EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

15 December 2011
CPMP/EWP/558/95 rev 2
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections

Draft Agreed by Efficacy Working Party	February 2010
Adoption by CHMP for release for consultation	18 February 2010
End of consultation (deadline for comments)	31 August 2010
Agreed by Infectious Diseases Working Party	July 2011
Adoption by CHMP	15 December 2011
Date for coming into effect	15 January 2012

This guideline replaces guideline CPMP/EWP/558/95 rev 1.

Keywords	*Bacterial infections; antibacterial activity; non-inferiority studies; superiority studies; prophylaxis; susceptibility testing; EUCAST; PK/PD relationship; bacteraemia; febrile neutropenia; eradication of carriage; drug-resistant organisms; PIP*

Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections

Table of contents

Executive summary

Following adoption of the *Note for Guidance on evaluation of medicinal products indicated for the treatment of bacterial infections* (CPMP/EWP/558/95 rev 1) it became apparent that some areas of the guideline would benefit from further explanation of the requirements for approval of new antibacterial agents and for significant variations to the marketing authorisation. Additional matters requiring guidance arose during provision of scientific advice to sponsors and the assessment of application dossiers. During the revision process it was decided to develop a separate addendum to CPMP/EWP/558/95 Rev 2 to provide details of requirements for clinical studies intended to support specific indications that are commonly sought and the evaluation of antibacterial agents with potential to be active against rare and/or difficult to treat bacterial pathogens, including organisms that are resistant to many of the available agents. Therefore, sponsors should consult relevant addenda to this guideline that have been or will be developed and/or should seek advice from EU Regulators.

In the non-clinical development programme the microbiological evaluation of a new antibacterial agent should include efforts to identify the precise mechanism of action. Activity against pathogens that are resistant to other antibacterial agents, including agents of the same class if this is applicable, should be explored. Organisms inhibited only at unusually high concentrations of the test antibacterial agent should be investigated for possible mechanisms of resistance and cross-resistance within and between classes. During clinical studies it is recommended that the confirmation of identification and susceptibility test results obtained from accredited local laboratories, isolate typing to distinguish relapses from new infections and serological studies should be conducted at designated centralised laboratories with appropriate expertise.

Pharmacokinetic/pharmacodynamic (PK/PD) analyses may be used to select dose regimens for clinical studies and to support interpretive criteria for in-vitro susceptibility testing. If the PK/PD relationship for an agent is very clear and the analyses are convincing it may be possible to omit clinical dose-finding studies.

Each study of clinical efficacy should aim to select patients who have infections that are strictly relevant to the indication sought and require antibacterial therapy by the route of administration specified. Enrolment criteria intended to differentiate complicated from uncomplicated infections do not necessarily distinguish infections according to degree of severity and may not be sufficient to identify infections that can be treated by oral, parenteral or topical routes of administration. Therefore additional steps should be taken to ensure that the patient population is optimal to support the indication claimed and the dose recommendations.

It is preferred that each clinical indication for use is supported by at least two randomised and controlled studies. The provision of a single pivotal study may be acceptable if this has been conducted in accordance with applicable CHMP guidance. Comparative studies should be double-blind whenever feasible. Most confirmatory studies of efficacy will aim to demonstrate non-inferiority between the test antibacterial regimen (which may consist of more than one active agent) versus an appropriate comparative regimen, which should be one of the best available treatments. The choice of non-inferiority margin requires particular attention in accordance with the available CHMP guidance. Further details will be provided in an addendum.

In some indications, or in some sub-populations of patients with particular types of infection, a non-inferiority study cannot reliably support a conclusion that the test antibacterial agent would be superior to placebo if the comparison were actually to be made. These will primarily be indications where the magnitude of effect of antibacterial therapy relative to placebo is not consistently reproducible or is not well quantified. In these cases, an alternative approach to the assessment of clinical efficacy of the test agent is required and this revision provides further clarification on requirements for studies intended to

demonstrate superiority against placebo or an active control, including a discussion of possible efficacy endpoints. Further details will be provided in an addendum.

Data on efficacy in relatively rare types of infection or infections caused by relatively rare pathogens, including those that demonstrate multidrug resistance and/or an unusual pattern of resistance to specific agents, may be collected during the course of indication-specific studies and/or in separate studies that aim to enrol patients with infections due to selected pathogens. Very occasionally the only way to accumulate clinical experience with specific antibacterial agents in the treatment of specific pathogens, which may or may not express multidrug resistance, could be in studies that enrol patients with well-documented infections regardless of which body site(s) is/are affected. Although numbers of treated infections due to these pathogens are likely to be small it is still preferred that data are obtained from randomised study designs whenever possible, even if these are underpowered. The minimum number of treated cases required to support a specific claim must be judged on a case by case basis.

In many instances the nature and course of bacterial infections is sufficiently similar between age groups that efficacy data obtained in adults may be used to support use of an antibacterial agent in the same indication in children of various ages provided that there are sufficient safety and pharmacokinetic data available to support age-specific dose recommendations. Bacterial infections that occur mainly in children or for which the pathogens or clinical course may differ by age group require specific data to be obtained on efficacy in children.

The evaluation of safety of antibacterial agents should include an assessment of the data generated within each indication and against each comparative regimen since pooling across all studies may be misleading. The final visit in each study should be conducted at a sufficient time interval after the last dose to detect possible late drug-related adverse reactions, such as severe skin reactions and antibiotic-associated diarrhoeal disease.

Some sections of the Summary of Product Characteristics (SmPC) for antibacterial agents require special consideration due to issues such as multiple indications for use, some of which may be age-specific, the possibility of indication-specific dose regimens and the need to describe the microbiological data, including the efficacy observed by pathogen in clinical studies. Recommendations for the content of relevant sections of SmPCs are provided in the last section of this guideline and should be followed as far as is appropriate for individual agents.

1. Introduction

The development of new antibacterial agents and new formulations, routes of administration and/or regimens of existing agents is recognised to be of great importance to human health. To facilitate clinical development programmes there is a need to allow for some flexibility in requirements while ensuring that each indication sought is supported by sufficient data to enable a sound assessment of the benefit-risk relationship. This revised guideline and the addendum that will follow build upon these principles.

2. Scope

This Guideline considers the microbiological and clinical data required to support indications, dose regimens and durations of therapy for antibacterial agents and the layout and wording of some sections of the Summary of Product Characteristics (SmPC). It applies to the initial development programmes for new antibacterial agents and to the data generated to support additions and changes to the clinical and microbiological elements of the marketing authorisation.

Indication-specific guidance will be provided in an addendum to this Guideline, which will cover issues such as patient selection criteria, primary endpoints for the analysis of efficacy, the selection of non-inferiority margins, the design of superiority studies and certain indications for which there is currently no established regulatory path to approval.

