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Comments should be provided using this template. The completed comments form should be sent to EWPSecretariat@ema.europa.eu

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Guideline on the Evaluation of Medicinal Products indicated for Treatment of Bacterial Infections

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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.

The microbiological evaluation of antibacterial agents 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 to other agents. During clinical studies the use of central laboratories is recommended for confirmation of identification and susceptibility test results, for serological studies and for typing of isolates to distinguish relapses from new infections.

Pharmacokinetic/pharmacodynamic (PK/PD) analyses may be used to select dose regimens for clinical studies and as one of the tools for setting the breakpoints for susceptibility testing. If the PK/PD relationship is well-established and the analyses are convincing it may be possible to omit formal dose-finding studies and proceed directly to the evaluation of one or very few regimens during indication-specific studies of efficacy.

Each study of clinical efficacy should aim to select patients with infections strictly relevant to the indication sought that 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 dosing 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 unless this is really not feasible. Most confirmatory studies of efficacy will aim to demonstrate non-inferiority between the test antibacterial regimen (which may consist of a single agent, a fixed drug combination, a hybrid molecule or combined treatment with a beta-lactam and a beta-lactamase inhibitor) 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.

In some indications 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 the active comparator relative to placebo is not consistently reproducible or is not well quantified. In these cases, a demonstration of superiority versus placebo or versus an active comparative regimen is required based on at least one clinically important endpoint.

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. Alternatively, and if feasible, sponsors may conduct separate studies with the specific aim of generating data on efficacy against the pathogen of interest. In both these possible approaches to collecting efficacy data the

number of cases treated is likely to be small but it is still preferred that the clinical experience is gained in randomised study designs whenever possible, even if these are underpowered. The number of treated cases required to support a specific claim in the SPC must be judged on a case by case basis.

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. In these exceptional cases a pathogen-specific indication for use may be possible (i.e. referring to treatment of named organisms regardless of the documented site of infection).

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 last visit in each study should be conducted at a sufficient 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 SmPCs 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 (background)

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. These developments may provide:

- Activity that is unaffected by one or more acquired mechanisms of resistance to other agents
- Activity against pathogens with inherent resistance to many antibacterial agents
- Activity against newly emerging pathogens for which there may be few treatment options
- Activity in indications additional to those already approved
- Improved pharmacokinetics with potential to provide better efficacy and/or a lower risk of selecting for resistant sub-populations
- Improved tolerability

Wherever possible, the revisions to CPMP/EWP/558/95 Rev 1 allow for some flexibility in order to facilitate drug development while ensuring that each indication sought is supported by sufficient data to enable a sound assessment of the benefit-risk relationship.

Proposals for major deviations from this guidance should be discussed with EU Regulators as early as possible in the development programme.

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 data generated to support additions and changes to the clinical and microbiological elements of the marketing authorisation. A detailed description of the design of studies that might support individual types of indications is not provided.

The guidance 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)
- Hybrid antibacterial agents (i.e. in which two active agents are chemically joined)

The following types of antibacterial agents are included:

- Antibacterial agents intended for systemic administration. Additional separate guidance is available regarding agents intended for the treatment of tuberculosis
- Antibacterial agents to be delivered by topical administration (e.g. to skin, ears and eyes)
- Antibacterial agents administered by inhalation. Additional separate guidance is available regarding inhaled antibacterial agents for the management of cystic fibrosis
- Antibacterial agents administered by the oral route with negligible systemic absorption and an intended effect that is confined to the gut lumen and/or gut mucosa.

The guidance does not cover bacteriophages, agents that affect bacterial virulence and agents that may inhibit the growth and replication of some bacterial species by an indirect effect (e.g. immunomodulators).

3. Legal basis

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

- Dose-Response Information to Support Drug Registration (ICH E4)
- Statistical Principles for Clinical Trials (ICH E9)
- Choice of Control Group in Clinical Trials (ICH E10)
- Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11)
- Guideline on development of paediatric formulations (in draft)
- The Extent of Population Exposure to Assess Clinical Safety for Drugs (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 pharmacodynamic/pharmacokinetic relationship (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/692702/08)

This guideline does not discuss non-clinical or clinical pharmacokinetic studies with antibacterial agents. It is assumed that sponsors will consult all relevant guidelines on pharmacokinetic studies developed by ICH and CHMP, including studies conducted in special populations and for the assessment of drug-drug interactions.

