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NOTE FOR GUIDANCE ON EVALUATION OF MEDICINAL PRODUCTS INDICATED FOR TREATMENT OF BACTERIAL INFECTIONS

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NOTE FOR GUIDANCE ON EVALUATION OF MEDICINAL PRODUCTS INTENDED FOR TREATMENT OF BACTERIAL INFECTIONS

This Note for Guidance replaces the Note for Guidance on Evaluation of New Anti-bacterial Medicinal Products (CPMP/EWP/558/95) that was adopted in April 1997. It incorporates a revision of the Note for Guidance on the Pharmacodynamic Section of the SPC for Anti-bacterial Medicinal Products (CPMP/EWP/520/96) that was adopted in June 1997.

This Note for Guidance should be read in conjunction with Directive 75/318, as amended, as well as all other pertinent elements outlined in current and future 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),

The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A),

Pharmacokinetics and Pharmacodynamics in the development of antibacterial medicinal products (CPMP/EWP/2655/99.

This Note is intended to assist applicants during the clinical development of antibacterial products. It is recommended that any proposals for major deviation(s) from this guidance should be discussed with EU Regulators before implementation. All such deviations should be explained and discussed in the Clinical Overview. In addition, it is not possible to provide specific and/or concise guidance in this document to cover every conceivable situation that may arise. Therefore, applicants may find it particularly useful to discuss certain matters with EU Regulators. For example, the use of alternative study designs (i.e. other than standard randomised active controlled trials to evaluate therapeutic efficacy), such as placebo-controlled studies, the possibility of providing a single study to support a specific indication, the choice of comparative regimens and of delta and the extent of the in-vitro data to be collected.

It may also be appropriate for applicants to consider the content of this note for guidance in conjunction with recent relevant documents that may have been 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 development programme should be discussed in the expert reports/clinical overview and also in individual study reports.

INTRODUCTION

This Note for Guidance is applicable to the design and implementation of clinical studies that may be performed to support an initial application for licensure and also to studies that may be performed in the post-licensure period (for example, to support additional indications). The focus of this Note for Guidance is on the evaluation of antibacterial agents when administered systemically. Many, but not all, of the principles of drug development that are outlined may be applicable to formulations of antibacterial agents that are intended for topical application. However, this document does not provide specific guidance on the clinical investigation of antibacterial agents when administered topically.

The Note considers the clinical trial data that should support the indications, the dose regimen(s) and the duration(s) of therapy but detailed guidance on studies that might support individual types of indications is not provided. The microbiological data that should be

obtained before and during the preliminary and confirmatory clinical trials are discussed in section V of the document, where the format and content of sections 4.1, 4.2, 4.4 and 5.1 of the SPC are addressed.

This revision of the previous Note for Guidance takes into account the fact that bacterial resistance to antibacterial agents may be considered to be an issue for the short and longer-term safety and efficacy of these drugs. Consideration has also been given to matters raised in response to the EMEA discussion paper on antimicrobial resistance (EMEA/9880/99, Rev. 1).

In May 1999, the Scientific Steering Committee of the European Communities stated that "morbidity and mortality may be increased by delay in administrating effective treatment for infections caused by organisms resistant to one or more antimicrobials which would normally be prescribed empirically". Thus, an important contribution to the combat of the threat to human health that is posed by bacterial resistance to therapy would be to attempt to optimise the mode of use of antibacterial agents. This first revision addresses those aspects of the drug development programme that are likely to be most relevant to identifying the optimal modes of use an antibacterial agent, including the specificity of the diagnosis, the selection of dose regimens and the duration of therapy. It is hoped that, by these means, the appropriate use of antibacterial agents may be fostered.

Additions to this Note for Guidance include a consideration of the possible approaches to the clinical evaluation of antibacterial agents that may be suitable for the treatment of infections due to bacteria that demonstrate resistance to several other drugs. In particular, the Note raises the possibility that an initial Marketing Authorisation or addition of an indication to an existing Marketing Authorisation might be possible based on limited data on the utility of an antibacterial agent for treating serious infections for which there are few therapeutic options.

I. PATIENT CHARACTERISTICS AND SELECTION OF PATIENTS

I.1 Selection and exclusion of patients

Much antibacterial therapy is actually initiated and terminated in accordance with the clinical findings, which are commonly non-specific for bacterial infections. There is a risk that studies might enrol a substantial proportion of subjects who do not actually have a bacterial infection and/or have an infection that would be likely to resolve without antibacterial therapy. This reduces the sensitivity of tests to detect differences in outcomes between the antibacterial agent under evaluation and the comparative therapy. Therefore, the inclusion and exclusion criteria should ensure that enrolment is limited to those patients who have the infection under study and who are in need of a course of antibacterial therapy.

Whenever possible, the enrolment of patients into clinical trials that are intended to support specific indications for use should not be based solely on the clinical findings. Enrolment may have to be based on clinical findings alone when there are no useful imaging tests and when the results of any microbiological tests are difficult to interpret (*eg.* acute exacerbation of chronic obstructive airways disease). If there are rapid diagnostic tests available that could be used to aid patient selection (eg. in streptococcal pharyngitis), protocols must clarify whether microbiological evaluability may reasonably be based on a positive result with such a test or whether a confirmatory positive culture is required.

The results of imaging can be used to aid patient selection provided that these are well documented and that the findings that are considered to support the diagnosis are pre-specified. For investigations that are not routinely employed (*eg*. novel methods that are still under evaluation) and/or are may be difficult to interpret (*eg.* chest radiographs in young children), it is preferable that there should be a review by an independent expert or panel of experts blinded to treatment assignment. If, as is likely, this review has to be conducted retrospectively, the primary analysis of efficacy may be based on primary investigators' diagnoses. However, an additional analysis based on the results of the secondary review may be appropriate, especially if there are notable discrepancies between the investigators' and experts' opinions.

For each indication, the range of patient ages, severity of disease, co-morbidity (*eg.* immunodeficiency), need for surgical intervention, need for concomitant anti-infective therapies, and relevant aspects of patient management should be sufficiently broad to cover the spectrum of intended use. The documentation of severity of infection, preferably with the aid of a well-established grading system is always recommended and is particularly important in studies with agents for parenteral administration. It is desirable that protocols and data analysis plans should plan for stratification of patients from the outset according to one or more factors as appropriate to the indication that are most likely to affect outcome (such as severity and type of infection within the general indication).

