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Evaluation of Medicines for Human Use

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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**POINTS TO CONSIDER ON PHARMACOKINETICS AND
PHARMACODYNAMICS IN THE DEVELOPMENT OF
ANTIBACTERIAL MEDICINAL PRODUCTS**

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Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document will be revised in accordance with the scientific advances made in this area.

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PHARMACOKINETICS AND PHARMACODYNAMICS IN THE DEVELOPMENT OF ANTIBACTERIAL MEDICINAL PRODUCTS

I INTRODUCTION

Pharmacokinetics (PK) describes the relationship between administered dose, the observed biological fluid/tissue concentrations of the drug, and time. Pharmacodynamics (PD) is concerned with the magnitude and time course of the observed pharmacological effect. A PK/PD model is a mathematical description that provides clinically relevant information about the relationship between the pharmacokinetics and the pharmacological effect. Antibacterial agents differ from other drugs by, ideally, exhibiting their pharmacological effects not on human eukaryotic cells, but exclusively on pathogenic bacteria. Thus, any direct effects on human cells and tissues are, by definition, adverse.

There is a mounting body of evidence to support the use of the PK/PD relationship for individual antibacterial agents in identifying those doses and dose intervals that are most likely to be efficacious and least likely to result in adverse effects and/or the selection of resistant organisms.

This concept has implications for the safety and efficacy of antibacterial drugs in human medicine.

Although PK/PD relationships have sometimes been taken into consideration during drug development for determining the optimum duration of therapy, there is insufficient evidence at present to support the use of such data for this purpose. Further studies into this important area are encouraged but any recommendations on such studies are not within the scope of this document.

Based on the current status of scientific investigations in this field, the CPMP is of the opinion that there seems to be sufficient evidence to support a recommendation that the PK/PD relationship for an antibacterial medicinal product should be investigated during the drug development programme. Although, the CPMP currently takes the position that data on the PK/PD relationship cannot replace confirmatory clinical trials of efficacy, but rather complement them to arrive more quickly at better dose recommendations, there may be areas in which detailed study of the PK/PD relationship might potentially impact on the content of the clinical programme (*e.g.* with reference to certain types of infections, patients, and medicinal products, see below). At present there is a lack of published studies that have sought to prospectively validate the correlation between the PK/PD relationship and clinical and bacteriological outcomes. In principle, the CPMP encourages attempts to validate and confirm the PK/PD concept during the clinical development programme.

As new data emerge in this field the CPMP may revise this *Points to Consider* document.

This points to consider document should be read in conjunction with the following:

- CPMP Note for guidance on Evaluation of new antibacterial medicinal products
- CPMP Note for guidance on the Pharmacodynamic section of the SPC for antibacterial medicinal products
- CPMP Note for guidance on Investigation of bioavailability and bioequivalence
- CPMP Note for guidance on Pharmacokinetic studies in man
- CPMP ICH Note for guidance on Dose response information to support drug registration

II PROBLEM STATEMENT

Difficulties in determining optimal dosage

Optimal dosage regimens are not well defined for antibacterial agents even though some have been available for clinical use for almost 60 years. The major reason for this is that the antibacterial activity of the drug is only one factor in determining the response to treatment. Host and pathogen factors that affect the course of an infection include the host defence mechanisms, the pathology of the infection, and the virulence and metabolic behaviour of the invading micro-organisms. Drug-related factors include the ability of the drug to reach its target i.e., the pathogen must be present in a tissue compartment which is accessible to the antimicrobial agent.

Dose-ranging studies with antibacterial agents are difficult to conduct and there are obvious ethical limitations especially in seriously ill patients. Therefore, dosing regimens have largely been deduced from the relationship between the MICs and MBCs of the new antibacterial agent for important pathogens and the pharmacokinetics of the drug in blood.

The MIC, MBC and the concentrations that can be achieved in blood, are fairly easy to measure. Blood levels are commonly used to estimate drug concentrations likely to occur at the site of infection. Nevertheless, it is usual for a limited number of studies to include measurement of human tissue and body fluid concentrations. While the accumulation of such data is encouraged for certain compartments, such as cerebrospinal fluid, unreliable information is generated from assays of drug concentrations in whole tissues (e.g. homogenates) because of methodological difficulties.

Until the last ten years, it was common practice to select antibacterial drug dosing regimens so as to achieve blood levels which were maintained above the MIC of the drug for the important target pathogens for most of the dosing interval. Whereas this approach was generally applied to all classes of antibacterial agents, it was initially based on clinical experience gained with agents that are not rapidly bactericidal, such as sulphonamides and tetracyclines, for which the dosing intervals were chosen according to plasma half-lives. This "time over MIC" concept was reinforced by the demonstration that maintaining penicillin concentrations above the MIC was an important determinant of efficacy against treponemes, streptococci and neisseria. More recently, the post antibiotic effect exerted by some drugs against certain pathogens has also influenced the selection of dose interval.

