unless new clinical efficacy studies are conducted that include sparse sampling from as
489 many patients as possible. For example, if a licensed agent is used as the comparator in a prospective
490 double-blind randomised active-controlled study, the samples obtained from the control arm could be
491 used to describe the E-R relationship. Sponsors who do not themselves plan to use the samples from
492 the control arm for this purpose are encouraged to consider offering stored samples to interested
493 parties.

494 **4.5.2. Analyses of E-R relationships**

495 Analyses of E-R relationships are confined to patients with documented outcomes, adequate PK data
496 and identified pathogens for which MICs of the test agent have been determined. [12, 13, 14, 22, 30]
497 Using these data clinical PK-PD indices can be evaluated as continuous or categorical variables.

498 Statistical approaches for evaluating univariable E-R relationships are based on the nature of the
499 variables for the efficacy endpoint and PK-PD index to be evaluated. Various approaches may be
500 acceptable depending on whether the efficacy endpoint is dichotomous, continuous or time to event [3,
501 4].

502 If other patient factors in addition to the PK-PD index are found to be predictive of the efficacy
503 endpoint based on the results of univariable analyses, multivariable analyses should be undertaken to
504 evaluate predictors of outcome. In such cases, it may be more appropriate to consider distributions
505 for such patient factors in addition to those for PK parameters when conducting simulations to assess
506 model-predicted percent probabilities of response.

507 It is expected that sponsors report the diagnostics of the fitting of E-R data to statistical models
508 (model building) and the evaluation of the predictability of the model (model validation).

509 **4.5.3. Applications of E-R relationships**

510 The E-R relationship can be used to identify the highest MIC of the test agent that can be treated with
511 confidence using a selected dose regimen, further supporting the initial predictions made based on
512 nonclinical PDTs. This may be achieved as follows:

- 513 • Using a POPPK model, simulation to generate an exposure distribution and knowledge of the E-
514 R relationship it is possible to generate model-predicted percent probabilities of response at
515 specific MIC values.
- 516 • Using a POPPK model, simulation to generate an exposure distribution and knowledge of a
517 clinically-derived PDT the PTA can be determined at specific MIC values.

518 Nevertheless, if the predicted PTA is low at a given MIC value (e.g. 60%) this does not necessarily
519 mean that the percentage of successful responses will be 60% at the same MIC value.

520 **4.6. Identification of beta-lactamase inhibitor dose regimens**

521 **4.6.1. Considerations for identifying dose regimens**

522 In a typical clinical study the proportion of the study population that is infected with beta-lactamase-
523 producing organisms that are resistant to a specific beta-lactam agent (BL) but susceptible to the
524 same BL when administered in conjunction with an appropriate beta-lactamase inhibitor (BLI) is
525 usually limited. Attempts to enrich the study population for BL-resistant, BLI-susceptible pathogens
526 can be attempted but such studies are usually of limited size, do not provide robust estimates of
527 efficacy and/or they take a very long time to enrol. Therefore it is expected that most of the support
528 for the adequacy of BLI dose regimens will come from PK-PD analyses.

529 Each BL has a range of inherent stability in the presence of various beta-lactamases. Thus, the dose
530 regimen of a BLI that efficiently protects one BL (i.e. such that there is no change in MIC of the BL
531 against a specific organism when it is and is not expressing a particular beta-lactamase) may need to
532 be adjusted to provide the same degree of protection of another BL in the same test system. For this
533 reason, investigations of the BLI regimen need to be BL-specific.

534 Each BLI has a range of inhibitory activity against various beta-lactamases. For each BLI the following
535 initial investigations are necessary to assess its potential range of inhibition:

- 536 • A comprehensive assessment of inhibitory activity in enzyme kinetics studies
- 537 • In-vitro testing in which various concentrations of the BLI and the proposed partner BL are
538 combined. MICs and time-kill curves for the BL alone and in the presence of different
539 concentrations of the BLI (i.e. potentiated MICs of the BL) should be compared against a range
540 of organisms known to express specific beta-lactamases, with or without additional
541 mechanisms of resistance to the BL (e.g. porin deficiencies or efflux pumps as appropriate to
542 the BL and the bacterial species). The strains tested should include genetically engineered or
543 naturally occurring organisms that are known to hyper-produce certain beta-lactamases since
544 the amount of beta-lactamase manufactured can impact on the potentiated MIC observed.

545 For some beta-lactamases these in-vitro data can suffice to conclude that the BLI has no potentially
546 useful inhibitory activity. For other beta-lactamases it will not be possible to draw conclusions without
547 additional nonclinical and clinical studies as described below.

548 **4.6.2. Approaches to identifying BLI dose regimens**

549 The PK-PD index should be established for each BLI [14, 16]. For example, among BLIs currently in
550 clinical use the PK-PD index has been established to be %T>threshold for tazobactam, with a threshold
551 that varies according to the organism and the beta-lactamase it is producing [29].

552 In nonclinical infection models the BL/BLI should be administered to mimic the anticipated mode(s) of
553 clinical use (i.e. with intermittent dosing separated by specific dose intervals and/or as a continuous
554 infusion) since the PK-PD index for the BLI may be different under different administration modes. The
555 BLI PK parameters of potential interest (C_{max} , AUC_{0-24} , %T>threshold) should be indexed to the
556 potentiated MICs. In this field in-vitro PD models have been especially valuable since they facilitate
557 experiments in which a large number of different combinations of BL and BLI dose regimens can be
558 evaluated to derive nonclinical PK-PD indices and PDTs for the BLI.