In studies in which therapy is, at least initially, to be administered parenterally to treat acute infections that cannot be managed by parenteral therapy at home it is not considered sufficient to state in protocols that those patients eligible for enrolment should *require hospitalisation and treatment with parenteral therapy*. Clinical opinion regarding who needs to be hospitalised and who needs parenteral medication, and admission policies in different healthcare systems, vary considerably on these matters. Therefore, enrolment into such studies should depend only on clear inclusion criteria.

The protocol-specified criteria for the post-baseline withdrawal of the assigned therapy should be kept to the minimum that are considered to be necessary to ensure patient safety. For example, it is often not necessary to mandate stopping the assigned therapy in patients who are improving when results from baseline specimens show organisms that are of intermediate

susceptibility or even resistant to study therapy(ies). The information that may be gained by continuing therapy is especially useful when the pharmacokinetic/pharmacodynamic (PK/PD) relationship suggests that an antibacterial agent may be effective in at least some sites of infection even when the MIC of the drug for some pathogens is relatively high. All withdrawals from the assigned treatment group must be explained in the study report and there should be detailed documentation of the clinical and microbiological findings on the day of withdrawal.

For all patients who do not complete the last study visit, a full description of clinical signs and detailed documentation of the microbiological findings up to the time of the last visit should be presented in the study report.

I.2 Validation of the microbiological diagnosis

A microbiological diagnosis, prior to or proven after enrolment and the commencement of study therapy, is highly desirable but is not possible in all indications. When establishing a microbiological diagnosis would involve an invasive procedure (such as sinus aspiration or tympanocentesis), this may be attempted in at least one of the studies conducted to support an indication or in a sub-population of patients.

When the indication permits, microbiological confirmation of the diagnosis should be obtained from pre-entry specimens or at least sought from baseline specimens. It is important that these tests are conducted and interpreted appropriately. For example, information on the methods that will be considered acceptable for the culture, identification and susceptibility testing of the pathogens should be clearly stated in the protocols. Protocols should also specify any other type of specific diagnostic tests (e.g. antigen or nucleic acid detection tests or serology) that might be accepted as evidence of infection. The use of a central laboratory for secondary confirmation of the microbiological or other diagnostic test results from local laboratories is encouraged. It may also be preferable for all serological testing to be performed in a centralised laboratory, using a single accepted methodology and set of interpretative criteria. Protocols should make it clear as to whether the results from local or centralised laboratories will be used in the primary analysis.

The relevance of the results of in-vitro susceptibility tests to clinical and microbiological outcomes may not be clear at the time that a study commences. Therefore, it may not be possible to state susceptibility test breakpoints in the protocol. If preliminary breakpoints are set, such as may be justified on the basis of PK/PD considerations, it should be made clear to investigators how they have been derived and that these are unconfirmed.

The correct designation of patients as being microbiologically evaluable or at least eligible for the analysis of outcomes in all patients with a pathogen is important. The inclusion of patients in these analyses when the species 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, it is important that those bacterial species that might and might not be considered true pathogens in the indication under study should be clearly specified in the protocol and that the applicant should be able to fully justify the list of species that is proposed.

II. METHODS TO ASSESS EFFICACY

II.1 Assessment of outcomes

The assessment of the clinical, and when possible, the microbiological outcomes should be performed at regular intervals up to the end of treatment and at designated post-therapy visits.

II.1.1 Clinical outcomes

At the test of cure (TOC) visit (see below), the clinical response to therapy should usually be categorised as either cure, failure or indeterminate. For most indications, cure should be defined as complete resolution of clinical signs and symptoms. However, in some types of indication a return to baseline status (*eg*. in AECB) or resolution to a point where no further antibacterial therapy is judged necessary (*eg*. in some skin infections) or other definition of cure (eg. in osteomyelitis and infections of the oral cavity) may be applied. The protocol should specify the criteria that should be met in order for a patient to fall into one of these outcome categories. Categorisation of patients as "improved" is too subjective for use in the primary analysis but may be an optional interim outcome assignment at the on-therapy visits and may be particularly appropriate when applied to the time of switch in IV/PO switch studies.

In some circumstances, the use of alternative measures of clinical outcome may be appropriate. For example, when the agent under study is being used to treat serious and/or life-threatening infections and/or there are limited therapeutic options, times to resolution of specific clinical signs or progression to defined events might be suitable outcome measures. Very occasionally, it might be appropriate to designate such alternative measures of clinical outcome as primary efficacy variables (see section II.2.1).

II.1.2 Microbiological outcomes

The eradication or persistence of bacteria that were identified at baseline is most often presumed from the clinical response due to the lack of a sample for culture. However, direct demonstration of eradication or persistence of the causative organisms by sensitive methods should be attempted whenever this is 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 estimates of residual bacterial load, as may be the case in some types of urinary tract infections, the interpretative criteria should be validated. In certain circumstances, such as discussed under II.1.1, time to sterilisation of a body compartment (such as blood or CSF) or time to eradication of specific pathogens from appropriate specimens may be appropriate microbiological outcomes.

The microbiological investigation (including comparisons of pre- and post-therapy susceptibilities of pathogens) of all patients who are clinical failures is mandatory whenever suitable samples can be obtained. For clinical failures in the post-therapy period, attempts should be made to differentiate cases of relapse from new infections (*eg*. using appropriate typing methods).

II.1.3 Timing of assessments

A clear rationale for the timing of the on-therapy study visits, the TOC and other post-therapy visits and the total duration of follow-up should be provided in the protocol. Realistic windows around each visit should be pre-determined in the protocol definition of the fully evaluable (or *per protocol*) population. Every effort should be made to obtain follow-up information, including further microbiological data, at each of the planned visits on as many patients as possible. The study reports should account for all missing data at each visit. If the study is to be conducted in outpatients, it may be appropriate for patients to complete diaries that employ validated scoring systems in order to supplement the data recorded at formal study visits. This may be particularly useful if there are plans to conduct time to event analyses (*eg*. time to disappearance of individual symptoms).

An assessment of outcome at the end of therapy (EOT) may be useful. However, unless there is a very high risk of re-infection before the TOC visit, outcomes at EOT should not be designated as the TOC outcomes.