The Guideline is relevant to the development of antibacterial agents that have a direct action on bacteria resulting in inhibition of growth and replication, with or without a rapid bactericidal effect, including:

- Antibacterial agents developed as single agents (including those that may need to be given with other licensed agents under some circumstances)

- Antibacterial agents developed only in combination with another active agent (e.g. fixed drug combinations and beta-lactam agents given with beta-lactamase inhibitors)

This Guideline primarily considers the clinical development of antibacterial agents that are administered systemically. Although no details are provided regarding the development of the following, many of the issues raised in this Guideline are also applicable. Limited additional guidance will be provided in an addendum:

- Antibacterial agents to be delivered by topical administration (e.g. to skin, ears and eyes)

- Antibacterial agents administered by inhalation

- Antibacterial agents administered by the oral route with an intended effect within the gut

The Guideline does not address:

- Antibacterial agents intended for the treatment of tuberculosis. See separate guidance [EMA/CHMP/EWP/14377/2008]

- Antibacterial agents for systemic or inhalational use in the management of cystic fibrosis. See separate guidance [EMEA/CHMP/EWP/9147/2008-corr*]

- Bacteriophages proposed to treat infections

- Agents that affect bacterial virulence

- Agents that may inhibit the growth and replication of some bacterial species by an indirect effect (e.g. immunomodulators)

- Non-clinical studies other than those intended to document the microbiological activity of a test antibacterial agent

- Clinical pharmacokinetic studies

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/83/EC as amended as well as all other pertinent EU and ICH guidelines and regulations, especially the following:

- Note for Guidance on Good Clinical Practice - CPMP/ICH/135/95 (ICH E6);

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

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

- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9);

- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10);

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

- Guideline on Pharmaceutical Development of Medicines for Paediatric Use - EMA/CHMP/QWP/180157/2011;

- 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 choice of non-inferiority margin - EMEA/CPMP/EWP/2158/99 Rev;

- Points to consider on application with 1. Meta-analyses 2. One pivotal study - CPMP/EWP/2330/99;

- Points to consider on the pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products - CPMP/EWP/2655/99;

- Guideline on clinical trials in small populations - CHMP/EWP/83561/2005;

- Extrapolation of results from clinical studies conducted outside Europe to the EU population - CHMP/EWP/692702/2008

4. Microbiological and clinical investigations

It is not possible for this Guideline to cover every conceivable situation that may arise. Sponsors may find it particularly useful to discuss specific matters with EU Regulators before initiating various stages of the development programme. For example, the use of alternative study designs to those suggested, the possibility of providing a single study to support a specific indication, the choice of comparative regimens, the selection of non-inferiority margins and the demonstration of clinical activity against rare infections or pathogens, including multidrug-resistant organisms.

It is recommended that the content of this Guideline should be considered in conjunction with recent relevant documents issued by learned societies in the field of infectious diseases and clinical microbiology. The influence of any such documents on the content of the clinical and microbiological development programme may need to be discussed with EU Regulators and should be described in the application dossier. The individual study reports and summary documents in the application dossier should provide a clear rationale for all the important features of each study and the overall development programme.

4.1. Microbiological studies

The programme of investigations should be tailored to the known or expected properties of the test antibacterial agent or combination of test agents under investigation.

4.1.1. Non-clinical assessment of anti-bacterial activity

Every effort should be made to document the mechanism of action of a new antibacterial agent.

During the microbiological and clinical development programmes the sponsor should collect sufficient data to characterise the in-vitro antibacterial activity of the test antibacterial agent against recent clinical isolates (e.g. obtained within approximately 5 years prior to filing an application dossier). It is

preferred that the method and extent of susceptibility testing should be in accordance with the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Clinical isolates selected for in-vitro susceptibility testing should belong to pathogenic species that are relevant to the clinical indications sought and should be sourced from various countries and regions, including a representative sample from within the EU.

- For commonly encountered pathogens it should be possible to test several hundred isolates of each species, including representative numbers of organisms that demonstrate resistance to individual and multiple classes of antibacterial agents. If the test antibacterial agent is of a known class then adequate data should be obtained to document the degree of cross-resistance within the class that can be expected.

- For rare pathogens and organisms with rarely encountered mechanisms of resistance or patterns of multi-drug resistance it is preferred that at least 10 organisms of each species or with each resistance mechanism/pattern are tested whenever possible.

- MIC distributions should be presented by species and, when appropriate, by sub-group (e.g. with and without specific resistance mechanisms of particular interest). The range of concentrations tested should be sufficient to provide a value for the most susceptible organisms (i.e. not just < x mg/L). The upper limit of the range of concentrations should be selected to provide a value for most of the least susceptible organisms (i.e. not just > x mg/L).

- Additional in-vitro studies should be conducted as appropriate. These may include an assessment of bactericidal activity, investigations of possible synergy or antagonism, post-antibiotic effects and, for certain antibacterial agents, an estimate of the rate of selection of resistant mutants and how concentrations above the minimum inhibitory concentration (MIC) may affect or prevent mutations. If the test antibacterial agent is converted to one or more major metabolites the in-vitro antibacterial activity of these should be assessed separately.

- The mechanisms of resistance that may be present in organisms for which the minimum inhibitory concentrations (MICs) of the test antibacterial agent are unusually high should be investigated and the potential for cross-resistance to antibacterial agents in the same class (if appropriate) and in different classes should be assessed.

For new beta-lactamase inhibitors the in-vitro studies should document whether or not the agent *per se* exerts antibacterial activity at clinically achievable plasma concentrations. There should be detailed data on enzyme kinetics against a range of beta-lactamases. The in-vitro data on the antibacterial activity of the beta-lactam agent plus the inhibitor to be co-developed should be sufficient to provide a preliminary assessment of the ratios to be evaluated in non-clinical models of efficacy and in clinical studies and should document the minimum concentration of the inhibitor needed to satisfactorily inhibit the target beta-lactamases.

If any antibacterial agent included in a fixed drug combination (FDC) is new its major microbiological properties should be investigated separately. However, the majority of the in-vitro susceptibility testing data should be obtained with the FDC, including as necessary an exploration of the ratio of active substances to be used.

The entire database derived from studies with collections of recent clinical isolates and pathogens isolated from patients enrolled into the sponsored clinical studies (see 3.1.3) should be sufficient to support an assessment of the likelihood of encountering pathogens resistant to the test antibacterial agent during routine clinical use in the clinical indications sought.

If appropriate non-clinical models exist for the types of infections to be studied in man some evaluation of efficacy of the test antibacterial agent should be performed (see also section 3.1.3 below). These

data may be of particular importance and provide valuable supportive evidence of efficacy when only limited clinical data can be generated.

4.1.2. Microbiological investigations during clinical studies

Patients may be enrolled into a study based on the clinical presentation with or without the results of rapid diagnostic and/or rapid susceptibility tests. Protocols should specify which rapid diagnostic tests (e.g. antigen or nucleic acid detection tests) can be accepted as evidence of infection for the purpose of enrolment and which, if any, can serve as an alternative to routine culture results in the analyses of microbiological outcomes by pathogen.

Microbiological documentation of bacterial infections should be sought from specimens obtained before or within a strictly-observed window after the first dose of study therapy is given. If obtaining a suitable specimen involves an invasive procedure (such as aspiration from a body cavity) that is not considered to be routine by all investigators then at least one of the studies or designated study sites within studies conducted to support an indication should mandate specimen collection.

Whenever possible the primary methods used for isolation and susceptibility testing of putative pathogens at study site laboratories should be standardised. It is preferable that all studies in the clinical development programme should employ re-confirmation of isolate identity and susceptibility testing at designated central laboratories. Protocols should plan for centralised laboratories to perform typing of post-baseline isolates to differentiate persistent and recurrent infections from new infections with the same species.

It is also preferred that central laboratory data should be used for the primary analyses of outcomes according to the in-vitro susceptibility of baseline and post-baseline pathogens, including those obtained from patients with persistent, recurrent and new infections. The central laboratory results should be supplemented by local laboratory results to fill in missing data.

If the method of susceptibility testing employed by the central laboratory or by local laboratories changes during the clinical development programme the sponsor should provide assurance that the change does not affect the results reported or should arrange for re-testing of isolates by a single method.

In some cases it is acceptable that identification of the causative pathogen is based mainly or solely on the results of serological studies (e.g. organisms that cause atypical pneumonia for which isolation rates are low even in experienced laboratories). Central laboratories with appropriate expertise should be used for the primary conduct of serological studies or for the confirmation of results. The results of serology performed at centralised laboratories should be used in the primary analysis.

