EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 December 2018
EMA/844951/2018 Rev. 3
Committee for Human Medicinal Products (CHMP)

Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3

Draft

Draft agreed by Infectious Disease Working Party	September 2018
Adopted by CHMP for release for consultation	19 December 2018
Start of public consultation	14 January 2019
End of consultation (deadline for comments)	31 July 2019

This guideline replaces the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev 2 (CPMP/EWP/558/95 Rev.2); and, Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013).

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

Keywords	***Microbiological investigations, pharmacokinetics and pharmacodynamics, dose selection, non-inferiority and superiority trial designs, infection site-specific indications, pathogen-specific indications, patients with limited treatment options***

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

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Executive summary

This guideline merges, revises and adds to the guidance previously included in the *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (CPMP/EWP/558/95 Rev.2) and the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections* (EMA/CHMP/351889/2013).

The revisions reflect scientific advice given on the development of antibacterial agents, decisions taken during regulatory procedures and alignments on clinical trial requirements that have resulted from discussions between regulators in the EU, United States and Japan, including revised recommendations for primary endpoints, primary analysis populations and non-inferiority margins in trials to support certain infection site-specific indications for use.

Other updates include clarifications on recommended clinical programmes for antibacterial agents expected to address an unmet need and for combinations of beta-lactam agents with beta-lactamase inhibitors. Guidance has been added on clinical trials to support treatment of uncomplicated urinary tract infections and uncomplicated gonorrhoea. Situations in which single pivotal trials may be accepted to support infection-site-specific indications are described. The guidance on the presentation of the microbiological data and the clinical efficacy data in the Summary of Product Characteristics (SmPC) has been revised.

Some of the information in the previous guidelines has been removed because separate and more detailed guidance has since been issued (see the *Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products* [EMA/CHMP/594085/2015] and the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to Mycobacterium tuberculosis* [EMA/CHMP/EWP/14377/2008 Rev 1]). Furthermore, guidance on paediatric development programmes has been removed due to parallel development of the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements* (EMA/CHMP/187859/2017).

1. Introduction (background)

The continued development of new antibacterial agents is recognised to be very important for human health. In the face of increasing problems posed by bacterial resistance, there is a pressing need for new antibacterial agents suitable for treating infections in patients with few remaining therapeutic options. Furthermore, in recent years there have been initiatives to re-evaluate dose regimens for some licensed agents to maximise their efficacy and minimise the risk of selecting for bacterial resistance. To facilitate clinical development programmes for new antibacterial agents and to support modifications to the uses and/or regimens for licensed agents there is a need to ensure that each clinical trial conducted can be designed to meet the requirements of multiple regulatory agencies.

2. Scope

This guideline is relevant to antibacterial agents with a direct action on bacteria resulting in inhibition of replication leading to bacterial cell death including:

- Antibacterial agents developed as single agents;
- Antibacterial agents developed for use in combination with one or more other specific antibacterial agent(s), whether co-formulated or co-administered;

- Beta-lactam (BL) agents developed for use with beta-lactamase inhibitors (BLIs), whether co-formulated or co-administered.

The guidance includes antibacterial agents administered systemically (including oral administration to treat pathogens that are confined to the gastro-intestinal tract) or formulated for topical administration to the skin. Specific guidance is not provided on the development of antibacterial agents formulated for topical administration to the ears and eyes or for inhalation, although many of the general principles are applicable.

Some principles covered in this guideline are also applicable to the development of the following, although additional considerations may apply that are not addressed:

- Bacteriophages proposed to treat infections;
- Agents that affect bacterial virulence;
- Agents that inhibit bacterial growth and replication by an indirect effect (e.g. immunomodulators);
- Monoclonal antibodies for treatment or prophylaxis of specific infections.

Clinical data requirements to support uses not addressed in this guideline must be considered on a case by case basis.

