Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products

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

Keywords	*Epidemiologic cut-off value; Exposure-response relationship; Minimal inhibitory concentration; Pharmacodynamics; Pharmacokinetics; Pharmacokinetic-Pharmacodynamic index, magnitude and target; Probability of target attainment; Wild-type distribution*

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Executive summary

This Guideline replaces the *Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products* (CPMP/EWP/2655/99). The Guideline has been developed to outline the regulatory expectations for application dossiers and reflects both the scientific advances in the field that have implications for antimicrobial agent development programmes and the regulatory experience since the adoption of CPMP/EWP/2655/99.

In a field that is continually advancing the Guideline does not attempt to provide detailed recommendations on issues such as methodologies for modelling and simulation. In addition, the Guideline does not specifically address the use of pharmacokinetic-pharmacodynamic (PK-PD) analyses to identify susceptibility testing interpretive criteria.

Sponsors are encouraged to discuss the use of PK-PD analyses to support the development of new antimicrobial agents and when planning to add to or amend the dose recommendations for licensed agents with EU Competent Authorities.

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

PK-PD indices may be identified from in-vitro and/or in-vivo PD models. Nonclinical PD targets (PDTs) should be established for the most important pathogens relevant to the intended clinical uses. The determination of the probability of target attainment (PTA) using simulations to support dose regimen selection requires adequate clinical PK data and the use of population PK (POPPK) models. Initially these PK data will come from healthy volunteers. Since there may be important differences in PK of the test agent between healthy volunteers and patients with acute infections the simulations used for preliminary assessments of PTA may need to be adjusted to anticipate the possible effects of infection-related systemic disturbances on PK. The PTA should be re-assessed when PK data have been obtained from patients with ongoing infectious processes.

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

The identification of beta-lactamase inhibitor dose regimens has also emerged as an important area for use of PK-PD analyses. PDTs should be identified for each inhibitor and simulations should be conducted that take into account the variability in PK of the inhibitor and the partner beta-lactam agent.

The use of PK-PD analyses to identify potentially efficacious dose regimens has reduced or, in some cases, replaced the need for dose-finding studies during the clinical development of new antimicrobial agents, allowing more rapid progress to pivotal efficacy studies. For reasons of lack of feasibility and/or as part of abbreviated clinical development programmes of test agents with a potential to address an unmet need, there may be occasions when very limited clinical efficacy data are generated to support application dossiers. In these cases it is essential that there are very robust PK-PD analyses to support

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the likely adequacy of the dose regimen and any dose adjustments that may be needed for special populations.

1. Introduction (background)

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

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

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

This Guideline has been developed to outline the regulatory expectations for application dossiers and reflects both the scientific advances and the regulatory experience. In a field that is continually advancing the Guideline does not attempt to provide detailed guidance on issues such as methodologies for modelling and simulation. In addition, it is recognised that sponsors may propose alternative strategies to those outlined in this Guideline, in which case discussion with EU Competent Authorities would be appropriate.

2. Scope

This Guideline is intended to be applicable to systemically active antibacterial agents, antimycobacterial agents and antifungal agents. The focus is on the use of PK-PD analyses to identify potentially efficacious dose regimens. The Guideline is applicable to the initial clinical development programme for new antimicrobial agents and to programmes intended to support the addition of indications involving different pathogens or the extension of use to special populations that may require alternative dose regimens to those already approved.

The Guideline addresses the following:

    a. The microbiological data that should be accumulated to support PK-PD analyses, including descriptions of MIC distributions and the conduct of time-kill studies to obtain preliminary information on the relationship between drug concentrations and antimicrobial effects.

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b. The identification of PK-PD indices and PK-PD targets (PDTs) from nonclinical data, including the use of in-vitro and/or in-vivo PD models.

c. The clinical PK data needed to support PK-PD analyses at various stages of the clinical development programme.

d. The determination of the probability of target attainment (PTA) using simulations to support dose regimen selection.

e. The evaluation of clinical exposure-response (E-R) relationships using data that are collected during clinical studies that assess clinical and microbiological outcomes in patients.

f. Identification of beta-lactamase inhibitor dose regimens.

g. The extent to which the results of PK-PD analyses may support or replace clinical data.

PK-PD analyses may also be used to explore the relationship between PK of the test antimicrobial agent and selected safety parameters. This is recognised to be a very important use of these analyses, which may influence the final dose regimen selection. The broad principles laid out in this Guideline are applicable to the use of PK-PD analyses to assess the relationship between exposure and specific safety parameters.