The correct designation of patients as being microbiologically evaluable or eligible for the analysis of outcomes in all patients with a pathogen is important. The inclusion of patients in these analyses when the organisms that have been isolated are very unlikely to be true pathogens in the type of infection under study is a major confounding factor in the assessment of microbiological outcomes. Therefore, the bacterial species that will be considered as true pathogens in the indication under study should be determined in the light of current opinion and specified in the protocol. Nevertheless, even when a potential pathogen is isolated from an appropriate specimen this does not necessarily confirm the presence of an infection that requires specific antibacterial treatment (e.g. sputum cultures from patients with clinical signs and symptoms of acute exacerbation of chronic obstructive airways disease).

4.1.3. The pharmacokinetic/pharmacodynamic (PK/PD) relationship

It is recommended that the evaluation of PK/PD relationships should be performed in consultation with experts in the field who are at the forefront of developing and improving the techniques used for these analyses. Detailed recommendations are beyond the scope of this document and would not be appropriate considering the current rate of advancement in the field.

Based on in-vitro susceptibility test data, information from non-clinical models of efficacy and human PK data, detailed PK/PD analyses may be used to support dose regimen selection and susceptibility testing breakpoints. In circumstances in which it is not feasible to generate extensive clinical efficacy data (e.g. in rare types of infections or against rare types of pathogens, including multidrug-resistant pathogens that are rarely encountered) PK/PD analyses may also provide important supportive information on the likely efficacy of the test antibacterial agent.

The overall assessment of the PK/PD relationship should be sufficiently comprehensive to assess with reasonable confidence whether or not the test antibacterial agent, when used at an adequate dose regimen, would have useful clinical activity against relevant pathogens that appear to be susceptible *in vitro*. The MIC distributions for wild-type populations of pathogens relevant to the indications sought should be taken into account so that the PK/PD analyses cover the highest MICs considered to be treatable with well-tolerated dose regimens.

Whenever possible it is recommended that the PK/PD analyses used for dose regimen selection should be based on PK data obtained from infected patients rather than from healthy subjects. If this is not the case when the initial analyses are performed they should be repeated using patient PK data when these become available to reassess the validity of the initial conclusions. As appropriate, free and total plasma concentrations of the test agent may need to be measured.

For some, but not all, test antibacterial agents the PK/PD relationship may be sufficiently straightforward and well-described that sponsors consider it possible to omit clinical dose-finding studies and to evaluate the efficacy of one or a very few regimens. However, the use of PK/PD to predict the optimal duration of treatment is not well established at present and sponsors should consider whether preliminary regimen-finding studies are needed to identify a suitable duration of treatment for any one indication.

It is desirable that the PK/PD relationship should be further explored during clinical studies in patients for each indication sought based on the in-vitro susceptibility of clinical isolates, patient PK data and clinical and microbiological outcomes. These investigations may constitute sub-studies within large clinical studies.

4.1.4. Breakpoints for susceptibility testing

It is recommended that sponsors should decide early in the development programme if they will participate in an agreement that will allow the breakpoints for susceptibility to be set by EUCAST since this decision has potential implications for the in-vitro susceptibility testing programme (for details please see SOP/H/3043). The final decision on the breakpoints will be made by the CHMP at the time of first approval. Additional breakpoints may be added later (e.g. when adding a new indication involves additional species or a different dose regimen for which different breakpoints would apply) or may be changed (e.g. if clinical experience suggests that the initial breakpoints set are not optimal).

For antibacterial agents or specific formulations of antibacterial agents that are anticipated to have only a local antibacterial action when administered:

- By the topical route (e.g. to skin, mucus membrane, ears and eyes)

- By inhalation

- By the oral route

it is currently not considered appropriate that susceptibility testing breakpoints should be set (regardless of whether there are established breakpoints applicable to systemic administration of the same active substance). The possible exception would be in the case that sufficient clinical experience has been amassed during routine use that a clinical susceptibility test breakpoint can be derived that is relevant to the local antibacterial effect. In all other instances it is currently recommended that Section 5.1 of the SPC should state that susceptibility test breakpoints relevant to the route of administration cannot be set. The section should provide information on epidemiological cut-off (ECOFF) values derived from the MIC distribution curves for the most pertinent pathogens to the indications granted. These ECOFFs serve to alert any laboratory that undertakes susceptibility testing to unusually high MIC values that might merit further investigation.

4.1.5. Post-approval studies of susceptibility and resistance

At the time of first approval of a new antibacterial agent sponsors should have plans in place to assess the emergence of resistance to the test antibacterial agent over a period of approximately 3-5 years. The duration of these studies may need to be prolonged beyond 3-5 years if particular concerns regarding the emergence of resistant organisms arise during the initial observation period.

It is considered that the most reliable information on the emergence of, or changes in, the prevalence of resistance to a new antibacterial agent will come from large and well-established surveillance networks that are able to detect trends over time based on the use of consistent criteria for inclusion of organisms by the collaborating centres, at least some of which should be located within the EU.

Whenever very few or no organisms resistant to a new antibacterial agent were isolated before initial approval any organisms obtained during surveillance studies for which the MICs are near or above the susceptibility test breakpoint or ECOFF should be investigated to identify possible mechanisms of resistance.

Information on emerging resistance, changing patterns of resistance and new mechanisms of resistance to an agent should be notified promptly to the CHMP with a discussion of the implications for section 5.1 of the SmPC, which should be updated as necessary.

4.2. Clinical studies

4.2.1. Studies of the treatment of bacterial infections

The following sections provide some general and broadly applicable guidance. Sponsors should also consult the addendum to this Guideline that will provide more details regarding the design of studies intended to support specific indications for use.

4.2.1.1. Patients and infections

Patient selection

In all studies the inclusion and exclusion criteria should be designed to restrict enrolment to patients who have the type of bacterial infection under study and, as far as is possible, have a range of clinical features that could support extrapolation of the results to the patient population likely to be encountered in clinical practise. It is particularly important that non-inferiority studies should try to avoid enrolment of patients with infections that are likely to resolve without antibacterial therapy

within a reasonable timeframe since this reduces the chance of detecting differences in efficacy between the test and active comparative regimens.

Some patients may meet criteria for the type of infection under study without having non-specific features of an ongoing infectious process, such as fever and elevated WBC and/or neutrophil counts.

Fever and/or elevated WBC count may be absent in the elderly or in other patient groups (e.g. diabetics) despite clear evidence of an ongoing bacterial infection. The presence or absence of fever is subject to influence from analgesics with an antipyretic effect that may have been consumed before or after enrolment. An elevated WBC may not occur in those with chronic underlying disease or malignancy. Hypothermia and/or a low WBC may occur in very severe infections. In addition, fever and/or elevated WBC count may be found in the absence of an acute bacterial infection.

Therefore it is not considered an absolute requirement that patients should have one or both of fever and elevated WBC before enrolment although their presence/absence should be documented at baseline and at later visits that record signs and symptoms.

Whenever possible, the enrolment of patients should not be based solely on the clinical findings. Additional evidence of infection at baseline may come from:

- Microscopy of suitable specimens. Microscopy of samples from normally sterile sites (e.g. CSF and joint fluid) or finding characteristic bacterial forms in certain specimens (e.g. in the provisional diagnosis of gonorrhoea) may provide important information on the likely pathogen.

