



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 16 December 1999
CPMP/EWP/2655/99 draft 4

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

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

DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)	September 1999
TRANSMISSION TO THE CPMP	December 1999
RELEASE FOR CONSULTATION	December 1999
DEADLINE FOR COMMENTS	March 2000

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.

The CPMP's position on this matter is now released for consultation. Any comments you may have should be sent to the EMEA, EWP secretariat (fax no +44 171 418 8613), before the end of March 2000.

PHARMACOKINETICS AND PHARMACODYNAMICS IN THE DEVELOPMENT OF ANTIBACTERIAL MEDICINAL PRODUCTS

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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.

There is a perception among clinical microbiologists and experts in infectious diseases that exploration of the PK/PD relationship for individual antibacterial agents in in-vitro and animal models of infection might be used to identify those doses and dose intervals most likely to be efficacious in man.

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

However, PK/PD considerations do not presently allow for determination of the optimum duration of therapy.

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. However, 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 at better dose recommendations. Whereas in principle the CPMP encourages attempts to validate and confirm the PK/PD concept during the clinical development programme, the CPMP cannot give detailed guidance on how these investigations might be performed due to the lack of published studies, which have sought to prospectively validate the PK/PD/Clinical outcome relationship.

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 guideline on evaluation of new antibacterial medicinal products.
- CPMP guideline on the pharmacodynamic section of the SPC for antibacterial medicinal products.
- The CPMP guideline on Investigation of Bioavailability and Bioequivalence.
- The CPMP guideline on Pharmacokinetic Studies in Man.

II PROBLEM STATEMENT

Difficulties to determine optimal dosage

Optimal dosage regimens are still poorly 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. Other factors, which affect the course of an infection, include the host defence mechanisms, the pathology of infection, the virulence and metabolic behaviour of the invading micro-organisms, and the pharmacological properties of the anti-microbial agent employed to treat the infection. Dose ranging studies 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, which can be achieved in blood, are fairly easy to

measure and blood levels can be used as indicators of 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 and the accumulation of such data is particularly encouraged for special infection sites, such as in the central nervous system. In contrast, measurements of the drug content in whole tissues (*eg.* homogenates) are subject to methodological and interpretation difficulties, which make such data unreliable.

Until the last ten years, it was common practice to select anti-microbial dosing regimens so as to achieve blood levels which were above the MIC of the drug for the important target pathogens and which were maintained above this limit for most of the dosing interval. The basis for this approach, which was generally applied to all classes of antibacterial agents, was the clinical experience gained with bacteriostatic agents, such as sulphonamides and tetracyclines, for which the dosing intervals were chosen according to plasma half-lives. Additional information came from experience in treating infections due to streptococci, neisseriae and *T. pallidum* with depot - penicillins, where it was noted that maintaining concentrations above the MIC was an important determinant of efficacy. 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 anti-microbial agents has substantially increased. At the same time, it has become clear that these drugs cannot be regarded as one class in this respect. For example, the antibacterial effect of the aminoglycosides has been shown to be related to the peak concentration achieved whereas that for the beta-lactams depends on the proportion of the dosing interval during which concentrations are maintained above the MIC for the pathogen under treatment.

PK/PD definitions and relationship

In-vitro and animal dose-response studies have determined antibacterial pharmacodynamic parameters which differ among anti-microbial agents with different mechanisms of action and which better describe the time course of anti-microbial activity than the determination of MICs. For example, for β -lactam antibiotics it has been shown that the time that free antibiotic concentrations exceed the MIC correlates with efficacy. In contrast, for aminoglycosides and fluoroquinolones the most important parameters for determining efficacy are the ratio of AUC and/or peak concentrations to the MIC.

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 by various dosing regimens in man. Thus, it is possible to investigate which pharmacodynamic parameters (*eg.* AUC, peak concentration or time over MIC) correlate best with antibacterial activity 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 vivo models

A number of specific infection models in a variety of animals have been described. One of the most important disadvantages of animal models is that the drugs are often eliminated faster in animals than in humans. This can sometimes be overcome by inducing renal failure in the animal or by fractionating dosages. An alternative or additional method has been to use a variety of multiple dose regimens to minimise the interdependence between major

pharmacokinetic parameters tested (duration of time above the MIC, AUC and peak-level).