4. Main Guideline Text

Application dossiers should include a discussion of the overall content of the development programme that has been undertaken to support initial licensure or to support a modification of the marketing authorisation. It is expected that the individual study reports and summary documents will provide a clear rationale for all the important features of each study and the overall programme. Any elements of the development programme that are not in line with the recommendations made in this guideline require special attention whether or not there has been prior discussion of these issues with EU Regulators.

It is not possible to provide specific and/or concise guidance in this document to cover every conceivable situation that may arise and sponsors may find it particularly useful to discuss certain 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 discussed in the application dossier.

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. In-vitro 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 recommended 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 animal 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) or used to manufacture a hybrid is new its major microbiological properties should be investigated. 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) or the hybrid (which should be treated as for a single active substance).

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 animal 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.

Whether or not rapid tests are used, 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 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.

In addition, each study, and preferably all studies in the clinical development programme, should employ re-confirmation of isolate identity and susceptibility testing at a single central laboratory. It is recommended 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 data 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.

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.

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, it must be borne in mind that 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 advancements.

Based on in-vitro susceptibility test data, information from animal models of efficacy and human PK data, an assessment of the pharmacodynamic/pharmacokinetic (PK/PD) relationship and 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 one or a very few regimens in confirmatory studies of efficacy. However, the use of PK/PD to predict the optimal duration of treatment is not well established at present. Therefore 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. If the sponsor opts out of this arrangement then the breakpoints will be set by the CHMP. In each case the final decision on the breakpoints will be made by the CHMP at the time of approval. Additional breakpoints may be added at a later date (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, even if there are already 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. 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. Instead, 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. These cut-offs 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 studies should be mentioned in the Risk Management Plan and specific commitments should be listed in the Letter of Undertaking. 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 independent surveillance networks that are able to detect trends over time based on the use of consistent criteria for inclusion of organisms by the same collaborating centres, at least some of which should be located within the EU. These networks may be partly or wholly funded by the pharmaceutical industry, including the sponsor.

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 epidemiological cut-off value 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

4.2.1.1. Patients and infections

Patient selection

There is a risk that a confirmatory efficacy study could enrol a substantial proportion of patients who do not actually have the type of bacterial infection under investigation or have an infection that would resolve without antibacterial therapy in a relatively short timeframe. This reduces the sensitivity of non-inferiority studies to detect any difference there may be between the efficacy of the test and active comparative regimens and therefore the inclusion and exclusion criteria should aim to restrict enrolment to patients who have the required type of bacterial infection and need antibacterial therapy. For placebo-controlled superiority studies the inclusion and exclusion criteria should define a population that can be generalised as far as possible to the likely use of the agent in clinical practise.

The study protocol should provide clear limitations set 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 an appropriate course (in terms of dose and duration) of treatment with another antibacterial agent or regimen.

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” (i.e. not approved by regulatory agencies for clinical use) 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 widely established (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. The protocol should specify which dataset is to be used in the primary analysis of efficacy with a planned secondary analysis based on the alternative dataset and a review of any notable discrepancies between the investigators’ and experts’ opinions.

Patient populations

All protocols should pre-define the full analysis set (FAS) consistent with the intent-to-treat (ITT) principle (i.e. all randomised patients). Appropriate modified FAS (modified ITT) populations may include (among others) all treated patients that meet all the clinical diagnostic criteria and all treated patients with a pathogen. The per protocol (PP) population(s) should include patients considered to be clinically evaluable and/or microbiologically evaluable and should be restricted to those who meet all the clinical diagnostic criteria, have no major protocol violations and have been assessed within the visit windows, with and without at least one relevant pathogen. The study report should account for all patients who are considered to be ineligible for inclusion in each of the pre-defined study populations.

The population or co-primary populations to be used for the pre-specified primary analysis should be stated in the protocol and justified according to the pre-defined study objectives.