The TOC visit is often scheduled to occur between 72 h and 10 days after the last dose of study therapy has been administered. However, the timing should be determined according to the indication and the pharmacokinetics of the drug *i.e.* there should be no or minimal levels of active drug remaining at the body site or in body fluids pertaining to the indication sought.

The timing of the TOC visit is more difficult to set when the protocol allows for the use of suppressive therapy (with the initial or another agent) after successful treatment for the acute infection (such as in the management of infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis). The need for this type of therapy must be clearly laid down in the protocol. The regimen(s) that may be offered should be specified. The primary analysis should focus on the responses to the initial course of treatment *i.e.* before the patient enters the suppressive treatment phase. A later post-therapy follow-up visit is appropriate in most indications and is most commonly held between 2-6 weeks post-therapy but may need to be later for infections such as endocarditis and osteomyelitis or for the evaluation of longer-term relapse rates (*eg*. in chronic obstructive airways disease). The timing of the last visit should be gauged to provide important information on recurrent infections, whether due to relapse or new infections, while taking into account the likely increase in numbers of patients that will be lost to follow up as time progresses.

II.2 Primary efficacy variables, populations and analyses

II.2.1 Primary efficacy variables

While both the clinical and microbiological outcomes should be assessed, one or the other should be designated the primary efficacy variable. The microbiological response is objective and is the preferred primary efficacy variable whenever this is appropriate to the indication (*eg*. urinary tract infections and most sexually transmitted diseases). However, in most indications the assessment of response to therapy will be based primarily on clinical outcomes. Whichever is designated as primary, 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.

As mentioned in section II.1, there may be instances in which alternative clinical and/or microbiological outcomes (such as time to event) provide valuable information on the overall response to treatment. Very occasionally, it might be appropriate that one or more alternative measures of outcome might be designated as primary alongside or in place of the more usual parameters (such as cure and eradication).

II.2.2 Patient populations

Protocols should pre-define the criteria that should be met by patients in order to be considered to be clinically evaluable and/or microbiologically evaluable. These subsets should normally include only those patients who have no major protocol violations and who have been assessed within the visit windows. All protocols should also pre-define at least one intent to treat (ITT) population (usually all randomised patients), and it is often useful to define several modified ITT populations (such as all treated patients and all treated patients with a pathogen) (see ICH E9). 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 sample size calculation should aim to ensure that adequate numbers of patients will be enrolled that meet the eligibility criteria for the patient population that is designated to be primary according to the data analysis plan (see III.3.1).

II.2.3 Analyses

Clinical and, where appropriate, microbiological outcomes should be presented and analysed for each of the relevant pre-defined study populations at TOC and at any other planned post-therapy visits. In indications in which more than one pathogen may be identified, microbiological outcomes should be analysed by patient and by pathogen.

The *per protocol* analysis should compare the results for the chosen primary efficacy variable between treatment groups at the TOC visit in the relevant (clinically or microbiologically) evaluable patient population. In studies that aim to demonstrate non-inferiority between test and reference treatments, the primary analysis for the study should usually be the *per protocol* analysis since this is the most sensitive for the detection of any real difference in efficacy between the groups.

Pre-planned analyses in other defined study populations are important since they may give a more realistic estimate of cure rates that will be achieved in clinical practice. Among others, these secondary analyses should include an evaluation of responses in all treated patients in which indeterminate outcomes are counted as failures. All such additional analyses should be compared with the findings of the primary analysis for consistency. It is essential to the overall interpretation and judgement of robustness of the findings that any incongruities should be explored and discussed. Appropriate analyses should also be pre-planned for all the designated secondary efficacy variables.

Outcomes should be presented according to age and gender and also according to other modes of patient classification, such as severity at baseline, surgical intervention and other factors relating to patient management. Formal analyses of outcomes between these patient groups may or may not be appropriate; the protocol should plan for these.

III. STRATEGY AND DESIGN OF CLINICAL TRIALS

III.1 The PK/PD relationship

(See also *Pharmacokinetics and Pharmacodynamics in the development of antibacterial medicinal products* [CPMP/EWP/2655/99] for elaboration on this topic).

Exploration of the in-vitro activity and the non-clinical pharmacokinetic and pharmacodynamic properties of an antibacterial agent should be sufficient so as to provide some indication of the dose regimens that should be explored initially in man. The evaluation of the PK/PD relationship and human pharmacokinetic data should be comprehensive enough to predict with reasonable confidence whether or not an antibacterial agent is likely to have useful clinical activity against organisms that appear to be susceptible to it, regardless of their susceptibility to other drugs. Thus, the mechanism of action of an antibacterial agent and, whenever possible, the potential mechanisms of bacterial resistance to it should be well described in the pre-clinical studies. In particular, any potential for bacteria that are already resistant to other agent(s) to show cross-resistance to the antibacterial agent under evaluation should be explored in detail, including those that possess relatively indiscriminate mechanisms of resistance (such as that mediated by membrane impermeability or efflux pumps).

It is desirable that the PK/PD relationship should be further explored during both the early and confirmatory clinical studies in infected patients to verify the conclusions drawn from the pre-clinical observations and pharmacokinetic data in healthy volunteers. As suggested in CPMP/EWP/2655/99, these investigations may constitute sub-studies within larger trials or may be studies that are specifically designed to address PK/PD relationships (see also section III.3.4).

III.2 Early Studies in Man

III.2.1 Pharmacokinetic studies

Human pharmacokinetic studies should fully characterise the absorption and disposition (including protein binding) of the active moiety(ies). Since there are methodological and interpretation problems associated with assays in whole tissues (e.g. homogenates) such studies are not generally helpful. However, drug concentrations at specialised sites (e.g. concentrations in the CSF) are useful and distribution studies in some other tissue fluids may be valuable. If such data are generated, they should be scientifically robust. In the case of intracellular localisation of the target pathogen, data on the activity of the drug in infected cells are encouraged. Factors that may influence the absorption, distribution and elimination of the agent (such as gender, drug interactions, effects of food and hepatic and renal insufficiency) should be evaluated.

III.2.2 Optimisation of dose, dose regimen and duration of therapy

It is important that effective and safe dose regimens for the treatment of specific infections are unequivocally established prior to the marketing of an anti-bacterial agent. If an antibacterial agent is also to be used for prophylaxis against specific infections, there must be a sound justification for the number of doses that are to be given and the timings of these. With regard to establishing the optimal dose and dose interval for treatment and prophylaxis, general guidance is provided in CPMP/EWP/2655/99 as referred to in III.1 above.