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, which might minimise resistance development without compromising treatment outcome.

Although there is currently insufficient knowledge regarding the dose regimen-related factors which are most critical for the selection of resistant subpopulations to presume that such considerations might also have benefits in this respect, more PK/PD/clinical outcome and resistance data should contribute to the clarification of these relationships. For example, current preclinical data suggest that the C_{max} MIC ratio for fluoroquinolones and aminoglycosides may predict selection of resistance.

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 are:

- A simple graphical approach.
- Use of correlation coefficients
- PK/PD models. These have included:
 1. Individual specific models.
 2. Naïve pooled models.
 3. Population models.

While a specific analysis method cannot be recommended above others at this time, it can be stated that results from population analyses are usually very informative in contrast to the use of correlation coefficients, which are extremely uninformative.

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) and, within a population analysis, that the covariate model is appropriate (i.e. that the covariates identified (such as age, weight, etc.) as being important are biologically realistic relationships). Other assumptions also made are specific to the computer program used and type of data analysis approach taken. 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 PROGRAMS

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 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 program aiming at establishing the PK/PD relationship should be used for determining those dose regimens which are 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 should incorporate a comparison of PK/PD parameters between the new agent and any relevant structurally related compounds, which have already been approved. Information derived from preclinical PK/PD studies may be included in section 5.1 of the SPC as seems appropriate.

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

Anti-microbial resistance

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. For the purpose of elucidating the possible relationship between PK/PD and emergence of resistant isolates, it is encouraged that serum sampling from patients in different clinical studies be performed along with sampling of bacteriological specimens in patients who respond and who do not respond to therapy. In this way, information on factors contributing to the selection of resistant micro-organisms, which is not usually a common event detected in clinical trials may be obtained.

Breakpoints

The tentative breakpoints as proposed by the applicant (to allow estimation of frequencies of acquired resistance in the SPC, section 5.1.) should consider PK/PD effect relationship as described in this document. The breakpoints proposed for a new compound should be discussed in relation to established breakpoints of related compounds, which have already been approved

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 analysis 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 PK/PD/ Clinical outcome relationship. Although available data clearly seem to indicate that the same PK/PD effect relationships exist in human infections as in animal experimental infections, the CPMP, at the current stage of knowledge, does not believe that having established the PK/PD relationship pre-clinically is generally sufficient to allow a significantly reduced clinical package with a smaller number of patients recruited to controlled clinical trials.

In principle, the PK/PD concept for an antibacterial medicinal product should be validated and confirmed during clinical drug development in order to test the predictive value of the *in vitro* and animal model investigations. However, 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. 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 greatest. In this regard, the sorts of clinical trials, which are most likely to show a clear relationship between plasma profiles and outcome might be studies in infections, which can be well-documented with respect to pathogen and outcome (eg. pneumococcal pneumonia) and in the treatment of bacterial infections in the grossly immunosuppressed, where the drug is practically unaided by the host.

Other regulatory implications of PK/PD information

The information which may be derived from the preclinical, animal model and clinical investigations suggested 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, the CPMP, at this point in time cannot provide definitive guidance on the acceptability of applications in which such data is proposed to partially or even wholly supplant formal clinical investigation, nor can it delineate circumstances in which such an approach might be acceptable. Therefore, the CPMP recommends that applicants who propose to use PK/PD data in this way should seek scientific advice at the EMEA regarding the justification for such an approach.

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

1. The choice of dose regimen for certain types of patient or infection. For example:
 - special populations (eg. children, patients with hepatic or renal impairment).
 - rare pathogens (eg. listeria)
 - certain types of infection (eg meningitis)

At present, it is common practise to recommend dose regimens for children and in those with impairment of renal or hepatic function which 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 which 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 in the immediate vicinity of the infection.

2. The data package needed to support applications for line extensions, such as new formulations or novel dose regimens.

In case of applications for similar (i.e. generic), modified and/or slow- release formulations of antibacterial agents, which have previously been approved, recognition of the clinical importance of the specific PK/PD relationships may prompt CPMP to request that such matters be explored by the applicant in addition to the demonstration of bioequivalence. Thus, studies aimed at showing that any differences in the actual plasma profiles achieved by the existing and the generic or 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 subtherapeutic levels between doses and the potential for selecting out drug-resistant organisms.