Characteristics of infections treated

It is accepted practise that individual clinical studies of efficacy enrol patients with a representative range of bacterial infections relevant to a single indication. For some indications it is also accepted practise that each study restricts enrolment to patients who have either uncomplicated or complicated infections based on definitions that are widely recognised. The following issues are pertinent:

- The actual study population enrolled and range of infections treated may not be fully representative of patients with the indication sought. For example, the range of infections treated, co-morbidities that may affect outcomes and range of other measures of relevance to patient management may be limited. If the clinical study experience is considered to be severely restricted in any way (e.g. a study in intra-abdominal infections in which the great majority of patients have acute appendicitis) this may occasionally result in a qualification of the indication. Alternatively the limitations of the data (e.g. in terms of the range of infections studied, lack of bacteraemic patients

and exclusion of any particular infections or patients with underlying conditions of considerable relevance to the indication) may be described in section 4.4 of the SPC. See section 3.

- 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 even 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 any additional post-therapy visits for the purposes of assessing patient progress and outcomes should be selected in accordance with the indication under study and the PK properties of the test and comparative antibacterial agents. For example, the TOC visit, which commonly takes place between 72 h and 10 days after the last dose of study therapy, should occur when it is predicted that drug concentrations at the site of the original infection would be undetectable or negligible. Realistic windows around each visit should be pre-determined. The last visit, which may be the TOC or a later 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 (e.g. in AECB) or no requirement for further antibacterial therapy (e.g. in some skin and soft

tissue infections). 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 most sexually transmitted diseases and urinary tract infections. 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 cases either the clinical or the microbiological outcome should be designated as the primary efficacy variable. 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 and most sexually transmitted diseases). 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.

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). In these cases the clinical (cure rate) and microbiological (eradication rate) outcomes should be regarded as co-primary efficacy variables and the study should be designed and adequately powered to provide clear conclusions for both outcomes.

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 TOC and at any other planned post-therapy visits. If multiple pathogens are possible then microbiological outcomes should be presented and analysed by patient and by pathogen.

In the primary analysis of the (co-) primary efficacy variable(s) the primary analysis population(s) should be selected accordingly. Analyses of outcomes based on the primary efficacy variable should be performed in and compared between each of the pre-defined patient populations to assess consistency. In all studies there should at least be a comparison between the 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.

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. Additional analyses should be planned and performed according to the designated secondary efficacy variables, such as time to event analyses.

4.2.1.3. Dose-finding studies

Following detailed PK/PD analyses it may still be necessary to perform one or more dose-finding studies to identify a suitable dose regimen for use in one or more clinical indications. In cases where the PK/PD analyses are considered to provide robust guidance regarding the dose and dose interval it may still be necessary to evaluate different durations of treatment before proceeding to confirmatory studies of efficacy. If dose-finding 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 different dose regimens during confirmatory studies of efficacy. 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 dose-finding or confirmatory 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.

4.2.1.4. Confirmatory studies

Number and location of studies

It is preferred that two confirmatory studies of efficacy are performed for each clinical indication sought. If a single confirmatory 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. Single-blind, evaluator-blind or open studies are considered to be less reliable than double-blind studies, especially when the judgement of outcomes is primarily based on investigator assessments of the clinical response. If a double-blind study is not feasible every effort must be made to ensure that the physicians who assess clinical outcomes remain unaware of treatment assignments.

4.2.1.4.1. Non-inferiority studies

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 previous studies, medical opinion or 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 some or all EU MS.

To facilitate interpretation, it is preferred that a single comparative regimen should be allowed within any one study. 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

As necessary, the protocol should specify the 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, in all cases where the use of additional agents is not mandatory from the outset the protocol must specify the criteria under which their use is permissible.

Switch from parenteral to oral therapy

If parenteral and oral formulations are available for the test antibacterial agent and the comparator 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 the minimum. In most types of infections and for most pathogens encountered it is not necessary to require that study therapy is stopped if resistant pathogens or pathogens that show reduced susceptibility are reported from culture of 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.

4.2.1.4.2. Superiority studies

There are several types of acute bacterial infections (e.g. acute maxillary sinusitis, acute exacerbations of chronic obstructive airways disease and acute otitis media in children) in which antibacterial agents have not consistently demonstrated superiority versus placebo in well-conducted randomised studies. Until such time that active antibacterial treatment has been established to be superior to placebo at least in well-defined subsets of patients with these types of infections, the clinical benefit of a test agent can only be reliably assessed in a study designed to demonstrate superiority versus placebo or versus active comparative therapy for at least one clinically important endpoint. Some considerations for the design and conduct of superiority studies include the following:

Placebo-controlled studies

The primary objective of the study 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.