However, in the last decade knowledge of the relevance of the interaction of pharmacokinetic and pharmacodynamic parameters to the efficacy of various antibacterial agents has substantially increased and it has become clear that these drugs cannot be regarded as one class in this respect. For example, the antibacterial activity of the aminoglycosides and fluoroquinolones has been shown to be related to the ratio of the peak blood concentration to the MIC or the area under the concentration-time curve (AUC) to the MIC. In contrast, the antibacterial activity of the beta-lactams depends on the proportion of the dosing interval during which blood concentrations are maintained above the MIC for the pathogen under treatment.

PK/PD definitions and relationship

In-vitro and animal dose-response studies have demonstrated that the pharmacokinetic and pharmacodynamic properties of antibacterial agents with different mechanisms of action can be used to better describe their activity than the determination of MICs alone.

As mentioned above, the PK/PD relationship which provides the best correlation with clinical cure and pathogen eradication differs between classes of antibacterial agents. There are also recognised differences between certain agents within classes that may be related to the

pharmacokinetics of individual compounds. Not surprisingly, there is also some evidence to suggest that the predictive value of PK/PD data varies between hosts (for example, related to their immunocompetence) and according to the site of the infection.

In-vitro models

A variety of *in-vitro* kinetic models (including both one and multiple-compartment models) to study antibiotic effects have been developed during the last decades. One of the advantages of *in-vitro* kinetic models compared to animal models is that human pharmacokinetics can more easily be simulated. In this way different bacterial species can be exposed to drug concentration profiles which would be achieved in blood by various dosing regimens in man. Thus, it is possible to investigate which pharmacokinetic parameters (e.g. AUC, peak concentration or time over MIC) correlate best with antibacterial activity, by changing drug concentrations to mimic the application of various doses and dose intervals and/or to examine the effects of different elimination half-lives.

In principle and within limits, *in-vitro* models may be used to test hypotheses. However, they are essentially simulations of infection in immunocompromised persons in that the total antibacterial activity observed is solely dependent on the drug. As such, *in-vitro* studies do not always reflect the target patient population, in which the host's immune system usually plays an important role in the clinical and microbiological outcome of infection. Also methodological differences between laboratories and the inherent difficulties of these systems (dilution effect etc) can make the data unreliable

In-vivo models

A number of specific infection models in a variety of animals have been described. One of the disadvantages of animal models is that the metabolic pathways and/or tissue distribution patterns which apply to an antibacterial agent in animals may not be the same as those which exist in man. This can sometimes be overcome by modification of the model to produce testing conditions which more closely resemble the human situation. With appropriate modifications, animal models have been used to evaluate a range of multiple-dose regimens in order to explore the interdependence between major pharmacokinetic parameters such as duration of time above the MIC, AUC and peak-level. Thus, PK/PD data may be obtained which are a valid basis for dose selection for initial studies in man.

Link between PK/PD and resistance development

As yet, it is not clear as to whether or how PK/PD studies might be used to identify dose regimens that might minimise resistance development without compromising treatment outcome.

Non-clinical data have suggested that the C_{max}/MIC ratio for fluoroquinolones and aminoglycosides may be important for predicting the risk of selecting drug-resistant organisms. Preliminary data drawn from studies of five different treatment regimens for nosocomial pneumonia in man have suggested that the probability of selecting for resistant organisms increased markedly when the AUC_{0-24}/MIC ratio fell below 100 (2). This conclusion applied to four beta-lactams (when chromosomally-encoded beta-lactamase production was not involved) and to ciprofloxacin.

The impact of antibacterial agents on the composition of the normal flora, particularly on gut bacteria, has been the subject of many studies. Far fewer data are available regarding the selection of drug-resistant organisms in the normal flora during the course of systemic antimicrobial chemotherapy. However, observations such as the association between fluoroquinolone excretion in sweat and the selection of drug-resistant *S. epidermidis* on skin indicate that such phenomena may be common occurrences. These organisms are potential

pathogens in the increasing number of immunosuppressed patients in hospitals and the community.

The CPMP is of the opinion that further exploration of these matters during the drug development process is to be encouraged.

III ASPECTS OF CHARACTERISING PK/PD RELATIONSHIPS

There are a variety of analysis methods available to characterise PK/PD relationships. Analysis methods that have been seen in regulatory submissions include:

- a simple graphical approach
- use of correlation coefficients
- PK/PD modelling

While a specific approach cannot be recommended in general, it can be stated that PK/PD modelling normally is more informative than the other approaches.