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

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

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

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

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

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

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

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

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

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

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

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

Guideline on reporting the results of population pharmacokinetic analyses (EMEA/CHMP/EWP/185990/2006)

Note for Guidance on General Considerations for Clinical Trials (ICH E8, CPMP/ICH/291/95)

Note for Guidance on Guideline for Good Clinical Practice (ICH E6, CPMP/ICH/135/95)

4. MAIN GUIDELINE TEXT

4.1. Microbiological data

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

- To describe the spectrum of activity of the test agent

- To identify from the spectrum the types of infections that may be treatable and

- To describe the MIC distributions for the most important pathogens relevant to the indications likely to be pursued

For the purposes of supporting PK-PD analyses the following investigations may be of particular importance whenever appropriate to the test agent and the intended clinical uses:

- A description of MIC distributions based on clinical isolates obtained from patients with types of infections that fall within the intended range of indications for the test agent

- Time-kill studies, including studies with different inocula and studies that document change in organism numbers over a specified and justified time period

- Evaluation of intracellular antimicrobial activity against pathogens with a large intracellular population

- Evaluation of MICs of the test agent in the presence of a range of resistance mechanisms

- Identification of organism subtypes (e.g. genotypes or serotypes) that have higher or lower rates of resistance, which may be mechanism-specific, compared to other subtypes

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

The MICs used for PTA analyses usually encompass values across the range observed and should always include values at the upper end of the MIC distribution for each pathogen or group of pathogens of interest. The selected values should usually include the MIC_{90} and/or the epidemiological

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cut-off values (ECVs) for each species of interest. If ECVs are used they should be derived from an adequate collection of isolates (ideally consisting of "wild-type" organisms that are known rather than assumed to lack mechanisms of resistance to the tests agent) within a single species and the methodology used to ECV identification should be described (e.g. simple visualisation of histograms or a mathematical approach).

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

4.2. Determining PK-PD indices and PK-PD targets (PDTs)

4.2.1. Introduction

The pharmacokinetic-pharmacodynamic index (PK-PD index) represents the quantitative relationship between a pharmacokinetic measure of exposure to the test agent (such as AUC) and a microbiologic measure of bacterial susceptibility (such as MIC).

Potentially a PK-PD target (PDT; a magnitude for a PK-PD index at which a desired level of predicted response is achieved) can be derived from nonclinical and/or clinical studies.

During development programmes for new antimicrobial agents the PDT is derived (at least initially) from nonclinical rather than clinical studies (see also section 4.5). These may include nonclinical in-vivo studies in animal models and/or in-vitro PD models. There are several in-vitro PD models that may be used and it is important that the relative advantages and disadvantages of the selected model(s) is/are discussed (e.g. their ability to assess the emergence of resistant populations). Before proceeding to conduct studies using these models the microbiological data described in section 4.1, including time-kill studies, commonly provide initial insight into PK-PD index or indices most likely to be associated with efficacy. For example:

- When a concentration-dependent pattern of bactericidal activity is observed in time-kill studies, the area under the plasma concentration time curve from zero to 24 hours (AUC_{0-24}):MIC ratio and/or the maximum plasma concentration (C_{max}):MIC ratio is/are usually found to be predictive of efficacy in PK-PD model systems.

- When a time-dependent pattern of bactericidal activity is observed in time-kill studies the percentage of the dosing interval during which the plasma concentration exceeds the MIC (%Time>MIC), trough/MIC and/or the AUC_{0-24}:MIC ratio is/are usually found to be predictive of efficacy in PK-PD model systems.

For most antimicrobial agents it should be possible to identify specific nonclinical PDTs for each pathogen or group of pathogens of interest that result in the following effects on organism counts over a justified time period:

- A net static effect, i.e. no log_{10} drop in colony forming units (CFU)

- A 1 log_{10} drop in CFU

- A 2 log_{10} drop in CFU

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4.2.2. Nonclinical PK-PD studies

The PK-PD index or indices most closely related with efficacy of an antimicrobial agent should be identified from nonclinical PK-PD infection models, which may be conducted *in vitro* and/or in appropriate animal models. In-vitro and in-vivo models each have strengths and weaknesses and may be regarded as complementary. Sponsors should provide a justification for the use of one or more in-vitro and/or in-vivo models and should discuss the possible advantages and shortcomings of the specific type(s) of model used.