- Rapid diagnostic tests. These rely on ready access to the infected site or to suitable clinical material. The use of "in-house" rapid diagnostic tests may be of assistance for the purposes of improving patient selection but the results should not be used in the analyses of microbiological outcomes by pathogen. If patients are enrolled based on the results of such tests the sample size calculation should take into account the positive and negative predictive values of the tests used.

- Imaging techniques. Some potentially useful imaging techniques may not be in routine use (e.g. newly-introduced or experimental diagnostic imaging) and/or may be difficult to interpret (e.g. chest radiographs in young children). In these cases there should be a retrospective review by independent experts who are unaware of treatment assignment and it is preferred that these decisions are used to determine the diagnosis and/or outcome in individual patients. There should be a review of any notable discrepancies between the investigators' and experts' opinions.

The study protocol should set limits on the duration of any prior antibacterial therapy for the infection to be treated in the study unless it is clear that the patient has already failed a minimum course (in terms of dose and duration) of treatment with another antibacterial agent. An exploratory analysis of outcomes in sub-groups of patients that did and did not receive prior therapy (e.g. within 72 h of enrolment) for the infection under study may be informative. Further details of acceptable prior therapy will be given in the addendum.

Analysis populations

With few exceptions (e.g. in urinary tract infections) it is not required that the primary analysis should be confined to the subset of patients with at least one acceptable baseline pathogen.

In studies with antibacterial agents that have a clinical primary endpoint it is suggested that the all-treated population and the clinically-evaluable population should be viewed as co-primary. In studies with a microbiological primary endpoint it is suggested that the co-primary analysis populations should be all-treated with a pathogen and microbiologically-evaluable.

Characteristics of infections treated

- In most instances, individual clinical studies of efficacy should aim to enrol patients with a representative range of diagnoses relevant to the type of infection under study.

- Inclusion and exclusion criteria intended to distinguish patients with complicated or uncomplicated infections in accordance with widely-accepted definitions do not necessarily distinguish patients with severe versus non-severe infections. Depending on the indication sought and the route of administration of the test antibacterial agent the protocol should aim to restrict enrolment to patients with infections of an appropriate degree of severity using the features laid down in widely-recognised grading systems. In cases where there is no established grading system for severity the enrolment criteria should at least attempt to exclude infections that are considered inappropriate for treatment with the planned regimens.

- Enrolment criteria that focus on the types of patients and infections eligible for treatment may not satisfactorily distinguish patients who are in need of parenteral therapy (either initially or throughout the treatment period) versus those who may be treated with an oral agent from the outset. Clinical opinions regarding the need for parenteral treatment, hospital admission policies and the availability of home parenteral therapy are very variable between healthcare systems and may differ between study sites within individual countries. Specific enrolment criteria should be developed in conjunction with all investigators within a study to standardise the basis for initiating parenteral therapy, whether this is administered in a hospital or at home.

Consideration should be given to stratification of patients according to specific factors (e.g. type of infection or severity of infection). Stratification by age (e.g. elderly patients versus younger adults or premature infants versus term infants versus young children) or by specific underlying conditions (e.g. ± immunosuppression) may also be appropriate in some studies. Whether or not formal stratification is employed there should be pre-planned secondary analyses of outcomes according to factors that are considered most likely to affect patient outcomes in the indication under study (e.g. whether or not there was a surgical intervention or abscess drainage within a specified time frame). The aim of these analyses is to demonstrate consistency of efficacy across subgroups defined by important prognostic factors. The size of the subgroups and the precision of the estimated efficacy in each subgroup might be considered when planning the study.

4.2.1.2. Outcomes, efficacy variables and analyses

Timing of assessments

The timing of the on-therapy, end of therapy (EOT), test of cure (TOC) and all other study visits at which patient progress and/or outcomes are to be assessed should be selected in accordance with the indication under study and the PK properties of the test and comparative antibacterial agents.

The primary judgement of antibacterial effect should occur at a protocol-defined time point after completion of treatment (i.e. TOC visit). Protocols often allow for different and variable durations of active treatments. It is recommended that the TOC visit should occur at a pre-defined number of days after randomisation. The selection of an appropriate window for the timing of the TOC visit relative to randomisation should take into account the maximum possible duration of active treatment and the half-lives of the antibacterial agents that will be compared.

A further follow-up visit (e.g. at least 1-2 weeks after TOC) is usually desirable and should occur within a pre-specified window of days post-randomisation. The last study visit should be timed to provide information on relapses and new infections. Effective follow-up mechanisms should be in place to maximise patient attendance or to obtain completed patient diaries from outpatients.

Clinical outcome

At the TOC visit the clinical outcome should be categorised as cure, failure or indeterminate. Cure should usually be defined as complete resolution of clinical signs and symptoms. Alternative definitions of cure may be considered appropriate in some types of infections. For example, return to baseline status and no requirement for further antibacterial therapy (e.g. when treating acute infections of chronic leg ulcers). The protocol should specify the criteria that should be met in order for a patient to fall into one of these outcome categories.

Microbiological outcome

Microbiological documentation (as opposed to presumption based on the clinical response) of eradication or persistence of causative organisms should be attempted whenever feasible and is mandatory in studies of urinary tract infections and some sexually transmitted diseases. If the judgement of microbiological response is to be based on achievement of a bacterial load below a pre-specified level, as may be the case in some types of urinary tract infections, validated interpretative criteria should be stated in the protocol.

Efficacy variables

In most indications the assessment of response to therapy will be based primarily on clinical outcomes. However, the microbiological response is objective and is the preferred primary efficacy variable whenever this is appropriate to the indication (e.g. urinary tract infections). For some indications it may be considered that the clinical and microbiological outcomes are of equal importance for the overall judgement of efficacy (e.g. osteomyelitis and bacterial endocarditis) so that the clinical (cure rate) and microbiological (eradication rate) outcomes should be regarded as co-primary efficacy variables and the study should be adequately powered to provide clear conclusions for both outcomes. In all cases the concordance between the clinical and microbiological outcomes should be evaluated and should be investigated for any demonstrable correlation with the in-vitro susceptibilities of the baseline and post-baseline pathogens.

There may be instances in which alternative clinical and/or microbiological efficacy variables (such as time to event) provide valuable information on the overall response to treatment. Occasionally, it may be appropriate that one (or possibly more than one) alternative measure of outcome is designated as primary alongside or in place of the more usual parameters (such as cure and eradication). As appropriate to the indication under study a range of secondary clinical and microbiological efficacy variables may be defined.

General approaches to analyses

Clinical and microbiological outcomes should be presented and analysed at the TOC visit and at any other study visits at which assessments of outcome are to be recorded. If multiple pathogens are possible then microbiological outcomes should be presented and analysed by patient and by pathogen.

Analyses of clinical and microbiological outcomes should be performed in and compared between each of the relevant pre-defined patient populations to assess consistency. In all studies there should at least be a comparison between the planned primary analysis and an analysis of all randomised patients in which indeterminate or missing outcomes are counted as failures. It is essential that any incongruities detected between analyses should be explored and discussed.

Additional analyses should be planned and performed according to the designated secondary efficacy variables, such as time to event analyses. Other pre-planned analyses may include, among others, outcomes according to age, gender, infection type and/or severity, surgical intervention and other factors relating to patient management.

It is anticipated that sponsors will wish to use the same clinical development programme to satisfy multiple regulatory authorities. There may be instances in which specific requirements for the design and/or analysis of studies with antibacterial agents differ between regulatory authorities. In most (or even all) of these cases it should be possible to use the same study to satisfy multiple regulatory authorities by pre-defining separate strategies for the statistical analyses (e.g. prioritisation of endpoints, time points or statistical technique) that will meet the requirements of the CHMP and other regulatory authorities.