With respect to characterising the PK/PD model, an important point is what assumptions have been made during the model-building process. These assumptions concern the accuracy of the data (i.e. correct dosing history and sampling times have been collected); that the structural model fit to the data is appropriate (e.g. one versus two compartment model). If a covariate model is included, the covariates identified should be biologically realistic. Other assumptions also made are specific to the computer program used and type of data analysis approach taken (individual specific, naive pooling, population analyses). The data analyst has to be aware of the assumptions being made and employ appropriate techniques to check these, otherwise the model could be worthless and any predictions made from it extremely misleading. Any interpretation can only be made within the limitations of how well the PK/PD model has been characterised.

PK and PD data from preclinical, early Phase I and Phase II studies could be used to build models that can then be used to help design Phase III trials. Through simulation, the influence of certain aspects of the planned Phase III trial can be assessed, and, the design (for example, with respect to dose or dosing interval) subsequently modified if needed.

IV IMPLICATIONS FOR ANTIBACTERIAL DRUG DEVELOPMENT PROGRAMMES

It has come to the attention of the CPMP that some sectors of the innovative pharmaceutical industry have already taken note of the developments in the field of PK/PD relationships and their potential predictive value with regard to efficacious dose regimens during the development of antibacterial medicinal products. It is probably correct that establishing the PK/PD relationship pre-clinically is in itself a major improvement compared with the more unclear rationale for dose recommendations pertaining to previous antibiotic drug development.

Based on the current knowledge as reviewed by the CPMP, the following regulatory viewpoint on the PK/PD relationship and its implications for drug development can be proposed.

In-vitro and animal model studies

The CPMP takes the position that a pre-clinical development programme which aims to establish the PK/PD relationship is useful for selecting dose regimens to be taken forward for evaluation in pharmacokinetic studies and in efficacy trials in man. These studies should focus on those pathogens most important to the indications sought and might incorporate a comparison of PK/PD parameters between the new agent and structurally related compounds.

Data derived from preclinical PK/PD studies may be included in section 5.1 of the SPC if it provides relevant information to prescribing physicians.

At the same time, it is accepted that further dose modifications might be necessary during clinical development due to observed clinical therapeutic response and safety concerns.

Antimicrobial resistance

As discussed above, the CPMP recommends that emergence of resistance be an integrated part of investigations of the PK/PD/outcome relationship to better understand the role of dosing to contain anti-microbial resistance. Furthermore, selection of resistance to one class of agents can also be associated with acquisition or maintenance of other resistance genes in some organisms (i.e. “co-resistance”). Hence, this could be another factor that might be elucidated during clinical trials. For example, population pharmacokinetic data might be obtained as part of studies in various indications along with susceptibility testing of presumed pathogens and non-pathogens in specimens from patients who have and have not responded to therapy.

An exploratory analysis of the data thus retrieved from clinical trials could aid in the PK/PD assessment of this particular aspect and would serve to allow an assessment of the impact of therapy on the composition and susceptibility of the normal flora.

Breakpoints

The tentative breakpoints as proposed by the applicant should also consider the PK/PD relationship. It is acknowledged that the selection of breakpoints which takes into account PK/PD data may result in proposals for a new compound which differ from those already approved for similar established antibacterial agents. Any such discrepancies need to be discussed and justified by the applicant.

Clinical studies

The link between the pre-clinically established PK/PD relationship and its potential to predict clinical outcome in human disease is mostly based on retrospective analyses of individual clinical trials in man or pooling of those trials. Very few clinical trials available in the literature have attempted to prospectively validate the predictive capacity of PK/PD data for clinical outcomes. Nevertheless, the available data from appropriate models indicate that similar PK/PD effect relationships exist in human infections as have been seen in animal experimental infections. This being so, as stated above, the identification of efficacious doses early in the drug development process may serve to reduce the number of Phase I/II studies. However, the CPMP does not believe that current knowledge would support the use of pre-clinical information on the PK/PD relationship to significantly reduce the scope and content of the Phase III development programme, including the number of patients recruited to controlled clinical trials. In addition, the numbers of patients exposed remains an important consideration for the assessment of the safety profile of a new antibacterial agent.

In principle, the PK/PD concept for an antibacterial medicinal product should be explored during the clinical development programme in order to assess the predictive value of the *in-vitro* and animal model investigations. It is recognised that, despite data on the PK/PD relationship, the actual dose regimens evaluated in Phase III trials may need to be a modification of those predicted due to other considerations predominantly related to safety.

