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

Draft

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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)

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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 of pharmacometrics 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 pharmacometrics to identify susceptibility testing interpretive criteria. Sponsors are encouraged to discuss the use of pharmacokinetic-pharmacodynamic (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 Regulators.

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 MICs of the test agent against individual species, genera or organism groups (e.g. enterobacteria) relevant to the proposed indications. Additionally, time-kill studies should be conducted to provide preliminary 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, leading to establishment of nonclinical PD targets (PDTs) 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. Other factors to take into account in simulations include test agent concentrations in body fluids (such as lung epithelial lining fluid) and the effects of other interventions such as positive pressure ventilation.

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. As for antimicrobial agents the PK-PD index and PDT 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 clinical 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 very limited clinical efficacy data generated to support application dossiers. In these cases it is essential that there are very robust PK-PD analyses to support the likely adequacy of the dose regimen and any dose adjustments that may be needed for special populations. Since the PK-PD index and PDTs do not change in the presence of bacterial

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

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) indices 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 of pharmacometrics. 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 indices and 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 emerged to be of great assistance in 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 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.

When developing new antimicrobial agents and when planning to add or modify dose regimens for approved agents sponsors either have and/or obtain external expertise when performing analyses of PK-PD relationships. Nevertheless, there are some crucial aspects of the data, analyses and interpretation of the findings that deserve attention in a regulatory guidance document. 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.

2. Scope

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

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.

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.

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 pharmacometrics to identify susceptibility testing interpretive criteria. Nevertheless, the Guideline takes into account the data requirements and PK-PD analyses recommended by EUCAST [19] and the CLSI [6] for the purpose of setting interpretive criteria.

3. LEGAL BASIS

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)

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

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

In addition, 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
- Assessment of any post-antibiotic effect [7]
- Evaluation of intracellular antimicrobial activity
- Evaluation of MICs of the test agent in the presence of a range of resistance mechanisms and, applicable, against any target species that demonstrate hetero-resistance
- 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 for entire populations 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 data should suffice to identify appropriate MICs of the test agent to be used in analyses to describe the PTA (see section 4.4). That is, having derived PK-PD indices and PDTs as described in section 4.2, to assess the PTA at selected MICs of the test agent when using specific dose regimens to treat relevant pathogens. Consideration should be given to selecting the MICs from the distributions

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

The MIC values used for PTA analyses usually encompass values across the range observed. The MICs should always include values at the upper end of the MIC distribution and would usually include the MIC_{90} for each pathogen or group of pathogens of interest and/or the epidemiological cut-off values (ECVs) for each species of interest. If ECVs are used they should be derived from an adequate collection of isolates within a single species and the methodology used to ECV identification should be described (e.g. simple visualisation of histograms or a mathematical approach [31]).

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

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) [8, 20].

It has been shown that PK-PD index values derived from studies in animals and those obtained by Classification and Regression Tree (CART) analysis of clinical exposure-response data are very similar [19]. 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 (e.g. chemostat and hollow fibre infection models). 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 AUC_{0-24}:MIC ratio and/or the 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 %Time>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 PK-PD index values (PDTs) for each pathogen or group of pathogens of interest that result in:

- 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

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 general, the use of in-vitro models is recommended initially so that i) there is no restriction on the number of organisms that can be tested ii) any studies that are conducted in animal models can be kept to a minimum iii) animal models can be used to answer specific questions that are not adequately addressed by in-vitro models.

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). It is recommended that a core set of organisms should be used in all the nonclinical models, 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 but fewer may be tested in in-vivo models and others tested in in-vitro models.

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

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 at least in in-vitro models.

<u>In-vitro models</u>

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

- Derive PK-PD indices based on larger numbers of representative organisms and a wider range of inocula than is possible and justifiable in animal models
- Assess the effects of multiple different PK profiles. Initial studies can be conducted before there are any clinical PK data available to derive nonclinical PK-PD indices and PDTs. 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 [15].
- Study the relationships between rates of emergent resistance, drug exposure and duration of therapy [10, 11, 17]
- Compare the test agent with other agents of the same class or, at least, other agents with a similar spectrum of activity

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

Animal models

Most animal models involve mice. In the commonly used neutropenic mouse thigh and lung infection models [1, 9] 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 (e.g. using non-neutropenic mice or using other species) may be used if supported by adequate data, such as a demonstration of the correlation of the results with neutropenic mice. 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*).

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. For example, in the common case that a Hill-type function is fit to PK-PD data the report should include the E_0, EC_{50}, E_{max} and Hill's constant.

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 magnitude of the PK-PD indices (i.e. PDTs) necessary to achieve net bacterial stasis, 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 or, at least, not for all pathogens. 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 active infection may alter the volume of distribution of the test agent and so impact on plasma/serum levels. On occasion the mean/median values for PK parameters may be similar between healthy volunteers and patients but inter-individual variability is considerably greater in the 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.

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

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

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. Further estimates should be obtained during a study with radiolabelled test agent (if conducted) or from samples collected during clinical PK studies. The data collected from infected patients should suffice support a robust estimation of unbound (free) concentrations of the test agent that can be used for PK-PD analyses.

As relevant to the test agent and its intended clinical uses, total and free test agent concentration-time data should be presented for specific body fluids and ~~compared~~ related to plasma/serum levels using compartmental PK modelling. 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) free drug concentrations when the test agent is to be used to treat pneumonia. Typically, these studies are conducted in 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.

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

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

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

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

4.4.1. Use of simulations

When a specific PK-PD index value has been identified for use as a PDT to predict the probability of successful treatment of a specific pathogen or group of pathogens as described in section 4.2 it is necessary to assess whether this applies across a typical patient population, taking into account that there will be some degree of inter-individual variation in PK. Actual data may not be available from patients when these simulations are first attempted and, even when available, 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 Simulations (MCS) but other methods may be used if adequately justified by sponsors [21].

The total number of simulated patients (which is commonly around 5,000) 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 PK-PD indices and PDTs, i.e. they are based on free test agent concentrations. Unless otherwise justified, adjustments should be made for the degree of human plasma protein binding.

Whenever possible the PK inputs for simulations should be based on a POPPK model built from or including PK data from infected patients. 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. The most common adjustment involves inflation of variability around the point estimate of drug clearance based on an assumption of the variability to be expected in infected patients with severe systemic upset. It is also 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. 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) [25, 26, 27]

The following should be taken into account when 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 the PDT associated with ≥ 1 $\log_{10}$ reduction in CFU is generally recommended.
- 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 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 PDT values to be used in analyses of PTA, including:

- A PDT value associated with minimisation of the risk of selecting for resistance (e.g. based on evidence derived from in-vitro models) [10, 18, 28]
- A PDT value associated with a rapid response to treatment
- A PDT value 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.

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 commonly 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 expected 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 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. [12, 13, 14, 22, 30] 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 [3, 4].

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 predictors 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.

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).

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.

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

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 or 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 since the amount of beta-lactamase manufactured can impact on the potentiated MIC observed.

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.

4.6.2. Approaches to identifying BLI dose regimens

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

In nonclinical infection models the BL/BLI should be 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. In this field in-vitro PD models have been especially valuable since they facilitate experiments in which a large number of different combinations of BL and BLI dose regimens can be evaluated to derive nonclinical PK-PD indices and PDTs for the BLI.

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. When interpreting the PTA it should be remembered that this is influenced by the proportion of isolates with a given potentiated MIC value that are actually producing a relevant β-lactamase [23]. Therefore the MIC distribution is critical to the conclusions of the dose-justification analyses.

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 will 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 PK-PD indices and 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 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

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.

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

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

PK-PD target - 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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