It is recommended that a core set of organisms should be used in all the nonclinical models selected, to which others may be added in specific models. Generally it is suggested that ~4-5 organisms of the major target species or organism groups should be tested. The organisms used in the models should be representative of those most relevant to the intended clinical uses and should exhibit MICs of the test agent that include values at the upper end of the wild-type distribution (see section 4.1). Sponsors are also encouraged to select organisms for use in the models that do and do not have specific mechanisms of resistance of potential relevance to the test agent (e.g. organisms that are resistant to other antimicrobial agents in the same class of the test agent). If the test agent is of a known class it may be useful to include an active comparator from the same class as an internal control.

In-vitro models

In-vitro models may be used to:

- Describe PK-PD relationships for representative organisms and a range of inocula

- Assess the effects of multiple different PK profiles. Initial studies can be conducted before there are any clinical PK data available. Once clinical PK data have been generated the models can be used to simulate typical plasma/serum profiles expected in infected patients (which may be based on POPPK model predictions of typical PK profiles) and assess the effect on organism numbers to provide further support for the PDTs.

- Study the relationships between rates of emergent resistance, drug exposure and duration of therapy. It may be useful to evaluate these relationships in multiple models of infection to aid in selecting a dose that suppresses or limits the potential for resistance development.

Animal models

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

Other nonclinical models (such as non-neutropenic mice) may be used if supported by adequate data and taking into account factors such as whether the test agent accumulates to a considerable extent in neutrophils. Additional specialised models may be used if the test agent is proposed to treat infections at sites where plasma/serum levels may not be predictive of compartmental levels, such as in meningitis and in infections involving intracellular organisms (such as *M. tuberculosis* and *L. monocytogenes*).

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4.2.3. Analyses of PK-PD relationships

Sponsors should provide details of the analysis methods used with the model parameters and goodness of fit (e.g. when a Hill-type function is fit to PK-PD data the fitting should be conducted using data from the whole time-course, including growth and death or net growth terms).

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

As a minimum the analyses should report the PDTs for achieving net bacterial stasis and 1- and 2-$\log_{10}$ reductions in bacterial densities for each pathogen or group of pathogens of interest, taking into account that not all agents will achieve 2-$\log_{10}$ reductions for all pathogens or in all models. Section 4.4.2 considers factors to be taken into account when selecting PDTs for use in analyses of PTA.

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

4.3. Clinical pharmacokinetic data to support PK-PD analyses

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

4.3.1. PK data from uninfected subjects

The initial PK data will come from healthy volunteers in whom intensive PK sampling is possible after single and multiple doses. These data should be sufficient to describe the PK properties of the test antimicrobial agent, including plasma/serum profiles and routes of metabolism and elimination. As appropriate, the effects of renal and/or hepatic impairment may need to be assessed. An initial POPPK model may be based solely on data from healthy subjects and can be used for the preliminary assessment of potentially efficacious doses for use in patients.

4.3.2. PK data from infected patients

The PK profile of a test antimicrobial agent in the infected target patient population may demonstrate several important differences compared to healthy volunteers. For example, some oncology patients and some intensive care unit patients, with or without ongoing infections, have been found to be in a state of renal hyperfiltration, whereby doses or dose frequencies of renally excreted agents may need to be adjusted to achieve the desired PTA. Another example is that there may be a considerable increase in the volume of distribution (Vd) of the test agent during active infection that is followed by a rapid reduction in Vd as the patient recovers, leading to marked changes in plasma levels during the treatment period. On occasion the mean/median values for PK parameters may be similar between healthy volunteers and patients but inter-individual variability may be greater in patients even in the absence of significant organ dysfunction and/or changes in plasma proteins. In addition, covariates that have a significant effect on PK in infected patients may not impact on PK in healthy volunteers.

PK data should be obtained from patients typical of the intended target population in terms of site of infection and severity of infection (but regardless of pathogen susceptibility) as early as possible in development and should be used to update the POPPK model based on healthy volunteer data. The

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updated model can support repeat PK-PD analyses and simulation to confirm or reject the likely sufficiency of the dose regimen before proceeding to further studies in patients.

In order to support analyses of clinical E-R relationships (see section 4.5) the PK sampling schema to be used in clinical studies (sparse sampling and/or intensive sampling) should be selected to allow accurate and precise PK parameter estimates to be obtained. For example, the schema for sparse sampling should be guided by some version of optimal sampling (e.g. the Fisher Information approach).