The following are not addressed:

- Clinical pharmacology studies. Available guidance on the pharmacokinetic evaluation of new chemical entities, including population pharmacokinetic analyses, should be followed;
- Pharmacokinetic-pharmacodynamic analyses. This guideline should be read in conjunction with the *Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/CHMP/594085/2015);*
- Paediatric development programmes. This guideline should be read in conjunction with the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements (EMA/187859/2017)*, which is under development;
- The clinical development of antibacterial agents intended for the treatment of tuberculosis. This guideline should be read in conjunction with the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to Mycobacterium tuberculosis (EMA/CHMP/EWP/14377/2008 Rev.1).*

3. Legal basis

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

- Note for Guidance on Good Clinical Practice - CPMP/ICH/135/95 (R2);
- Note for Guidance on General Considerations for Clinical Trials - CPMP/ICH/291/95 (ICH E8);
- Dose-Response Information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4);
- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9);
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10);

- Note for Guidance on population exposure: The Extent of Population Exposure to Assess Clinical Safety for Drugs - CPMP/ICH/375/95 (ICH E1A);
- Guideline on the choice of non-inferiority margin – (EMEA/CPMP/EWP/2158/99);
- Points to consider on application with 1. Meta-analyses 2. One pivotal study - CPMP/EWP/2330/99;
- Extrapolation of results from clinical studies conducted outside Europe to the EU population - CHMP/EWP/692702/2008;
- Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products EMA/456046/2015;
- Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to *Mycobacterium tuberculosis* EMA/CHMP/EWP/14377/2008 Rev 1.

4. Microbiological investigations

4.1. Non-clinical assessment of anti-bacterial activity

4.1.1. Spectrum of antibacterial activity

Every effort should be made to elucidate the mechanism of action of new antibacterial agents.

The methods used for determination of minimum inhibitory concentrations (MICs) should be described in detail and justified. Appropriate active controls should be included. The MIC_{50}, MIC_{90} and MIC range should be presented by species and, when appropriate, by sub-group (e.g. with and without specific resistance mechanisms) in tabular form. The MIC distributions should be presented in histograms.

The in vitro activity of previously unlicensed antibacterial agents and of combinations of beta-lactams and beta-lactamase inhibitors (BL/BLIs; see further in section 4.1.3) should be determined against clinical isolates obtained within 5 years prior to filing an application dossier. These isolates should belong to pathogenic species relevant to the indication(s) 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 that demonstrate resistance to individual and multiple classes of antibacterial agents. For rare pathogens and strains with rarely encountered mechanisms of resistance or patterns of multi-drug resistance it is recommended that at least 10 organisms of each species or with each resistance mechanism/pattern are tested whenever possible.

The in vitro antibacterial activity of any major metabolites formed in humans should be assessed separately. If any metabolite appears to exert antibacterial activity that could make an important contribution to efficacy, an appropriate range of in vitro studies should be conducted as would be done for parent drug. The overall antibacterial effect of parent and metabolite when used at a ratio typically observed in humans should be investigated.

The total in vitro susceptibility database derived from studies with collections of recent clinical isolates and pathogens isolated from patients enrolled into the sponsored clinical trials should be sufficient to estimate resistance rates (i.e. resistance defined by the final susceptibility test interpretive criteria) that are likely to be encountered during routine clinical use at the time of approval.

4.1.2. Combinations of antibacterial agents

The in vitro susceptibility data should provide sound support for the use of the combination compared to each agent alone against specific pathogens and/or against organisms that express certain mechanisms of resistance. Alternatively, or in addition, the data should support a conclusion that the risk of selecting for resistance to the agents in the combination is reduced when they are used together compared to use of each agent alone (see section 4.1.4). The in vitro studies should support the ratio(s) of active substances to be investigated in nonclinical and clinical studies.

4.1.3. Beta-lactamase inhibitors

The mechanism of beta-lactamase inhibition should be investigated for new beta-lactamase inhibitors (BLIs) and enzyme kinetics should be investigated using a wide range of beta-lactamases to determine the expected spectrum of inhibition. The in-vitro studies should document whether the BLI itself has any antibacterial activity at clinically achievable plasma concentrations.

The BL/BLI combination should be tested against strains that are resistant to the BL alone for which the mechanisms of resistance have been determined. The investigations should suffice to support recommendations for in vitro testing of the combination using a fixed concentration of the inhibitor or using a fixed ratio of BL to BLI to provide reproducible susceptibility test results. The choice of testing method should be discussed considering the pharmacokinetic-pharmacodynamic (PK-PD) index for the inhibitor. The rationale for the final proposed in vitro susceptibility testing methodology should be considered when selecting dose regimens for non-clinical models of efficacy and the relevance of the method to the posology for clinical use should be justified.