Incomplete eradication of pathogenic organisms from the site(s) of infection may result in clinical relapses with attendant increased morbidity and the persistence of pathogenic organisms may contribute to the selection and spread of drug-resistant bacteria. Conversely, unnecessarily prolonged exposure to an antibacterial agent increases the degree of disruption of the normal flora and increases the selection pressure in favour of resistant micro-organisms (bacterial and other).

It is considered important that the duration of therapy for each indication should be scientifically justified. Clinical studies that seek to evaluate the efficacy of various durations of therapy (by indication and possibly also patient population) are encouraged. If possible, these should be performed early in the clinical development programme. For example, studies may set out to compare two or more durations of therapy with the test agent to a licensed comparator or, if there is a consensus for the duration of therapy in a specific indication, the test drug should be evaluated at this duration and at alternative duration(s). It is encouraged that protocols should plan to evaluate the relationship between duration of therapy and outcome in a meaningful fashion that is related to the type and severity of the presenting infection and the causative pathogen.

The information on dose and duration from early studies should then be taken forward to the confirmatory studies of efficacy, in which it may be appropriate to evaluate more than one dose regimen and/or duration in at least some indications. Whether or not a study sets out to formally compare more than one duration of therapy, consideration may be given to allowing a range of duration of therapy in individual studies that includes the minimum treatment period that is thought likely to be successful.

III.3 Therapeutic Confirmatory Studies

While it is not essential that the confirmatory clinical studies to support the indications sought should be performed in the EU, the applicant should be able to demonstrate that the data on efficacy are applicable throughout the EU. As part of this justification, the dossier should describe and discuss the anticipated prevalence of resistance to the antibacterial agent in the EU among the pathogens that are most relevant to the indications sought (see also section V for further guidance on this matter).

III.3.1 Randomised controlled studies

Ideally, each indication for the treatment or prophylaxis of infection that is sought should be supported by at least one randomised and double blind trial. Each study should be adequately powered to show at least non-inferiority to an acceptable active comparative regimen or superiority to placebo (whenever considered to be possible) or, possibly, both. If a single trial were performed in an indication, it would have to be of very robust design and show unequivocal results in order to allow the indication to be granted.

Blinding and randomisation

Single-blinded, evaluator-blinded or open studies are considered to be less reliable than double blind studies, especially when the clinical outcome is the designated primary efficacy variable, and should be used only if a double blind comparison is not feasible. Special attention should be paid to maintaining the blind during studies in indications that require relatively long-term treatment. When a double blind design is not used, every effort must be made to ensure that the physicians who assess the clinical responses do not become aware of the patients' treatment assignments.

It is recommended that randomisation should be performed by a centralised telephone or computer system and not by means of envelopes distributed to individual study sites.

Active controls

The majority of randomised controlled studies of the treatment of bacterial infections will aim to demonstrate non-inferiority of the antibacterial agent under evaluation with respect to an active comparative treatment. The study design should minimise the possibility that a false conclusion of non-inferiority might be reached. Section III.3.3 deals with special considerations for active comparative studies and further advice is provided in the ICH E9 (*Statistical Principles for Clinical Trials*) and ICH E10 (*Choice of Control Group in Clinical Trials*) guidance documents.

The choice of delta should be very carefully considered for each individual study. In many instances, the appropriate value of delta is likely to be 10%. The applicant's justification for the value that is proposed in each protocol should take into account the anticipated efficacy of the reference treatment in the indication under study. Further advice is provided in CPMP's Points to Consider on the Choice of Delta (CPMP/EWP/2158/99).

The comparative regimen that is chosen for any one trial and indication must be considered to be one of the best available treatments and, whenever possible, should consist of a single agent. The applicant must be able to fully justify both the agent and the dose regimen that is employed, taking into account medical opinion and indication-specific treatment guidelines from appropriate specialist bodies as well as the prevalence of resistance to the comparator at the sites identified for study participation. It is preferable that the comparative agent should be administered at a dose regimen that is licensed in all, or as many as possible, of EU Member States.

It is possible that on occasion the dose regimen of the comparator that is considered to be most appropriate for an indication is not that approved or recommended in some or all EU Member States. It is also possible that the comparator that is considered optimal may not be approved in some or all EU Member States for the indication under study. In these situations, the applicant should provide a detailed justification for the comparative regimen.

Placebo controls

A placebo-controlled study will not be feasible in some or all of the indications sought but may be possible when spontaneous cure rates could be expected to be high. However, if the applicant does not intend to conduct a placebo-controlled study in a specific indication, this

position should be justified. If a placebo-controlled study is possible, this would be desirable and applicants should discuss the provision of such a study as part of the clinical development programme with EU Regulators. The study population should fully reflect that likely to be encountered in clinical practise (see section 1.1). As appropriate to the indication, the randomisation ratio could be used to minimise the number of patients assigned to placebo. It is desirable that placebo-controlled studies should incorporate a third (active treatment) study arm if an established treatment is available. The rescue treatment and the conditions under which it should be instituted should be pre-defined in the protocol.

Prophylaxis

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 should be possible. In both cases, there must be a sound justification for the number of doses of the test antibacterial agent that are to be given and the timings of these.

III.3.2 Alternative study designs

An alternative study design might be acceptable if the applicant is able to provide sound evidence to support a conclusion that at least one adequately powered randomised and controlled clinical trial to support an indication would not be feasible. . All alternative study designs should be carefully justified in the application dossier and their acceptability to support an indication would be assessed on a case by case basis.

Whenever possible, the study should still include a randomisation step because the availability of an internal control group makes the interpretation of the outcomes considerably more reliable than in trials that do not employ randomisation. Therefore, even when enrolment is expected to be limited by patient availability, a randomised and controlled clinical trial is usually preferable to an uncontrolled study or one that attempts a comparison with external or historical controls. Consideration may be given to employing unbalanced randomisation as a compromise between exposing a sufficient number of patients to the test antibacterial agent while still including an appropriate internal control group.

An uncontrolled study should usually be selected only when there is no possibility of acquiring a sufficient number of patients to perform a useful prospective comparison between treatments, such as may pertain to the treatment of very rarely encountered conditions and pathogens.