4.3.3. Other relevant data

The degree of binding of the test agent to human plasma proteins in the presence of clinically relevant concentrations should be assessed. Initially this may be evaluated *in vitro* by spiking human plasma with different concentrations of the test agent to determine whether there is concentration-dependent binding. Depending on the in-vitro data, estimates of in-vivo protein binding may be needed using samples collected during clinical studies, including studies in infected patients to support a robust estimation of unbound (free) concentrations of the test agent that can be used for PK-PD analyses. Consideration should be given to factors that impact on the determination of protein binding since correct quantification of protein binding has a major effect on subsequent PK-PD modelling.

As relevant to the test agent and its intended clinical uses, total and, if appropriate, free test agent concentration-time data should be presented for specific body fluids and related to plasma/serum levels. At the present time it is considered important to provide data on the following:

- Urinary concentrations when a significant amount of the test agent is excreted unchanged in urine and it is intended for treatment of urinary tract infections.

- Epithelial lining fluid (ELF) drug concentrations when the test agent is to be used to treat pneumonia.

- Cerebrospinal fluid (CSF) concentrations whenever the test agent is intended to treat meningitis.

Typically, ELF and CSF are obtained from uninfected patients each of whom is assigned to receive a single dose of the test agent at a specific time prior to a scheduled bronchoscopy or lumbar puncture. However, if possible, sponsors are encouraged to obtain some data on tests agent concentrations in ELF from infected patients.

If supported by emerging scientific data, it may be appropriate to assess drug concentrations in non-homogenate tissues (e.g. using microdialysis).

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

4.4.1. Use of simulations

When a PDT has been identified as described in section 4.2 it is necessary to assess whether this applies across a typical patient population. Pharmacokinetic data may not be available from patients when simulations are first attempted and patient data may be limited to relatively small numbers when dose regimens are selected for pivotal studies. Therefore a statistical approach is taken to simulate individual patient PK profiles for which the inputs include measures of central tendency statistics for PK parameters and their associated variance.

The statistical method most often used is Monte Carlo Simulation (MCS) but other methods may be used if adequately justified by sponsors.

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

In the majority of cases, the simulations are based on the nonclinical-derived PDTs, i.e. they are based on free test agent concentrations. Adjustments should be made for the degree of human plasma protein binding unless this is known to be low for the test agent under study.

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

If only healthy volunteer PK data are available the POPPK model should be adjusted so that the simulation results reflect the potential degree of inter-individual variability in the target patient population and any changes in the PK covariates and PK parameters. For example, one approach is to inflate the variability around the point estimate of drug clearance based on an assumption of the inter-individual variability to be expected in infected patients with severe systemic upset. Whenever renal clearance is important for the test agent it is necessary to include a distribution for creatinine clearance that is usually found in the target patient population.

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

4.4.2. Probability of target attainment (PTA)

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

- By selected MIC values of the test agent (see section 4.1)

- By PDT associated with stasis, 1-$\log_{10}$ kill and 2-$\log_{10}$ kill (see section 4.2.3)

Sponsors should provide detailed justification for the selected PDTs use in analyses of PTA. The following represent some considerations for selecting PDTs for use in analyses of PTA when the aim is primarily to achieve clinical and microbiological response rates expected to be at least as good as those associated with best available standard of care:

- For potentially life-threatening infections that usually involve high organism burdens (e.g. hospital or ventilator-acquired pneumonia [HAP/VAP]) and low spontaneous resolution rates it is generally expected that the PDT associated with at least ≥ 1 $\log_{10}$ reduction in CFU is selected. However, whenever possible it is suggested that simulations are also conducted using the PDT associated with 2 $\log_{10}$ reduction in CFU.

- For infections that may be associated with lower organism burdens and/or may be treated with antimicrobial therapy in conjunction with other types of therapeutic intervention (such as some types of acute bacterial skin and skin structure infections and intra-abdominal infections in

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which surgical intervention is often used) the PDT associated with at least net stasis may be considered sufficient.

Sponsors may consider several other aims of therapy when selecting PDTs to be used in analyses of PTA, including:

- A PDT associated with minimisation of the risk of selecting for resistance (e.g. based on evidence derived from in-vitro models)

- A PDT associated with a rapid response to treatment

- A PDT appropriate for a specific patient population (e.g. profoundly neutropenic)

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

Sponsors should discuss the adequacy of the cut-off(s) that are applied to the simulated PTAs for the purposes of selecting dose regimens. The following are some general considerations:

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

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

A PTA <90% may sometimes be acceptable. For example, if the dose needed to achieve >90% PTA is known to be poorly tolerated and the test agent addresses an unmet need. Otherwise, sponsors would have to justify the acceptability of a PTA < 90% based on issues such as low severity of the infection type or very few organisms with MICs at the upper end of the range such that PTA is >90% at MICs observed for the vast majority.