4.1.4. Resistance

Mechanisms of resistance that may be present in organisms for which MICs are unusually high (e.g. at or above the upper end of the MIC distribution curve) or above the interpretive criterion for susceptibility testing (if this has been established for the species being tested) should be investigated. For test antibacterial agents of a new class, in vitro susceptibility studies should assess the potential for cross-resistance to occur between the test agents and licensed agents of other classes. These studies should include strains (any of clinical isolates, laboratory strains or genetically engineered organisms that express specific resistance mechanisms) that demonstrate multi-drug and/or multi-class resistance, including resistance that is mediated via impermeability or efflux pumps if applicable to the test antibacterial agent and the target species. For test antibacterial agents of existing classes, in vitro susceptibility studies should document the extent of cross-resistance within the class.

For previously unlicensed antibacterial agents and for combinations of antibacterial agents or BL/BLI combinations not previously licensed as co-formulated products or recommended for co-administration, the frequency of selection of resistance may be estimated initially by exposing strains of species relevant to the indication(s) sought to drug concentrations below, at or above the MIC. It is recommended that the risk of selecting for resistance is also evaluated in an in vitro pharmacodynamic model using drug concentration profiles that mimic those achieved or predicted in infected patients.

Before or after approval, any information that becomes available to the sponsor on emerging resistance, changing patterns of resistance or new mechanisms of resistance to the antibacterial agent should be notified promptly to EU regulators with a discussion of the possible implications for section 5.1 of the SmPC.

4.1.5. Other in vitro studies

Minimum bactericidal concentrations (MBC) should be determined and time-kill studies should be conducted with relevant species and/or with organisms that express specific mechanisms of resistance.

For some antibacterial agents it may be appropriate to investigate the potential for synergy or antagonism to occur with other agents likely to be co-administered and to examine post-antibiotic effects against certain species.

4.1.6. In vivo studies

If appropriate non-clinical models exist that are relevant to the intended clinical use(s), an evaluation of the efficacy of the test antibacterial agent against the most likely causative pathogens may be informative. Such studies may be very important for supporting efficacy against very rare pathogens (see section 6.4.). It is important that appropriate active controls are used in these studies. Sponsors should also consult the *Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/456046/2015).*

4.2. Interpretive criteria for susceptibility testing

In the EU it is usual that interpretive criteria for susceptibility testing are identified and published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). These criteria may be amended, or additional criteria may be developed (e.g. if an indication is added that requires criteria to be set for additional pathogens or to reflect a new dose regimen), in the post-approval period.

The application dossier should include a justification for the proposed interpretive criteria, which should include reference to the PK-PD analyses used to select the dose regimen(s). Although a relationship between MIC values obtained from baseline pathogens and clinical and microbiological outcomes is not commonly observed, the data should be presented. The CHMP should be updated on progress made towards agreed susceptibility testing interpretive criteria during the procedure and it is expected that the criteria will be finalised before an opinion is reached on the application.

It is not expected that relevant interpretive criteria for susceptibility testing can be identified for antibacterial agents that have been formulated to have only a local antibacterial action. These include products administered via:

- Topical routes (e.g. to skin, mucus membrane, ears and eyes);
- Inhalation (e.g. using nebulisers or other devices);
- Oral administration when the antibacterial agent is expected to exert efficacy only within the gastro-intestinal tract.

5. General considerations for clinical programmes

In clinical trials with antibacterial agents the population of interest and the primary endpoint are not the same for all types of infection. Section 6 provides recommendations for the clinical criteria for patient enrolment, the primary endpoint and the primary analysis in infection site-specific trials, including some exceptions to the general recommendations outlined below.

5.1. Patient selection

The patient selection criteria should maximise the likelihood that patients have the type of bacterial infection under study and minimise enrolment of patients with infections that are likely to resolve rapidly without antibacterial therapy. Patients may be enrolled into efficacy trials based on clinical signs and symptoms with or without the results of relevant imaging studies and microbiological findings, which may include rapid diagnostic tests (RDTs) and rapid susceptibility testing.