4.2.1.3. Dose-finding studies and duration of treatment

Following detailed PK/PD analyses it may still be necessary to identify a suitable dose regimen and/or duration of treatment from preliminary efficacy studies in one or more clinical indications. If such studies are performed they should be based on a careful consideration of the sample size needed to provide a clear answer regarding the regimen to be selected for further evaluation.

Alternatively, sponsors may consider evaluating a small number of regimens during the major clinical studies intended to support each indication for use. In some cases it may be acceptable that a flexible study design is used to identify the best regimen. If this approach is considered it is essential that the design is discussed with Regulators before initiating the study.

Whether or not a study sets out to formally compare several durations of therapy the protocols should usually allow for some latitude regarding the duration of treatment with test and reference treatments within a defined window.

In the case of antibacterial formulations intended to exert a local effect (e.g. topical, inhalational and intra-gut antibacterial activity) adequate clinical and microbiological data would be needed to support regimen selection.

4.2.1.4. Major (Pivotal) Studies

Number and location of studies

It is preferred that two major (pivotal) studies of efficacy are performed for each clinical indication sought. If a single study is proposed the CHMP guidance on submission of a single pivotal study will apply.

It is preferred that investigative sites in the study or studies performed in each clinical indication are geographically dispersed and that protocols should plan for secondary analyses of efficacy by country and/or region. It is not required that confirmatory clinical studies should include investigative sites located within the EU but the sponsor should provide a rationale to support the relevance of the efficacy data to EU patients.

Blinding

All studies should be double-blind unless this design is considered to be impossible. If a double-blind study is not feasible every effort must be made to ensure that the physicians who assess clinical outcomes and report adverse events remain unaware of treatment assignments.

4.2.1.4.1. Non-inferiority studies

The rational design of non-inferiority studies with antibacterial agents requires the application of clinical trial endpoints that capture the benefit of treatment and some knowledge of the magnitude of the treatment effect in the specific type of infection under study.

In a valid non-inferiority study against an active comparative treatment:

- There must be confidence that the test antibacterial agent would have demonstrated superior efficacy to placebo if such a study had actually been performed.

- The study design should minimise the possibility of reaching a false conclusion of non-inferiority.

Choice of comparative therapy

The choice of comparative regimen, including the antibacterial agent(s), dose, dose interval and duration) is critical to the overall validity of the study. The regimen selected should be considered one of the best available treatments based on one or more of previous studies, medical opinion, indication-specific treatment guidelines from appropriate learned societies and the anticipated prevalence of resistance to the comparative agent at the investigative sites.

The comparative regimen should be relevant to clinical practise in the EU. However, it is recognised that a comparative regimen that the sponsor adequately justifies is the most appropriate for any one study may not be approved (for the indication and/or at the dose regimen selected) or recommended for use in the indication under study in all EU Member States.

It is preferred that a single comparative regimen should be allowed within any one study since this facilitates interpretation of the analyses. If a substitution of the comparator with an alternative agent is to be allowed once the results of culture and susceptibility testing are available the criteria for switching and the agent(s) allowed must be pre-specified.

Combination therapy

The protocol should specify any additional agents (including the dose regimens) that must or may be used in conjunction with the test antibacterial agent and/or the comparator. When combination therapy is to be used in one or more treatment groups from baseline the protocol must specify if/when and under what circumstances patients may revert to monotherapy. Similarly, if the use of additional agents is optional the protocol must specify the criteria under which this is permissible.

Switch from parenteral to oral therapy

If parenteral and oral formulations are available for the test and comparative antibacterial agents the patients in both treatment groups may be switched to oral treatment using pre-specified response criteria. Comprehensive data on the condition of patients at the time of switch must be captured in the case report forms and presented in the study report. The minimum duration of initial parenteral treatment should be stated in the protocol and should take into account any change in plasma exposure that may occur with oral compared to parenteral administration of the same active substance. If the test antibacterial agent can only be given parenterally but a switch to oral therapy is desirable for routine patient management the sponsor should provide a rationale for the choice of follow-on therapy.

Withdrawal from study therapy

The protocol-specified criteria for mandatory post-baseline withdrawal of patients during study therapy should be kept to a minimum. In most types of infections and for most pathogens it is not necessary to require that study therapy is stopped if pathogens with resistance or reduced susceptibility to study treatment are reported from baseline specimens provided that the patient is improving. The information that may be gained by continuing therapy in these cases may be especially useful when the PK/PD relationship suggests that the test antibacterial agent could be effective in at least some sites of infection even when the MIC of the drug for some pathogens is relatively high. If patients are withdrawn from therapy there should be detailed documentation of the clinical and microbiological findings on the day of withdrawal.

Selection of the non-inferiority margin (delta)

The selection of the non-inferiority margin must be tailored to the indication under study and should be performed in accordance with CHMP guidance, taking into consideration the need to indirectly demonstrate superiority of the test agent to placebo and to assess relative efficacy between the test agent and the active comparator. The final choice of the non-inferiority margin should take into account clinical judgement regarding how large a difference between the test and reference treatments could be considered clinically important in each type of infection.

Historical data are often used to estimate the no-treatment effect but the relevance of these data to current medical practise may be questionable. Sponsors are encouraged to explore alternative and emerging methods for estimating the no-treatment effect (e.g. using pharmacometric-based approaches).

4.2.1.4.2. Superiority studies

Antibacterial agents have not consistently demonstrated superiority versus placebo in well-conducted randomised studies in certain types of acute bacterial infections that are associated with considerable spontaneous resolution rates (e.g. acute maxillary sinusitis, acute exacerbations of chronic obstructive airways disease and several types of infection that are commonly treated with topical applications of antibacterial agents). There are also some types of infections in which superiority of active treatment versus placebo may have been demonstrated only in very specific sub-populations (e.g. otitis media in specific age groups and with well-defined signs and symptoms). In infections and/or sub-populations of patients with infections in which active antibacterial treatment has not been established to be superior to placebo (or to vehicle in the case of topical formulations) the clinical benefit of a test agent cannot be assessed with confidence in a non-inferiority study.

In these circumstances efficacy should be evaluated in studies that are designed to demonstrate superiority versus placebo or versus active comparative therapy for at least one clinically important endpoint. It is recognised that a placebo control group will not be considered acceptable in some types of infections and/or sub-populations in which a superiority study design is considered necessary. In addition, it may not be reasonable to expect that superiority can be demonstrated versus an active comparator based on clinical cure or microbiological eradication rates. These issues will be given further consideration in the addendum. However, some general considerations for the design and conduct of superiority studies include the following:

Placebo-controlled studies

The primary objective is to demonstrate a statistically significant advantage of the test agent over placebo with a lower bound of the 95% 2-sided confidence interval around the difference in cure rates that is above zero. In addition, clinical judgement should be applied to assess whether the observed difference in cure rates between the test antibacterial agent and placebo is clinically relevant. The rescue treatment for any patient who does not respond to blinded assigned therapy and the conditions under which it should be instituted should be pre-defined in the protocol. Patients who require rescue therapy should be counted as failures in the statistical analysis.

It is preferred that placebo-controlled studies should incorporate a third study arm that is randomised to an active comparator. The difference between the comparator and placebo can be used to help assess the clinical relevance of the difference between the test antibacterial agent and placebo. For example, if the test antibacterial agent has performed better than the comparator it is more straightforward to assume that the test agent provides a clinically relevant benefit. If the comparator has not demonstrated statistical significance over placebo or has not performed as expected from past experience the results observed with the test antibacterial agent would have to stand alone. If this situation does occur the possible reasons for the unexpected results obtained with the comparator

should be discussed. Inclusion of an active comparator can also help inference when the test agent fails to demonstrate superiority over placebo (i.e. a failed study) as it provides information on the assay sensitivity.