It may sometimes be justifiable to perform an uncontrolled study to support use in an indication in which very high cure and eradication rates associated with low spontaneous cure and eradication rates are required (such as acute gonococcal urethritis in males). This approach would be acceptable provided that there are adequate comparative safety data from the rest of the clinical development programme.

Occasionally, an uncontrolled study also may be used to supplement the data obtained from randomised and controlled studies (see section III.3.4.b).

Whatever the justification for the uncontrolled study, 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%

confidence interval estimating the response rate. The minimum acceptable cure rate should be defined prospectively based on currently available treatments and experience.

III.3.3 Special considerations for active comparative studies

Combination therapy

In some indications, either the test and/or the comparative regimen(s) may have to consist of more than one active agent so as to cover all the known or potential pathogens. In order to facilitate a double blind study design, it is preferable that the use of a combination regimen should be fixed throughout the treatment period or that the same agent is added to both test and comparative regimens under identical circumstances. Alternative designs make it very difficult to conduct a double blind study and should only be used when these are unavoidable.

The protocol should specify both the additional drugs and dose regimens that must or may be used in conjunction with the core test and comparative therapies. Information on the prevalence of bacterial resistance to the core test and comparative agents should be taken into consideration to assess the need for and composition of combination therapy. 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.

In general, protocols should at least outline the criteria that should be met before adding, discontinuing or amending dose regimens of any additional antimicrobial agents that may be allowed during the study. Prior to the start of the study, potential study sites should confirm that local opinion and practice are sufficiently compatible with the instructions in the protocol that they expect to be able to comply with these throughout the conduct of the study.

Switch from parenteral to oral therapy.

<u>If both parenteral and oral formulations of the test drug are available:</u>

Individual studies may allow for a switch from parenteral to oral therapy when protocol-specified criteria are met. In such cases, it is preferable that both parenteral and oral formulations of the chosen comparative drug are also available so that patients in both treatment groups may be switched using identical criteria and it should be possible to maintain a double blind study design.

The minimum duration of parenteral treatment requires careful consideration. A very early switch (eg. after only one or two days of parenteral therapy) has the potential to encourage the enrolment of patients who might have responded well to oral therapy from the outset. Conversely, dictating too long a period of parenteral therapy should be avoided, since this is inconvenient for hospitals and patients. Protocols should provide the criteria that should be met before switching to oral therapy. The clinical condition of patients at the time of switch should be recorded in detail and discussed in the study reports.

Consideration should be given to whether the change to oral therapy represents a simple switch or whether the change also represents a "step-down" in the dose. The doses of the oral formulations of the test and reference therapies used for follow-on therapy should be justified. Provided that these matters are taken into account, the interpretation of the results of such studies should be relatively straightforward.

<u>If the test and/or comparative agent can be given by only one route:</u>

It may be that the test agent is available for administration only by the oral route but it is considered desirable to study its efficacy as follow-on to another parenteral agent. In such

cases, the potential for carry-over effects from the parenteral to the oral treatment periods complicates the assessment of efficacy of the test oral agent.

Alternatively, difficulties may arise when the test agent can only be given parenterally but a switch to oral therapy is desirable for routine patient management. In such cases, the choice of the agent used for oral follow-on therapy will require careful justification.

III.3.4 Infections due to resistant organisms

There are particular issues surrounding the choice of study design to evaluate the efficacy of antibacterial agents in infections due to organisms that are resistant to most or even all licensed antibacterials. In some cases, a Marketing Authorisation might be possible based on limited data on the utility of the antibacterial agent in such circumstances (see also section III.3.5). In addition, a pathogen-specific ± site-specific indication for use might be considered appropriate (see section V.1).

Need for clinical data

a. When the activity of the antibacterial agent is completely unaffected by one or more mechanisms of resistance to other agents

In-vitro studies may show that the activity of an antibacterial agent against a certain species is completely unaffected by some or all of the mechanisms of resistance that individual strains of that species might possess against other antibacterials. Therefore the demonstration of clinical efficacy of such an agent in any one indication against the species (whatever the resistance profile of the strains actually treated) can, within the same indication, be extrapolated to all other organisms of that same species that do not exhibit resistance to the test agent. Thus, it would not be necessary to seek out organisms with specific types of resistance to other antibacterial agents in clinical trials in order to establish the activity of the test agent against them (see section V for details of how this information might appear in the SPC). For example, the satisfactory demonstration of clinical activity of an oxazolidinone against methicillin-susceptible *S. aureus* (MSSA) in a particular indication could be extrapolated to MRSA regardless of how many MRSA might have been treated.

b. When the activity of the antibacterial agent is affected to a modest degree by one or more mechanisms of resistance to other agents

There will be cases in which the in-vitro activity of the test antibacterial agent is somewhat less against organisms with a particular type(s) of resistance compared with strains of the same species that do not possess those mechanisms but is still potentially sufficient to be efficacious. For example, MICs of a modified glycopeptide derivative whose activity is relatively unaffected by mechanisms of resistance to vancomycin may still be slightly higher (by one or two doubling dilutions) for vancomycin-resistant compared with vancomycin-susceptible strains within a species. Even though the test agent may still be thought likely to be clinically active based on PK/PD considerations, the potential clinical relevance of these in-vitro observations may require investigation.

The extent of these clinical investigations will inevitably depend on the frequency with which a particular type of resistant organism is encountered. In general, comparative clinical data in at least one indication should be provided if a particular type of resistant organism is commonly encountered and a licensed comparative agent is available for study (such as MRSA in skin and soft tissue infections). An uncontrolled clinical study may be acceptable if a particular type of resistant pathogen is rarely encountered (see sections III.3.2 and III.3.5). An uncontrolled study may also be used to supplement the data on activity against more common pathogens with specific mechanisms of resistance obtained from controlled studies. For example, a supplementary study in community acquired pneumonia that attempts to enrol a high proportion of infections due to pneumococci with varying susceptibility to penicillin.

In both these instances, outcomes should be analysed according to MICs of the antibacterial agent for the pathogens treated.

The total number of organisms isolated from patients that demonstrate a particular type of resistance that should be treated with the test antibacterial agent in order to gain an endorsement for use must be considered on a case by case basis. In addition, it may be that the number of organisms with specific types of resistance that have been treated in any one indication is very small. An extrapolation of efficacy between indications may or may not be appropriate. Such decisions will depend on factors such as PK/PD considerations and have implications for sections 4.1 and 5.1 of the SPC (see also section V).