5.1.1. Clinical evidence of infection at enrolment

It is recommended that patients are categorised according to the extent and/or severity of the infection to be treated using any available and widely recommended scoring schemes. Consideration should be given to stratification at randomisation by disease factors known to be very important for influencing outcomes.

Patients should demonstrate a protocol-defined minimum number of signs and symptoms associated with an ongoing acute infectious process. Considerations for the selection criteria include the fact that fever and/or an elevated white blood cell (WBC) counts may be absent in the elderly, in other patient groups (e.g. diabetics) or for other reasons (such as recent use of antipyretic agents) despite other evidence of ongoing bacterial infection and that hypothermia and/or a low WBC may occur in very severe infections.

If specialised or experimental imaging studies are used for patient selection based on interpretation by trial site staff, it is recommended that there is a retrospective review by a panel of independent experts who are unaware of treatment assignment and whose readings are used to determine patient eligibility for pre-defined analysis populations.

5.1.2. Microbiological evidence of infection at enrolment

Microscopy and staining of suitable specimens from normally non-sterile sites may suggest the presence of certain organisms when organisms have a characteristic morphology (e.g. *Neisseria gonorrhoeae*) and may increase the rate of positive cultures obtained. Microscopy of suitable specimens obtained from normally sterile sites may be used to select eligible patients (e.g. for trials in septic arthritis and osteomyelitis).

Rapid diagnostic tests (RDTs) may be used to maximise the proportion of patients enrolled who will have a culture-confirmed pathogen. Protocols should specify which RDTs (e.g. antigen, toxin or nucleic acid detection tests) may be used for patient selection. Due to variations in the sensitivity and/or specificity of tests, it is recommended that the same RDTs are used at all trial sites to avoid the potential that:

i) Sites using very sensitive tests will enrol more patients with low bacterial loads than sites using less sensitive tests, with possible implications for outcomes;

ii) Sites using very specific tests may have much higher rates of patient eligibility for the microbiological intent to treat population (defined as all randomised patients with at least one baseline pathogen that is listed in the protocol as being relevant to the type of infection under study) and the microbiologically evaluable population than sites using less specific tests (see sections 5.2.4 and 5.5.1).

If available, rapid susceptibility tests may be used to:

i) Exclude patients likely to be infected with pathogens that are insusceptible to study therapies;

ii) Enrich the study population with patients infected with organisms with genes encoding specific mechanisms of resistance or expressing resistance determinants.

The same considerations for test selection and conduct apply as for RDTs.

If an experimental RDT (i.e. one that is not CE-marked and has not been subjected to an appropriately detailed review by another regulatory agency) is used for patient selection purposes all participating laboratories should receive adequate training in using the test. Data on the estimated sensitivity and specificity of experimental RDTs should be included in the clinical trial report.

5.1.3. Prior antibacterial therapy

The selection criteria should set a limit on the duration and/or numbers of doses of prior antibacterial therapy for the infection to be treated in the study. Usually, except for patients who clearly failed to respond to any prior treatment, no more than 24 hours of a potentially active antibacterial regimen, including any peri-operative or per-procedural prophylaxis, should be allowed prior to enrolment. Prior therapy should be restricted to one dose of an agent with a long elimination half-life. It is recommended that prior antibacterial therapy is not allowed in trials of treatment for infections that tend to respond clinically within a few days. In other cases, a limit (e.g. no more than 30% of the total enrolled; after excluding any patients who clearly failed prior treatment) should be set on the proportion who received prior potentially active antibacterial treatment.

5.2. Causative pathogens

5.2.1. Specimen collection

Appropriate specimens for performing RDTs, culture or serology should be obtained at baseline from all patients (i.e. even if culture results are available from earlier samples). If the most relevant samples are obtained during interventions (e.g. during surgery or during an invasive diagnostic procedure), they should be collected within a pre-defined window around the time of randomisation, which should not usually exceed 24 hours before or 12 hours after the first dose of assigned treatment.

5.2.2. Confirmation of causative pathogens by culture

Confirmation of the causative pathogen by culture allows for typing and susceptibility testing to be conducted and should always be attempted. The methods used for primary isolation and routine susceptibility testing at local site laboratories should be standardised. Isolates should be shipped to designated central laboratories for confirmation of isolate identity and susceptibility testing, including determination of MICs of the test antibacterial agent and investigation of possible resistance mechanisms. Central laboratories with appropriate expertise should perform any typing of baseline and post-baseline isolates that is required to differentiate persistent infections and relapses from new infections with the same species.