Other possibilities for study design include the use of delayed therapy in the placebo group such that all patients with no improvement or worsening of protocol-specified signs and symptoms after a fixed number of days on placebo are declared failures and offered an active treatment. It is also possible that patients could be randomised to a range of doses of the test agent, including one or more that is likely to be insufficient. The results might provide an assessment of dose-response that is sufficient to demonstrate a benefit for treatment with an adequate regimen.

Active controlled studies

In these studies a demonstration of superiority of the test agent versus the active comparator based on clinical cure rates is unlikely to be feasible. Subject to prior discussion with EU Regulators it may be appropriate that the demonstration of superiority is based on one or more alternative clinically relevant efficacy variables. These could possibly include time to bacterial clearance, time to specific clinical response measures or improvements in clinical parameters (e.g. lung function). In these instances there must be a very strong rationale for the study hypothesis and the patient selection criteria.

4.2.1.4.3. Alternative study designs

There may be instances in which the sponsor considers that it is not feasible to conduct at least one adequately powered randomised and controlled clinical trial to support an indication. For example, this may apply when the test antibacterial agent is predicted to be clinically efficacious in the treatment of relatively rare types of infections (e.g. infective endocarditis and bacterial meningitis), with or without restriction to specific pathogens.

Even when small numbers of patients are expected to be enrolled it is always preferred that a randomised (which may be unbalanced) and controlled clinical study is conducted rather than an uncontrolled study or a comparison with external or historical controls (which may also be used to provide supplementary information). The randomisation step provides an internal control group that makes the interpretation of the outcomes considerably more reliable compared to studies that do not employ randomisation. The justification for a randomised study planned with lower than standard levels of statistical power must include comment on the prevalence of the infection and on the statistical performance characteristics of the trial (e.g. Type I and Type II errors to investigate an effect size of interest)

If it is agreed between the sponsor and EU Regulators that an uncontrolled study cannot be avoided, every attempt should be made to generate a precise and unbiased estimate of efficacy in a clearly defined patient population in order to facilitate the interpretation of the data. Where possible, the number of patients recruited should be sufficient to exclude unacceptably low cure rates from the 95% 2-sided confidence interval estimating the response rate. The minimum acceptable cure rate should be defined prospectively based on currently available treatments and experience.

On occasion there may be a rationale for employing a flexible (e.g. adaptive) study design. In these cases it is essential that the study design is developed in conjunction with EU Regulators and that agreement is reached on the mode of primary analysis of outcomes, including the primary patient population.

4.2.1.5. Special considerations

4.2.1.5.1. Test antibacterial agents consisting of more than one active substance

Special considerations apply to clinical development programmes in the following circumstances:

- Fixed drug combination (FDC) of antibacterial agents for parenteral or oral administration, one or more of which may not be licensed.

The CHMP guidance regarding FDC products generally applies, including the need to provide a strong rationale for the agents selected. There are many possible scenarios that may occur and it is not possible to provide specific guidance on the clinical development programme that would necessarily apply in all circumstances. It may be possible to justify the content of the FDC, including the doses included, based on microbiological and PK/PD considerations so that clinical studies of the FDC versus the components (if these are possible) are avoided and the focus is on studies that demonstrate the efficacy of the FDC versus appropriate comparative regimens in each indication sought.

- Beta-lactam agent plus a beta-lactamase inhibitor, co-administered or as a FDC for parenteral and/or oral administration. One or both of the two agents may not be licensed.

Since the partner antibacterial agent will be vulnerable to hydrolysis by certain beta-lactamases and since it would be expected that studies will be performed in indications in which the pathogens include organisms that can express these beta-lactamases it is not feasible to require comparisons between the combination and the partner beta-lactam alone. The clinical development programme should demonstrate the efficacy of the beta-lactam agent plus the inhibitor versus one of the best available comparative therapies. The clinical studies should aim to provide as much data as possible on efficacy of the FDC against organisms that express the beta-lactamases that are expected to be inhibited. However, it may not be possible to provide clinical efficacy data for all the enzymes that are predicted to be inhibited and the data for individual enzymes may be very limited. Hence the provision of sound and extensive non-clinical data is expected to be very important to support the available clinical data.

If the partner beta-lactam agent is new and is also to be marketed separately to the inhibitor for some indications then a separate and routine clinical development programme would be needed. If it is only to be recommended for use with the inhibitor in all indications it is not necessary to perform studies in which it is administered alone.

4.2.1.5.2. Rare infections and rare pathogens

For indications in which a clinical study is not feasible (such as for inhalational anthrax) the possibility of obtaining an indication for use based on in-vitro data, animal model data, PK/PD analyses that employ human PK data and clinical experience of some relevance (e.g. for inhalational anthrax a demonstration of efficacy in one or more types of pneumonia would be considered relevant) should be discussed between sponsors and EU Regulators.

The possible study designs to obtain data on the clinical efficacy of a test antibacterial agent in the treatment of rare infections and/or pathogens are discussed in section 3.2.1.4.3, where it is stated that a randomised study is always preferred even if the numbers are very small. These infections may be due to otherwise common pathogens (e.g. osteomyelitis due to *S. aureus*) or both the type of infection and organism may be rarely encountered (e.g. Listeriosis).

In the case of relatively rare pathogens that can cause common types of infections (e.g. community-acquired pneumonia due to *Legionella spp*.) clinical efficacy data could be collected during the course of large indication-specific studies and/or from targeted studies (e.g. in which patients are enrolled based on a positive urinary antigen test for Legionella). In these cases it is generally expected that

efficacy data are generated for at least 10-20 cases in each of the test and comparative groups in any one indication. Data on efficacy against a specific pathogen obtained from more than one study in a single indication may be pooled if these are of the same or very similar design.

For very rare types of infections the acceptability of uncontrolled data and the numbers that should be treated to support a specific claim must be addressed on a case by case basis. For very rare pathogens it may be appropriate to conduct studies in which patients with clinically confirmed infections due to these organisms are enrolled regardless of the site of the infection.

4.2.1.5.3. Pathogens resistant to one or more antibacterial agents

In-vitro studies may show that the activity of a test antibacterial agent is completely unaffected or little affected (i.e. MICs still fall within a range considered to be treatable based on PK/PD analyses) by certain mechanisms that confer resistance to other antibacterial agents in the same or different drug classes. The findings may also suggest that the clinical efficacy of the test antibacterial agent would be comparable for organisms of a species that do and do not express certain mechanisms of resistance.

However, patients who are infected by drug-resistant organisms, especially if they express multidrug resistance, may differ in many respects from patients who are infected with more susceptible strains of the same species. For example, patients harbouring multidrug-resistant pathogens are more likely to have already received other antibacterial agents and to have underlying conditions that complicate the clinical course so that clinical and microbiological success rates may be lower and more variable.

Due to these uncertainties, it is required that some clinical data on the treatment of these organisms are obtained to support statements regarding efficacy in the SmPC (see section 3.3). Since the extent of the data that can be provided will reflect the relative frequency of the types of resistant pathogens sought, it is not appropriate to mandate a minimum number of cases that would have to be treated in any one indication or across types of infections to support a specific claim in the SPC. The following considerations apply:

For more common drug-resistant organisms for which there are available comparative therapies (e.g. MRSA in skin and soft tissue studies, penicillin-insusceptible *S. pneumoniae* in CAP) it should be possible to select appropriate study sites so that comparative data are obtained on at least 20-30 cases, with or without pooling data across studies in the same indication.