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.

The rescue treatment for any patient that 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.

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 the best available comparative therapy. The clinical studies in any one indication should provide data on efficacy against organisms that express the beta-lactamases that are expected to be inhibited although relatively few organisms that express some types of enzymes will be isolated.

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.

- Hybrid antibacterial agents

In hybrid antibacterial agents there is a chemical linkage between the molecular components and the final molecule may exert antibacterial activity that cannot be predicted from data on each of the actives used to form the hybrid. Therefore a full range of microbiological studies with the hybrid molecule is needed. Provided that there is a strong rationale for the creation of the hybrid based on microbiological and PK/PD considerations it is not required that the clinical development programme should include comparisons between the hybrid and the agents that have been used to create the molecule when given alone or co-administered. The clinical studies with the hybrid in each indication should be conducted versus appropriate comparative regimens.

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 alternative study designs to obtain data on the efficacy of a test antibacterial agent in the treatment of rare infections and/or pathogens are discussed in section 3.2.1.4.3, stressing that a randomised study is always preferred over an uncontrolled study 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 may occasionally cause more common types of infections (e.g. community-acquired pneumonia due to *Legionella spp*.) clinical efficacy data could be collected during the course 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 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 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 during the indication-specific studies. The extent of the data that can be provided will reflect the relative frequency of the types of resistant pathogens sought. For this reason 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. In these circumstances it should not be necessary to pool data across studies in different clinical indications.

When the type of resistance or pattern of multidrug resistance is relatively rare (e.g. carbapenemase-producing gram-negative aerobes in hospital-acquired pneumonia with or without resistance to antibacterial agents in several other classes) it may be appropriate to conduct studies in which patients with clinically confirmed infections due to a particular resistant pathogen (including multidrug-resistant pathogens for which there are few or no remaining treatment options) are enrolled regardless of the site of the infection. Whenever possible these studies should employ a comparative study group but it is recognised that this will not always be feasible. Alternatively, sponsors may be able to collect data on treatment of these types of organisms across studies in different clinical indications and it may be justifiable to allow pooling of the experience when considering how to reflect the information in the SmPC.

4.2.1.5.4. Consideration of some specific indications

Bacteraemia

For the purposes of considering the efficacy of an antibacterial agent, bacteraemia may be defined as the isolation from blood culture(s) of one or more species likely to be responsible for or contributing to the clinical signs and symptoms of infection in the patient.

A qualified indication for the treatment of bacteraemia when occurring in association with [a specific type of infection, with or without restriction to specific pathogens] might be considered possible on provision of a sufficient number of cases. The minimum number that might be considered adequate can only be judged on a case by case basis, taking into account the nature of the infection and following review of the data.

Unqualified indications for the treatment of bacteraemia or for the treatment of bacteraemia due to [specific pathogens] imply that the antibacterial agent has been shown and can be used to treat any underlying focus of infection that was identified before or after discovery of the bacteraemia. It is not at all likely that sufficient data could be provided in an initial marketing authorisation for any antibacterial agent to support an indication for the treatment of bacteraemia even if qualified by species. However:

- If an antibacterial agent has been shown to be efficacious and is indicated for use in a range of infections that collectively account for a substantial proportion of cases of bacteraemia observed in clinical practice (e.g. including community and/or hospital-acquired pneumonias, urinary tract infections, skin and soft tissue infections and intra-abdominal infections) and
- If the studies are considered to include a sufficient number of bacteraemic cases in each indication

then an indication for use in the treatment of bacteraemia (which could still require qualification by specific pathogens) might be considered possible.

Febrile neutropenia

Indications for use such as *empiric treatment of febrile neutropenia* or *treatment of febrile neutropenia* or *treatment of bacterial infections in neutropenic patients* are not acceptable because:

- Antibacterial agents do not treat either neutropenia or fever
- All these indications imply that the antibacterial agent may be used to treat bacterial infections in neutropenic patients regardless of any pathogen(s) involved and regardless of the site of any foci of infection. This is not a plausible scenario.
- In clinical studies in febrile neutropenic patients, with or without microbiological confirmation of a bacterial infection, the antibacterial agent administered may be treating an established bacterial infection and exerting a prophylactic effect simultaneously.