Selection of the comparative regimen(s)

When a comparative study is considered to be both desirable and feasible, the selection of an appropriate comparative agent (or combination of agents) is particularly difficult. That is, the comparative agent(s) that may be active against the same range of multi-resistant organisms as the test antibacterial drug may not always be the preferred therapy against susceptible strains of the same species. Therefore, it may be necessary to adopt one of several alternative strategies in order to optimise patient management and yet still provide a robust comparison with the test antibacterial agent. For example, and assuming patients already known to have resistant organisms will not be eligible for randomisation:

a. If the study is to be conducted in centres where organisms that are resistant to the preferred comparative agent for the indication are uncommonly or rarely encountered
    - All patients in the comparative arm should initially receive the preferred agent
    - Patients found to be infected with a pathogen(s) resistant to the preferred comparative regimen would be switched to another agent that is active unless their clinical course indicates to the investigator that a switch is not necessary.
b. If the study is to be conducted in centres where organisms that are resistant to the preferred comparative regimen for the indication are frequently encountered:
    - All patients in the comparative arm should initially receive an agent that is active against the expected resistant pathogens
    - Patients found to be infected with pathogen(s) that are susceptible to the preferred comparative regimen would be switched to that regimen as soon as possible.

In both instances, the study should plan to compare the test antibacterial agent with the "comparative regimen" so that patients in the comparative group who were switched based on baseline microbiological results becoming available should be eligible for the evaluable population.

If patients in the comparative group had to be switched to the test antibacterial agent because there was no other suitable therapy available, they should be analysed separately.

It is unlikely that these studies could be double blind. However, every effort should be made to ensure that clinical assessors are unaware of the treatment assignment.

III.3.5 Infections due to rare, difficult to treat pathogens and infections that are rarely encountered

There may be instances in which the test antimicrobial agent has properties that would likely make it suitable for treating rarely encountered difficult to treat pathogens (such as *Listeria monocytogenes*) and/or rarely encountered infections (such as endocarditis and meningitis). As in III.3.4, the extent of the clinical investigations that are possible will depend on the frequency with which the particular organism or type of infection is encountered. An initial Marketing Authorisation might be possible based on limited data on the utility of an

antibacterial agent in these clinical situations. Other indications for use could be added at a later date as further studies are completed. Alternatively, the use of an antibacterial agent for rare, difficult to treat pathogens and/or rare infections might be added to the indications already granted for an existing Marketing Authorisation.

III.4 Studies in children

For infections that can occur at any age, and when the properties of an antibacterial agent would not preclude its administration to children, applicants should consider the development of suitable dose sizes and formulations for paediatric patients of all ages in accordance with ICH E11.

A potentially suitable initial dose range for children can usually be surmised from limited data on the pharmacokinetics in adults, the PK/PD relationship, and any available information on safety and efficacy. Further exploration of the pharmacokinetics across the entire age range 0-18 years should be undertaken, usually by means of limited blood sampling during clinical studies in which infected paediatric patients receive the drug. Special attention should be paid to the evaluation of pharmacokinetics 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) during limited studies in paediatric patients. 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. It is accepted that these will likely be uncontrolled studies.

However, some infections are more prevalent in the paediatric population (such as otitis media). 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

At the time of initial licensure, all the relevant information already available in children should be mentioned in the SPC (eg. in sections 4.8 and 5.2) even if there are insufficient data at that time to support a formal indication for use in one or more age groups. In these instances, the satisfactory completion of investigations in children would be a post-authorisation commitment and a timetable should be provided.

IV. CLINICAL SAFETY EVALUATION

The assessment of the safety of an antibacterial agent does not usually have the benefit of any comparisons with placebo. There are some special considerations for an assessment of safety that must rely to a considerable extent on comparisons with licensed antibacterial agents. In particular, the assessment of the safety profile of the novel agent may be heavily influenced by the safety profiles of the comparative agents that have been employed throughout the clinical development programme. There are potential advantages, then, in employing a range of comparative agents from different drug classes to broaden the comparisons that may be made. However, it is recognised that this strategy may not always be possible or appropriate, especially for the initial application for a Marketing Authorisation.

Whereas a comparison of pooled safety data for the antibacterial agent under evaluation and comparative agents from all the studies is often provided, this may be very misleading due to the variety of indications that were studied and range of test and comparative regimens that were administered. In addition to the individual comparisons between test and comparator that must be made in each study report, it is especially important that the summary of safety

should provide tabulations of adverse events by dose of the test agent and against each comparative regimen. It may also be appropriate to tabulate data according to the duration of therapy, especially in indications that require longer-term treatment, such as osteomyelitis and endocarditis.

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 should be separated out for those who did and did not receive additional agents.

The disease processes and the potentially large number of concomitant medications pose additional problems for the characterisation of the safety profile and the categorisation of adverse events according to drug-relatedness, especially in seriously ill patients. As for all medicinal products, tables should also summarise adverse events according to relevant patient characteristics, such as general condition at baseline (eg. age, gender, hepato-renal function) and severity of the infection, and according to at least the commonest concomitant medications.

Furthermore, adverse reactions to study drug and the pathological processes triggered by the infection itself may involve the same organs and their functions. 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.

IV.1 Specific adverse events to be monitored

The pre-clinical data may indicate that there is a need to evaluate the potential for drug toxicity in individual organs. Targeted monitoring and, sometimes, special studies are advisable for certain types of adverse reactions that are anticipated on this basis or from chemical and/or pharmacological similarities between the antibacterial agent under evaluation and licensed medicinal products. For example, data may point to the possibility of unwanted effects on cardiac conduction, photosensitisation, and major organ function. Applicants should consult relevant guidelines regarding these investigations.

An evaluation of the potential for an antibacterial agent to select for micro-organisms with inherent or acquired resistance to it is encouraged especially if the drug is from a class that is already known to have a high propensity to select for certain organisms or is the first in a new class of agents. It is particularly desirable that effects on target pathogens and the host flora should be explored in hospitalised, debilitated or immunosuppressed patients. The microbiological assessment of patients who experience adverse events that may be a result of effects on the host flora is also encouraged. Studies in healthy subjects might also be useful, depending on the pharmacological properties of the drug.