When the non-clinical data and PK/PD analyses strongly suggest that a test antibacterial agent could be clinically active against organisms with a rarely encountered type of resistance or pattern of multidrug resistance (e.g. carbapenemase-producing gram-negative aerobes with or without resistance to antibacterial agents in several other classes) a different approach to the assessment of efficacy is needed, which will be given further consideration in the addendum.

One possible approach would be to conduct one or more randomised controlled studies in at least one major indication relevant to the microbiological and pharmacokinetic spectrum of the new agent to obtain evidence of clinical efficacy in patients whose clinical condition is comparable with that expected in the population most likely to have multidrug-resistant pathogens. Ideally such studies would enrol at least some patients infected with the types of pathogens of most interest. If the test agent is active against only one or very few species a controlled study may still be possible but would require enrolment based on results of rapid diagnostic techniques. Consideration should be given to the feasibility of obtaining additional clinical data specific to multidrug-resistant pathogens from a study that attempts to target patients with such infections.

4.2.2. Studies of the prophylaxis of bacterial infections

The design of studies that are intended to support an indication for the prophylactic use of an antibacterial agent is subject to several additional considerations. When the role of antibacterial agents in preventing a particular type of infection in defined clinical circumstances is already established, a comparative study against a licensed therapy is possible. If the role of prophylaxis has not been established under the circumstances proposed for study, a placebo-controlled study is required. In both cases, there must be a sound rationale for the number and timing of doses of the test antibacterial agent that are to be given and there must be a clear definition of "breakthrough" cases.

4.2.3. Studies in children and adolescents

Sponsors should consult the regulations on the submission and approval of Paediatric Investigation Plans (PIPs) and the guidance available in ICH E11. Plans should be made for the early development of suitable dose sizes and age-appropriate paediatric formulations.

A potentially suitable initial dose range for children in specific age sub-groups across the range 0-17 years can usually be surmised from comparisons of PK data obtained from limited sampling of infected children who are treated with the test antibacterial agent and data from adults enrolled into successful indication-specific studies of efficacy. Dose selection should take into account relevant PK/PD analyses and all the available information on safety and efficacy. Special attention should be paid to the evaluation of PK in neonates and infants.

In indications that are common to several age groups, it may be reasonable to extrapolate efficacy data from adults to paediatric patients provided that sufficient pharmacokinetic and safety data have been generated with the intended dose regimen(s) in paediatric patients and the disease mechanisms and causative pathogens are similar across age groups. Safety data should be collected in studies and analysed descriptively in studies that include a comparator arm to facilitate interpretation of the findings. It may sometimes be necessary that data on therapeutic response should also be collected in at least some age groups in order to validate the dose recommendations.

Some types of infections, such as acute otitis media, occur almost exclusively in children. Also, compared with adults, certain infections in children may be due to different predominant pathogens or to different underlying conditions (such as anatomical abnormalities predisposing to urinary tract infections). In these instances, confirmatory randomised and controlled studies in children of different age groups will be required to support efficacy and safety

4.2.4. Evaluation of safety

Sponsors should consult the regulations and guidance available regarding the development of comprehensive Risk Management Plans and the requirement to establish suitable functioning Pharmacovigilance Systems before placing a drug on the market. The following sections focus on issues that are of most relevance to antibacterial agents and are intended to supplement the routine presentation and analysis of the safety data required for any new active substance.

General considerations

As for all other medicinal products, the size of the safety database that would be required before initial approval of an antibacterial agent or before approval of additional indications and alternative dose regimens must always take into account the demonstrated and anticipated benefits and risks. In the specific case of antibacterial agents an initial application for use in one or very few clinical indications and/or against specific pathogens is likely to be supported by a relatively small safety database. Such an approach may be considered acceptable particularly when the new antibacterial agent has been

shown to have efficacy in the treatment of infections or pathogens (including multi-drug resistant pathogens) for which there are limited therapeutic options.

The assessment of the safety of an antibacterial agent does not often have the benefit of studies in which there has been a direct comparison with a placebo and usually relies wholly or mainly on comparisons with licensed antibacterial agents. As a result, the perception of the safety profile of a new antibacterial agent can be influenced by the safety data obtained with the comparative regimens. This fact points to some potential advantages in using comparative agents from different drug classes during the development programme.

Adverse reactions to an antibacterial agent and the pathological processes triggered by the infection itself may involve the same organ and have a similar effect on organ function. For example, any renal toxicity of an antibacterial agent may be confused with direct damage that can be caused by a severe pyelonephritis unless determined efforts are made to investigate the cause. Also, under-perfusion during the course of very serious infections can inflict widespread organ damage with a host of symptoms and laboratory abnormalities that could be mistaken for adverse reactions.

In the majority of studies and indications patients will be treated with a test antibacterial agent or with comparative therapy for less than two weeks but they may need to be followed for up to 4-6 weeks post-therapy, depending on the pharmacokinetics of the test antibacterial agent. Longer-term safety monitoring may apply if there is a possibility that adverse reactions could manifest some weeks or more after therapy has been completed (such as ototoxicity).

Presentation of the safety data

As appropriate to the database, the summary of safety should provide tabulations of adverse events and reactions by dose regimen of the test antibacterial agent against each comparative regimen, including different durations of therapy, and by indication. Separate tabulations are required when parenteral and oral formulations have been administered and/or when a different agent was administered as oral follow-on therapy. When combination antibacterial therapy has been optionally administered with the core test or comparative regimen, adverse events and reactions should be separated out for those who did and did not receive additional agents.

A comparison of pooled safety data for the test antibacterial agent versus pooled data for the comparative agents may also be performed. However, this must be interpreted with care because it is potentially misleading. For example, pooling safety data for the test agent regardless of one or more of indication, dose regimen or duration or pooling of data with a wide range of comparative agents, which may be from different drug classes, may confound rather than assist the assessment of the safety database.

Discussion of the safety database should not only reflect the relative safety of the test and the reference agents but should also consider the absolute safety profile of the test agent (i.e. as compared to background rates of adverse events that would be anticipated in the population treated).

4.3. Considerations for the SmPC

4.3.1. Section 4.1   Indications

The introductory sentence should be confined to:

{Drug name} is indicated for the treatment of the following infections in {age range, e.g. adults, adults and children from the age of x years}.

This general approach may be modified if some indications are approved only for specific age groups.

There should be a cross-reference to section 5.1 inserted as a routine.

In the majority of cases the indications will describe the specific types of clinical infections for which the risk-benefit relationship is considered to be favourable. For example:

- Community-acquired pneumonia

- Complicated skin and soft tissue infections

If the range of infection types that has been studied within each indication is considered to be limited or was restricted to specific pathogens it might be considered necessary to further qualify the indication. In addition, a qualification of an indication may be needed if there is clear evidence that the test agent does not provide adequate efficacy in a specific and important subset of patients that would otherwise be assumed to be included under the indication.

An alternative to qualification of the indication is to mention the limitations of the data only in section 4.4, with a cross-reference from section 4.1. For example, this may apply when very few cases of concomitant bacteraemia or very few cases of a particular type of infection have been treated within any one indication and when an indication for use has been based on very limited data.

If the activity of the antibacterial agent is unaffected by particular mechanisms of resistance (e.g. fluoroquinolone activity is not affected by alterations in PBPs that mediate insusceptibility to penicillin in *S. pneumoniae*) it is not acceptable to qualify the clinical indications (e.g. by stressing that the fluoroquinolone is active against penicillin-insusceptible pneumococci) even when efficacy has been demonstrated satisfactorily against these organisms. Instead, the lack of effect of certain mechanisms of resistance on clinical efficacy would be mentioned in section 5.1.