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

4.5.1. Potential value of E-R relationships

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

- Lack or rarity of pathogens with MICs of the test agent that are near to or above the upper end of the wild-type distribution

- The limited range of infection types and pathogens that are treated

- Lack of certainty regarding the actual or major causative pathogen(s)

- The impact of various non-treatment-related factors on outcomes (e.g. host immune systems, adjunctive treatments, surgical interventions)

- The dose regimen(s) studied will have been chosen based on PK-PD analyses with the aim of achieving high PTA in the patient population as a whole. Thus, a simple analysis of outcomes by dose regimen will not identify those patients who may have failed due to inadequate exposures.

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

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

- The clinical programme included very limited numbers of patients (e.g. as may sometimes apply to new antimicrobial agents with potential to address an unmet need)

- High clinical success rates were observed in conjunction with a dose regimen that resulted in the majority of patients having plasma/serum exposures that were very high relative to MICs of the test agent for their pathogens (i.e. there were insufficient clinical failures to support identification of a clinical PDT).

- Most or all patients received the test agent in conjunction with another antimicrobial agent active against the responsible pathogens.

- Clinical outcomes are heavily confounded by underlying diseases and/or surgical interventions.

- The exact identity of the infecting pathogen(s) is debatable.

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

4.5.2. Analyses of E-R relationships

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

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

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

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

4.5.3. Applications of E-R relationships

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

- Using a POPPK model, simulation to generate an exposure distribution and knowledge of the E-R relationship it is possible to generate model-predicted percent probabilities of response at specific MIC values.

- Using a POPPK model, simulation to generate an exposure distribution and knowledge of a clinically-derived PDT the PTA can be determined at specific MIC values.

4.6. Identification of beta-lactamase inhibitor dose regimens

4.6.1. Considerations for identifying dose regimens

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

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

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

- A comprehensive assessment of inhibitory activity in enzyme kinetics studies

- In-vitro testing in which various concentrations of the BLI and the proposed partner BL are combined. MICs and time-kill curves for the BL alone and in the presence of different concentrations of the BLI (i.e. potentiated MICs of the BL) should be compared against a range of organisms known to express specific beta-lactamases, with and without additional mechanisms of resistance to the BL (e.g. porin deficiencies or efflux pumps as appropriate to the BL and the bacterial species). The strains tested should include genetically engineered or naturally occurring organisms that are known to hyper-produce certain beta-lactamases.

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

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4.6.2. Approaches to identifying BLI dose regimens

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

In establishing the PK-PD index, studies should include nonclinical infection models in which the BL/BLI is administered to mimic the anticipated mode(s) of clinical use (i.e. with intermittent dosing separated by specific dose intervals and/or as a continuous infusion) since the PK-PD index for the BLI may be different under different administration modes. The BLI PK parameters of potential interest (C_{max}, AUC_{0-24}, %T>threshold) should be indexed to the potentiated MICs.

Simulations along the lines described in section 4.4 are used to estimate PTA but they are inevitably more complex since the BL and BLI are to be co-administered. To support simulations, POPPK models should be developed for the BL and BLI. The simulations should take into account the variability in plasma/serum exposures to each of the BL and the BLI as well as any PK interaction that may occur between the BL and the BLI when they are co-administered to patients.

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

4.6.3. Additional analyses to assess the BLI dose regimen

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

4.7. Regulatory implications

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

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

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

- Investigations of unexpected findings, such as lower success rates in sub-populations of patients for no obvious reason

- Identification of the need for and prediction of dose modifications in patient subsets (e.g. hepatic and renal insufficiency, children, elderly, obese, those with specific genetic factors affecting drug disposition)

- Identification of appropriate dose regimens with new formulations that result in modified PK profiles; these may be developed during or after initial licensure

- Interpretation of the possible clinical importance of the results of food-drug and drug-drug interaction studies

- Identification of dose regimens that may serve to reduce the risk of selecting for resistance

- Implementation of adaptive trial designs

- Validation of biomarkers

- Estimation of the no-treatment effect, which may then be used to derive well-supported non-inferiority margins for active-controlled studies

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5. DEFINITIONS

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

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

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

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

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

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

PK-PD target (PDT) - A magnitude for a PK-PD index at which a desired level of predicted response is achieved

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

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

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