IV.2 Extent of population exposure to assess clinical safety

The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A) applies. In the case of antibacterial agents that have clinically useful activity against organisms that are resistant to one or more other drugs, it may be acceptable to allow initial licensure based on a relatively small safety database. However, this would be possible only if no major concerns have been raised by the pre-clinical or clinical data.

IV.3 Long term safety

In the majority of cases, patients in clinical studies will be treated for less than two weeks. However, it is recommended that they should be followed for up to 4-6 weeks post-therapy. This is long enough to detect most cases of adverse effects such as late onset serious skin reactions and antibiotic-associated colitis. There may also be longer-term exposure data when studies have been performed in indications such as osteomyelitis and endocarditis.

Longer-term safety monitoring may apply when there is a potential that adverse effects may become manifest some weeks or more after therapy has been completed (such as ototoxicity). Such effects may or may not have been anticipated based on the pre-clinical findings. Depending on the indication for use and the type of adverse effect that could be expected it might be acceptable that these data can be obtained after initial licensure.

Finally, the emergence of inherently resistant organisms and organism with acquired resistance should be addressed as a safety issue (see section V.4.2). The periodic re-assessment of the risk-benefit relationship for the antibacterial agent should take into account knowledge of the changes in prevalence of acquired resistance (*eg*. from literature reports, company data and other sources) since the time of initial licensure.

V. CONSIDERATIONS FOR THE SPC

The content of sections 4.1. (Indications), 4.2. (Posology), and 5.1. (Pharmacodynamics) of the SPCs for antibacterial agents require considerations that are particular to these types of medicinal products. While this Note for Guidance is primarily intended to apply to new or recently authorised antibacterial agents, in principle, the following sections are applicable to the SPCs of all antibacterial agents.

V.1 Section 4.1 Indications

In principle, an indication would be granted only if the clinical data support a favourable benefit/risk ratio and reflect the range of type and severity of infections that are commonly encountered. General statements (such as lower respiratory infections) are no longer acceptable and should be replaced by specific indications (such as community-acquired pneumonia) according to the clinical studies. For some indications, qualification by uncomplicated or complicated designations may be appropriate if these are sufficiently well defined and agreed terms when applied to infections at specific sites. If the actual infection type that has been studied is in some way limited (*eg*. by a very predominant type of infection within an indication, a single or very predominant pathogen or only mild to moderate infections), it might be considered necessary to further qualify the indication.

A pathogen-specific rather than an infection site-specific indication may be appropriate when an antimicrobial agent is expected to be active against rare and/or multi-resistant pathogens but only limited clinical data have been provided (see sections III.3.4 and III.3.5). Such an approach would also have to depend on whether an extrapolation of efficacy in one indication to infections at other body sites can be justified. A pathogen-specific indication is also appropriate for infections due to *H. pylori*. In addition, depending on the antimicrobial spectrum of the agent and the nature of the studies conducted, a pathogen-specific and site-specific indication may be appropriate (*eg*. staphylococcal osteomyelitis). Depending on the sequence of the clinical development programme, these specific indications may appear with or without other more general indications for use.

In order to encourage the appropriate use of antibacterial agents and to acknowledge any differences in opinion regarding the optimal use of individual agents between Member States, the following standard sentence must be added to this section exactly as written:

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

V.2 Section 4.2 Posology and Method of Administration

Where evidence exists, both the dose regimen and the duration of treatment courses should be stated by indication. The durations that are recommended should be in accordance with the range that was documented to be effective in clinical trials for each indication. On occasion, it may also be appropriate to specify the duration of treatment for certain types of pathogens at specific body sites.

V.3 Section 4.4 Special Precautions

Comments may be necessary to highlight the extent/limitation of clinical experience in treating certain types of infection and/or pathogen.

V.4 Section 5.1 Pharmacodynamics

V.4.1 Collection of data on susceptibility and resistance

During the pre-clinical and clinical development programme, the applicant should collect sufficient data to characterise the in-vitro antibacterial activity of the agent against clinical isolates from various countries/regions within the EU and to describe the epidemiology of resistance. Due to the variety of circumstances that may apply, it is not possible or appropriate to set definitive numbers of organisms to be tested but some general considerations follow. To some extent, the amount of data to be collected will depend on whether the antibacterial agent under evaluation belongs to an existing class for which there are already data on the prevalence of acquired resistance and the potential for cross-resistance. The isolates tested should belong to species that are the most relevant pathogens in the indications sought. The number of isolates of each species that are tested and their origin require justification. The frequency with which various pathogens cause infections within the indications sought should be used to select the proportion of the total number of organisms tested that should be of each species. This selection process should also take into account information that may be already available on the prevalence of bacteria that possess various types of mechanisms of resistance and the known or unknown potential for these mechanisms to affect the activity of the antibacterial agent under evaluation.

These investigations, together with information on the bacteria isolated from patients in clinical trials, should result in estimates of the likely prevalence of resistance to the antibacterial agent that may be encountered across the EU at the time of initial licensure. The latter should take into account the potential for bacteria to demonstrate cross-resistance between the agent under evaluation and antibacterials of the same or other classes. When a particular problem with clinical efficacy against one or more species is anticipated from these data in at least some EU Member States, this information should be conveyed in section 5.1 as described below.

Subject to agreement with the CPMP, the breakpoints for susceptibility that appear in the SPC will be those recommended by the Europ.ean Committee on Antimicrobial Susceptibility Testing (EUCAST). However, there may be instances where the EUCAST recommendations differ from those of the NCCLS (for example, this might occur particularly for fastidious species). In such cases, it may be permissible to mention those NCCLS recommendations that are different in addition to the EUCAST recommendations. For topical preparations of anti-bacterial agents, the breakpoints applicable to systemic use should be stated in the SPC. These should be accompanied by a note that these breakpoints may not be applicable to topical application of the drug due to the local concentrations that are reached and the local physicochemical conditions that may influence the overall activity of the agent at the site of application.