A pathogen-specific indication for use that is not qualified by site(s) of infection would be exceptional. However, this may be appropriate when the antibacterial agent has been shown to have clinical efficacy against particular pathogen(s) and/or against pathogen(s) that express certain types or patterns of resistance (including multidrug-resistant organisms) at a range of body sites.

The following standard sentence must always appear at the end of section 4.1 exactly as written:

Consideration should be given to official guidance on the appropriate use of antibacterial agents

The inclusion of this standard sentence is intended to encourage the responsible use of antibacterial agents and to direct prescribers to take note of any existing national or local guidance and opinions on how antibacterial agents should be used.

4.3.2. Section 4.2 Posology and Method of Administration

- The dose regimen and the duration of treatment courses should be tabulated by indication unless there is only one regimen and duration applicable to all indications.

- The duration of therapy should reflect the range that was documented to be effective in each indication.

- It may be necessary to recommend a different regimen within an indication if specific pathogens are implicated or in specific patient sub-populations in accordance with the clinical data.

4.3.3. Section 4.4 Special Precautions

See the recommendations made under 3.3.1 regarding the reflection of the limitations of the data within any one granted indication in section 4.4.

It is not appropriate to make statements in section 4.4 about lack of data in any type of infection that would not be included in the clinical indications granted. However, if the test antibacterial agent has been evaluated in other clinical indications or against certain pathogens and shown not to have acceptable efficacy this fact should be reported in section 4.4 so that physicians are alerted to the need to switch to another agent or add an agent if such an infection develops or type of pathogen is reported during treatment.

4.3.4. Section 5.1 Pharmacodynamics

It is intended that the following recommendations should be implemented prospectively and should apply to new antibacterial agents. The format presented may also be applied when next revising this section of the SmPC for antibacterial agents approved in the recent past since data are likely to be available to make this feasible.

The format is not suitable for older agents since the types of data that would be needed to satisfactorily comply with these recommendations are not likely to be available.

- Due to limitations of older clinical studies it is not appropriate to designate species for which clinical efficacy has been demonstrated

- The section on breakpoints should follow the recommendations made below.

The section should contain only the most critical information for the prescriber. The details of the microbiological properties of the new antibacterial agent, including the full in-vitro antibacterial spectrum and available information on resistance, will be summarised in the EPAR.

Section 5.1 should include the following information in the order shown:

ATC classification

Mode of action

This section must be confined to what is known about how the antibacterial agent exerts its effect.

Resistance

As appropriate to the antibacterial agent, the section should cover:

- Known resistance mechanisms in pathogens relevant to the indications.

- The potential for cross-resistance to occur within the same class, mentioning any specific lack of cross-resistance that has been documented.

- The potential for associated resistance to occur. This includes the possibility that organisms resistant to antibacterial agents of other drug classes may be resistant to the test antibacterial agent as a result of mechanisms affecting a range of therapies (e.g. due to some types of multidrug efflux pumps or impermeability of the outer membrane in Gram-negative species). It also includes co-transference of a range of resistance determinants (e.g. such that genes encoding resistance to the test agent are linked to genes encoding resistance to different types of agents).

- The section may mention the lack of effect of other resistance mechanisms on the activity of the test antibacterial agent if this would be pertinent to the pathogens most relevant to the indications for use.

- The potential for induction of the expression of resistance, whether temporary or permanent, when certain organisms are exposed to the test antibacterial agent

- The possible occurrence of intermediate susceptibility, whether inherent or acquired.

Data on laboratory-determined rates for the selection of resistant organisms should not usually appear since the relevance of the findings to the clinical situation is unknown. The exception might be when resistance to an antibacterial agent can occur by means of a single mutational event.

The section should describe current problems with pathogens relevant to the indications that are resistant to the antibacterial agent, focussing on the risk of encountering such organisms within the EU. It should not attempt to provide comprehensive information on the prevalence of resistance to the antibacterial agent across the EU although the provision of such information would be expected in accordance with section 3.1.5. It should highlight important existing or emerging patterns of resistance with implications for the routine use of the antibacterial agent. For example, it should take into account estimates of the prevalence of resistance that might have important implications for the anticipated efficacy of an agent against a particular pathogen. The section should be updated whenever it is considered necessary to do so by the sponsor and/or CHMP.

<u>Susceptibility testing breakpoints</u>

See section 3.1.4.

- Either the EUCAST breakpoints or the breakpoints determined by CHMP for pathogens that are relevant to the indications granted should appear in Section 5.1. In both cases the final decision on the breakpoints is made by the CHMP at the time of approval.

- No other breakpoints should be listed.

- Breakpoints may be added at a later date (e.g. if adding a new indication involves additional species or a different dose regimen for which different breakpoints would apply) or may be changed based on new microbiological or clinical data that become available over time

- For antibacterial agents or specific formulations that are anticipated to have only a local antibacterial action relevant susceptibility test breakpoints cannot be set unless there is sufficient experience to set a clinical breakpoint. In these cases the section should provide information on epidemiological cut-off values derived from the MIC distribution curves for the most pertinent pathogens to the indications granted.

<u>PK/PD relationship</u>

This section should describe only the most pertinent features of the PK/PD relationship. No claims should be made for efficacy that go beyond what ahs been demonstrated in clinical studies.

<u>Clinical efficacy against specific pathogens</u>

The introduction to the section should state that:

Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to [drug name] in vitro.

- The section should be sub-headed according to each indication granted.

- Under each indication the species for which CHMP considers that clinical efficacy has been demonstrated should be listed. If the pathogens are the same for one or more of the indications then they may be listed under a single joint heading. Pathogens that are relevant to indications and susceptible to the antibacterial agent *in vitro* but for which there are no or insufficient data to confirm clinical efficacy should not be listed.

- For indications that have been qualified by reference to specific pathogens, with or without mention of particular mechanism(s) of resistance, the species that have been satisfactorily treated should be listed and, where necessary qualified by the type of resistance expressed.

- The routine designation that clinical activity has been demonstrated against strains of an individual species that lack a specific mechanism of resistance to the antibacterial agent is not usually necessary. For example, if the antibacterial agent is a carbapenem it is redundant to specify *non-carbapenemase-producing strains* against gram-negative species that may express these enzymes. However, for a beta-lactam agent with no activity against methicillin-resistant staphylococci it would be appropriate to state *S. aureus* (methicillin-susceptible).

- If the test antibacterial agent showed convincing clinical efficacy against pathogens that were resistant to one or more agents of the same (or very closely-related) drug class (e.g. a lipoglycopeptide showed efficacy against vancomycin-insusceptible enterococci) then this should be stated.

Antibacterial activity against other relevant pathogens

If there are pathogens of major relevance to the indications for which clinical efficacy has not been established during clinical studies it may occasionally be considered to mention some of these under an additional heading. Sponsors should note that this heading will not always be considered appropriate and that the list of organisms should be short, including only the species of most importance.

If such a section is to be included, it should be separated into two sections, introduced by the following sentences:

Clinical efficacy has not been established against the following pathogens although in-vitro studies suggest that they would be susceptible to {drug} in the absence of acquired mechanisms of resistance:

In-vitro data indicate that the following species are not susceptible to {drug}:

Data from clinical studies

The clinical data from the efficacy studies will be presented in the EPAR and generally do not belong in the SPC. This section is rarely needed and should be included only when there is a particular problem with the clinical efficacy data over and above any limitations of the database that have been mentioned in section 4.4. For example, if the data demonstrated an important deficiency that was unexpected and which needs to be highlighted so that prescribers do not place inappropriate reliance on the antibacterial agent when treating certain types of infection.