Studies that enrol neutropenic patients suspected of having a bacterial infection on the basis of fever should demonstrate at least non-inferiority of the test antibacterial agent, alone or co-administered with other agents as necessary, versus a suitable comparative regimen. The primary analysis should be based on outcomes in the subset of patients who have well-documented bacterial infections. However, it is not possible to separate any treatment effect from any prophylactic effect of the anti-infective agents administered and therefore these studies really provide a general assessment of the utility of the antibacterial agent as part of the overall management of neutropenic patients with fever. To reflect what is actually demonstrated the indication for use based on results from a satisfactory study might read *[Drug name] may be used in the management of neutropenic patients with a fever suspected to be due to bacterial infection*.

Catheter-related infections

Localised (e.g. at the site of entry), more extensive (e.g. with limb cellulitis) and systemic (e.g. bacteraemia associated with catheter colonisation) infections in patients with various types of indwelling catheters represent a very heterogeneous group of infections. These infections may result from an existing and distant focus of infection, which may or may not have been identified, and may also result in distant infections that persist or are only first discovered after removal of the suspect catheter. In some cases removal of the catheter is all that is necessary while other patients require protracted courses of antibacterial agents to resolve pre-existing or seeded infections.

As a result of these and several other problematic issues (e.g. there are no widely accepted criteria to define what constitutes a catheter-related infection) it is not considered possible to interpret the data from studies in these types of patients even when protocols attempt to standardise patient management as far as possible.

Eradication of carriage

All indications for use must be linked to a clear demonstration of clinical benefit. Indications that relate to the reduction or eradication of a pathogen from a specified body site are not acceptable unless the microbiological findings were shown to result in a measurable clinical outcome. For example, if the antibacterial agent reduces the carriage of potential pathogens from the gut lumen this must be shown to result in a reduction in invasive infections in a defined time period or period of risk (e.g. during neutropenia) or a reduction in antibiotic-associated diarrhoea and colitis.

The clinical benefit associated with the effect on carriage should be assessed in a placebo-controlled study. Demonstration of non-inferiority versus an active regimen would only be acceptable if current clinical opinion rules out the possibility of using a placebo. In most examples that could be envisaged the provision of published data alone to support a link between an effect on carriage and a clinical benefit would not be acceptable. A possible exception might be the eradication of *S. aureus* carriage at some body sites prior to specific types of surgical procedures to reduce the rate of post-operative

infections in which case it is essential that the level of evidence to supplant the need for studies with clinical endpoints is discussed with EU Regulators at an early stage.

Fully validated microbiological techniques must be used to detect and quantify pathogens to support claims of reduction in or eradication of carriage. It may be necessary to conduct preliminary clinical studies with the specific aim of describing the sensitivity of the methods used to detect very small numbers of residual organisms. In some instances it may be appropriate to use very sensitive detection methods such as PCR in addition to culture of specimens.

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 can usually be surmised from comparisons of PK data obtained from limited sampling of infected children of various age groups (0-18 years) 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 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 approval for use in one or very few clinical indications and/or against specific pathogens may be possible 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 minimum acceptable safety database must be considered on a case by case basis.

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}. See section 5.1.

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

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 (e.g. one or very few types of pathogen treated, predominantly mild/moderate infections) it might be considered necessary to further qualify the indication. For example:

- Community-acquired pneumonia of mild to moderate severity
- Acute osteomyelitis due to S. aureus
- Hospital-acquired pneumonia caused by carbapenemase-producing gram-negative aerobes.

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.

Alternatively, it may be considered sufficient that the limitations of the data may be mentioned only in section 4.4, with a cross-reference added as necessary from individual indications listed in 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. fluoroquinolones and penicillin-insusceptible *S. pneumoniae*) it is not acceptable to qualify the clinical indications 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 unusual. 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.

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 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.

However, 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. In these cases the general format described in CHMP/EWP 558/95 rev 1 should be maintained except that:

- 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 th 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.

Susceptibility testing breakpoints

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.

PK/PD relationship

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.

Clinical efficacy against specific pathogens

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.