The assignment of an asterisk to denote that efficacy has been demonstrated against a particular species in clinical studies can only be decided on a case by case basis. As a general principle, and for commonly encountered pathogens, it would be preferred that clinical efficacy data are available on at least 20 treated cases due to a single species within any one indication. However, it is recognised that it may not always be possible to obtain this minimum number for less commonly encountered pathogens for each indication so that lower numbers or pooling across similar indications may be acceptable in some instances. The decision to accept lower numbers and/or pooling would take into account not only the total number of organisms that have been treated but also the types of infections that they caused. For example, if it is not felt appropriate to extrapolate efficacy against a species in one indication to all other indications to be granted, it may be appropriate that a footnote indicates that the designation of clinical efficacy against a particular species applies only in a single indication.

A further consideration may apply if activity is claimed against organisms within a single species that are less susceptible to the agent *in vitro* as a result of a particular mechanism of resistance. In such cases, it may or may not be considered necessary to separate out the demonstration of activity against organisms that do or do not possess a specific mechanism of resistance.

V.4.2 The format for section 5.1:

General properties

ATC classification

Mode of action

PK/PD relationship

This section should describe the PK/PD relationship as far as this might be of use to prescribers.

Mechanism(s) of resistance

The section should cover the known resistance mechanisms in targeted pathogens (beta-lactamase production, PBP mechanisms etc), the potential for cross-resistance to other antimicrobial agents (same or related class) and the potential for co-resistance due to any known genetic linkage of resistance determinants. If appropriate, information should be provided on the frequency of selecting drug-resistant organisms during treatment, including where appropriate to the drug and the species, any potential for induction of expression of resistance.

Data from rates selecting out resistant organisms derived from in-vitro studies in which organisms were exposed to the agent should NOT appear since the relevance of these to the clinical situation is unknown.

The phenomenon of intermediate susceptibility, whether inherent or acquired, may also be discussed in this section if it is a well-established and widely recognised phenomenon (for example, intermediate susceptibility to beta-lactam drugs in pneumococci and gonococci due to modifications of penicillin binding proteins).

Breakpoints

The breakpoints that appear should be clearly ascribed to the recommending body. As discussed above, these will usually be those of EUCAST but may sometimes be those agreed between CPMP and the applicant. Also, on occasion, NCCLS breakpoints might be added if these differ from those of EUCAST. In each case, the breakpoints should be expressed exactly as recommended by these bodies.

Information on the susceptibility of species that are relevant to the approved indications should be tabulated as shown below (see also notes on content below).

Within each of the three sections, species should be listed alphabetically in the following order: aerobic Gram-positive micro-organisms, aerobic Gram-negative micro-organisms, anaerobic micro-organisms, and "other" micro-organisms (such as Chlamydia, Mycoplasma, Spirochetes and Mycobacteria).

The following standard statement should be included before the table:

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Categories 1 (*Commonly susceptible species*) and 2 (*Species for which acquired resistance may be a problem*) in the table (example shown below) will include both normally susceptible species and species with natural intermediate susceptibility. However, species with natural intermediate susceptibility (*i.e.* against which the antibacterial agent exerts only moderate activity *in vitro*) should be identified by superscripts and a footnote, as shown below. Whether a species belongs in category 1 or 2 can only be considered on a case by case basis. Due to the possibility that resistance rates may vary greatly across the EU and will change at different rates over time, no specific percentage can be quoted for categorisation. However, an indication that the prevalence of resistance in a species has reached 10% or more in any one country/region may merit inclusion of that species in category 2.

The third category shown below (*Inherently resistant organisms*) should include only those species that are never naturally susceptible to the drug but might be encountered in the indications that are to be granted. For example, enterococci are inherently resistant to currently licensed cephalosporins.

Commonly susceptible species
List of species
Species for which acquired resistance may be a problem
List of species as above
Inherently resistant organisms
List of species as above

Superscripts in, and footnotes to, the table should include:

- An asterisk (*) should be used to denote those species against which it is considered that activity has been satisfactorily demonstrated in clinical studies, with specification of the indication if this appears necessary from the data.

- A second superscript (+) should be used in category 2 (*Species for which acquired resistance may be a problem*) to denote any species for which high rates of resistance (generally more than 50%) have been observed in one or more areas/countries/regions within the EU. On occasion, it may be necessary to elaborate on the problems that have been encountered.
- A third superscript ($) should be used to denote those species that show natural intermediate susceptibility (in the absence of acquired mechanisms of resistance) to the antibacterial agent. For example, as documented for *H. influenzae* and erythromycin and for *S. pneumoniae* and ciprofloxacin.

Individual species should NOT be separated according to different acquired mechanisms of resistance (such as beta-lactamase positive or penicillin-resistant) when the presence of the acquired mechanism of resistance DOES NOT affect the activity of the antibacterial agent. For example, it is both inappropriate and redundant to state that a fluoroquinolone is active against both beta lactamase positive and negative *Haemophilus influenzae* or *parainfluenzae* or against both penicillin-susceptible and resistant pneumococci. The potential or lack of potential for cross-resistance should be described under the section on resistance.

The exceptions to this rule would be cases in which there is a high degree of co-resistance, such as the very high incidences of resistance to fluoroquinolones and expression of constitutive MLSB resistance to macrolides that are found in MRSA. In these cases, it may be necessary to separate organisms of the same species that have different mechanisms of resistance to other drugs into different sections of the table.

It IS relevant to specify an organism according to mechanism of resistance if this may have an effect on the likely activity of the antibacterial agent. For example, to differentiate methicillin-susceptible and methicillin-resistant staphylococci in SPCs for beta-lactam drugs.

If there are particular issues surrounding the prevalence of resistance in one or more species within the EU that are noteworthy for prescribers, these may be covered either as footnotes to the table or as additional paragraphs.

After initial licensure, it is anticipated that the most reliable information on changes in the prevalence of resistance would likely come from large independent (i.e. non-sponsored) surveys that are able to detect trends over time or from large co-operative studies that are partly or wholly funded by the pharmaceutical industry. Even if susceptibility to the individual agent is not being evaluated, the information on the tested agents can be helpful if there is a potential for cross-resistance to occur. The applicant should monitor this information, together with other reliable data derived from any sponsored studies that may be conducted and from other sources.

Initially, relevant published or unpublished information from sponsored or non-sponsored studies should be provided as part of the PSURs. Later on, relevant data from well-conducted sponsored or non-sponsored studies should be provided at the time of renewal.

Information from clinical studies

In exceptional cases, such as when a novel agent is initially approved only for limited indications and/or for pathogen-specific indications, a brief mention of the data on efficacy may be placed at the end of this section of the SPC.