Moreover, it is acknowledged that clinical trials are not primarily designed to prospectively quantitate the relationship between plasma levels and efficacy (clinical and microbiological) and safety outcomes, and in many types of infection in immunocompetent persons, it may be difficult to show such a relationship. Therefore, the CPMP suggests that certain special investigations might be considered as may be appropriate to individual antibacterial agents. For example, centres participating in multicentre trials, which have the capability to perform timed

sampling for drug level determination might be designated to participate in substudies within each indication aimed to evaluate PK/PD relationships. Also, that such investigations would likely be most fruitful in those indications where the pathogen(s) can be identified with greatest certainty and/or the role of the drug in determining outcome is likely to be greatest. In this regard, the sorts of clinical trials, which are most likely to show a clear relationship between plasma (or other body fluids) profiles and outcome might be studies in infections that can be well-documented with respect to pathogen and outcome (and in the treatment of bacterial infections in the grossly immunosuppressed, where the drug is practically unaided by the host's defence factors).

It is understood that these substudies within major Phase III trials could be viewed as "exploratory" in nature. Nevertheless, the study protocol and analysis plan should describe which investigations and which data are intended to be used to evaluate the PK/PD relationship. The model applied to and/or deduced from the pre-clinical data should be incorporated into the exploratory analysis of the study results.

Other regulatory implications of PK/PD information

The information that may be derived from the pre-clinical animal model and clinical investigations undertaken by the applicant may be very important to the design and content of the overall clinical development programme. There may be instances where detailed consideration of the PK/PD relationship in a dossier could help support a justification for limited clinical investigations in certain types of patients and/or infections. However, at present the CPMP is not able to provide definitive guidance on the acceptability of applications in which such data are proposed to partially or even wholly supplant formal clinical investigation, nor can it delineate circumstances in which such an approach might be acceptable. Therefore, it is recommended that applicants who propose to use PK/PD data in this way should seek scientific advice from the CPMP regarding the justification for and acceptability of such an approach.

Areas in which detailed study of the PK/PD relationship might potentially impact on the content of the clinical programme could include:

1. The choice of dose regimen for certain types of patient or infection. For example:
 - special populations (e.g. children, patients with hepatic or renal impairment)
 - uncommon or rare pathogens (e.g. *Listeria monocytogenes*) or pathogens with reduced susceptibility (e.g. fluoroquinolone-resistant or penicillin-resistant *S. pneumoniae*)
 - certain types of infection (e.g. meningitis)

At present, it is common practise to recommend dose regimens for children and those with impairment of renal or hepatic function that provide AUCs similar to those obtained in normal healthy adults. However, several dosing regimens may give the same total exposure yet differ greatly in time over MIC and/or peak concentrations reached and, according to the PK/PD relationship for the drug, would not necessarily provide the same antibacterial activity. Therefore, in identifying appropriate dosing regimens for different patient types, the regimen should be designed not only to avoid the potential toxicity of total higher exposure but also to provide a pharmacokinetic profile in blood that is appropriate to the PK/PD properties of the drug.

Similarly, in making recommendations for infections due to certain pathogens and/or in certain body sites, it may be important to consider how the dosing regimen could be designed such that a sufficient peak concentration and/or time over MIC may be reached at the site of the infection.

With regard to classes of antibacterials, for which the PK/PD relationship has already been established from pre-clinical studies, and for which there may be substantial clinical efficacy data, the possibility for some reduction in the clinical package required to support efficacy in a new indication may be explored. It would be appropriate that the applicant should discuss an approach with the regulatory authority prior to submitting the application.

2. The scope and extent of the data needed to support the approval of new formulations, or new dosing regimens.

With regard to the development of modified release formulations of antibacterial agents which have previously been approved as immediate-release preparations, CPMP may consider it appropriate that the applicant should discuss the pharmacokinetic data relevant to the old and new formulations in the light of the PK/PD relationship for that active substance. In order to comply with such a request, the applicant may have to undertake investigation of the PK/PD relationship as part of the application. Thus, studies aimed at showing that any differences in the actual plasma profiles achieved by the existing and the new formulation do not negatively impact on the pertinent concentration/effect relationship may have to be undertaken. In addition, depending on the drug and the plasma profile achieved, it may be important for the applicant to explore the relationship between the duration of sub-therapeutic levels between doses and the potential for selecting out drug-resistant organisms.

3. The ratio and/or fixed content of one component of a combination drug product

In the development of preparation which combine two antibacterials or which combine an antibacterial agent with another active substance, such as an inhibitor of beta-lactamase, the choice of the ratio of the two components could be supported by considerations of PK/PD data. Similarly, when both components of the combination product are involved in the overall antibacterial activity, the choice of a ratio or of a fixed content of one of the two components might be justified by exploration of the PK/PD relationships of different combinations of the two active substances.