559 Simulations along the lines described in section 4.4 are used to estimate PTA but they are inevitably
560 more complex since the BL and BLI are to be co-administered. To support simulations, POPPK models
561 should be developed for the BL and BLI. The simulations should take into account the variability in
562 plasma/serum exposures to each of the BL and the BLI as well as any PK interaction that may occur
563 between the BL and the BLI when they are co-administered to patients. When interpreting the PTA it
564 should be remembered that this is influenced by the proportion of isolates with a given potentiated
565 MIC value that are actually producing a relevant β -lactamase [23]. Therefore the MIC distribution is
566 critical to the conclusions of the dose-justification analyses.

567 For BLs and BLIs that are predominantly excreted in urine, simulations should be conducted to assess
568 dose adjustments for various degrees of impaired renal function. Simulations are particularly useful
569 when total and/or renal clearance is different for the BL vs. the BLI. The results may indicate that dose
570 adjustments for the BL do not match those needed for the BLI. In such instances, if the BL and BLI are
571 presented for clinical use only in a fixed dose combination product the results will preclude its use
572 below a specified creatinine clearance value.

573 **4.6.3. Additional analyses to assess the BLI dose regimen**

574 In active controlled clinical studies that compare a test regimen of the BL/BLI vs. an appropriate
575 comparative regimen any benefit from addition of the BLI to the BL is unlikely to be evident from
576 analysis conducted in the all-treated or defined evaluable patient populations. Therefore it is important
577 to conduct an additional analysis in the subset of patients infected with beta-lactamase-producing
578 pathogens that are not susceptible to the BL but are susceptible to the BL/BLI even though the
579 denominators in the two treatment groups are likely to be rather small and no inferential testing will
580 be possible. The findings should be taken into account in the assessment of the benefit-risk
581 relationship.

582 **4.7. Regulatory implications**

583 The identification of PK-PD indices and PDTs followed by assessments of PTA using well-conducted
584 simulations based on relevant POPPK models may serve to replace the need for clinical dose-finding
585 studies but they cannot wholly replace the need for clinical efficacy data.

586 As discussed in CPMP/EWP/558/95 Rev 2 and in EMA/CHMP/351889/2013, application dossiers can be
587 greatly strengthened by provision of PK-PD analyses. Such analyses are expected to be critically
588 important components of all application dossiers for new antimicrobial agents. For antimicrobial agents
589 that have undergone limited clinical development programmes (e.g. because of feasibility issues
590 and/or their ability to address an unmet need) PK-PD analyses are expected to provide much of the
591 evidence to support the adequacy of the dose regimen for the target multidrug-resistant pathogens.

592 There are several other potential uses of PK-PD analyses, which may include a good understanding of
593 clinical E-R relationships. In application dossiers for new antimicrobial agents or to support the addition
594 or amendment of dose regimens, some of the uses of these analyses include, but are not limited to:

- 595 • Investigations of unexpected findings, such as lower success rates in sub-populations of
596 patients for no obvious reason
- 597 • Identification of the need for and prediction of dose modifications in patient subsets (e.g.
598 hepatic and renal insufficiency, children, elderly, obese, those with specific genetic factors
599 affecting drug disposition)

- 600 • Identification of appropriate dose regimens with new formulations that result in modified PK
601 profiles; these may be developed during or after initial licensure
- 602 • Interpretation of the possible clinical importance of the results of drug-drug interaction studies
- 603 • Identification of dose regimens that may serve to reduce the risk of selecting for resistance
- 604 • Implementation of adaptive trial designs
- 605 • Validation of biomarkers
- 606 • Estimation of the no-treatment effect, which may then be used to derive well-supported non-
607 inferiority margins for active-controlled studies

608

609 **Definitions**

610 **Clinical exposure-response (E-R) relationship** - The relationship between plasma/serum
611 exposures and clinical efficacy in infected patients.

612 **Epidemiologic cut-off value (ECV)** – The MIC value that separates microbial populations into those
613 with and without acquired and/or mutational resistance mechanisms based on their phenotypes
614 (MICs). The ECV for an individual drug and species or genus is defined as the MIC value that best
615 defines the estimated upper end of the wild-type population.

616 **Minimal inhibitory concentration (MIC)** - The lowest concentration of an antimicrobial agent that
617 prevents visible growth of a microorganism in an in-vitro susceptibility testing system.

618 **Pharmacodynamics (PD)** - The relationship between the unbound drug concentration over time and
619 the resulting antimicrobial effect.

620 **Pharmacokinetics (PK)** - The study of the time course of drug absorption, distribution, metabolism,
621 and excretion.

622 **Pharmacometrics** - The use of mathematical models of biology, pharmacology, disease and
623 physiology to describe and quantify interactions between medicinal products and patients, including
624 beneficial effects and adverse effects.

625 **Pharmacokinetic-pharmacodynamic index (PK-PD index)** – The quantitative relationship
626 between a measure of drug exposure (such as AUC) and a microbiologic parameter (such as MIC).

627 **PK-PD magnitude** – The numerical value of the PK-PD index.

628 **PK-PD target** - A magnitude for a PK-PD index at which a desired level of predicted response is
629 achieved.

630 **Probability of target attainment (PTA)** – For reporting of outputs from simulations, including
631 Monte Carlo simulations, the PTA is the probability that at least a specific value of a PDT is achieved at
632 a certain MIC.

633 **Wild-type** – the population with MIC values at or below the ECV that are presumed to possess no
634 acquired and/or mutational resistance mechanisms.

635

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