Central laboratory data should be used for the analyses of outcomes according to baseline pathogens and in vitro susceptibility (MICs of test and control agents). If central laboratory results are missing for individual patients because organisms did not survive shipping or cultures were contaminated, available local laboratory results may be used instead.

5.2.3. Confirmation of causative pathogens by other methods

The use of alternatives to culture to confirm the presence of pathogens or their toxins that mediate disease may be acceptable subject to justification that the proposed test method has high sensitivity

and specificity and that reliance on culture alone may result in under-diagnosis (e.g. when the organism is difficult to culture) or over-diagnosis (e.g. because the disease is caused by a toxin and both toxigenic and non-toxigenic organisms are known to occur). Some examples of acceptable methods include the following:

- Confirmation of invasive pneumococcal infection may be based on a positive urinary antigen detection test;
- Confirmation of species that are causative in atypical pneumonia (i.e. *Legionella spp.*, *Mycoplasma spp.* or *Chamydophila spp*.) may be based on serological studies, which should be conducted in appropriate central laboratories;
- Confirmation of Legionellosis may also be based on a positive urinary antigen detection test;
- Confirmation of the presence of *Clostridium difficile* in stool may be based on toxin detection.

5.2.4. Acceptable causative pathogens

Protocols should list the pathogens that may be considered causative in the type of infection under study. Only those patients with at least one baseline pathogen on the list should be included in the microbiological-ITT and microbiologically evaluable populations (see sections 5.1.2 and 5.5.1).

5.3. Dose regimens

This section is applicable to previously unlicensed antibacterial agents and to previously unlicensed combinations of antibacterial agents or BL/BLIs.

5.3.1. Selection of the test antibacterial dose regimen

In accordance with the *Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/456046/2015)*, clinical dose-finding trials are not required if it is considered that the PK-PD analyses can provide adequate support for the dose regimen(s) selected for pivotal efficacy trials. The duration of therapy that is allowed in clinical efficacy trials may be supported by a combination of treatment guidelines and the pharmacokinetics of the test antibacterial agent (e.g. special considerations may apply to agents with exceptionally long elimination half-lives). The risk of selection of resistance in residual organisms should be considered when selecting dose regimens. If possible, in vitro pharmacodynamic models that mimic human plasma exposures during multiple dose treatment should be used to assess the risk of selection of resistance when selecting dose regimens.

In the case of antibacterial formulations intended to exert a local effect (e.g. topical, inhalational and intra-gut antibacterial activity) it is not currently possible to use PK-PD analyses to select appropriate dose regimens. Therefore, dose-finding clinical trials should be conducted.

If a dose-finding clinical trial is considered necessary, it is recommended that the appropriate infection site-specific guidance provided in section 6 should be followed regarding patient selection criteria and primary endpoints.

5.3.2. Switch from parenteral to oral therapy

If parenteral and oral formulations of the test antibacterial agent are available, patients who meet pre-specified criteria may be switched to oral treatment after a minimum duration of intravenous treatment. If PK data and PK-PD analyses indicate that the probability of target attainment (PTA) is

satisfactory and similar with parenteral and oral dose regimens, trials that allow a switch may support approval of both presentations for treatment of the type(s) of infections studied.

If there is no oral presentation of the test antibacterial agent, it is recommended that trials do not allow a switch to a licensed oral follow-on therapy. If allowing a switch is considered essential for trial feasibility reasons it is recommended that parenteral therapy with the test antibacterial agent is given for at least 5 days regardless of the type of infection under study. The oral follow-on agent should be of the same class as the test agent whenever possible.

5.3.3. Co-administration of the test antibacterial agent with licensed agents

If the spectrum of antibacterial activity of the test agent does not cover all the major pathogenic species relevant to the infection under study, the protocol should specify any additional agents (including the dose regimens) that must or may be co-administered. Any additional agent should have a spectrum that does not overlap or minimally overlaps with that of the test antibacterial agent (e.g. it should cover only Gram-positive organisms if the test agent covers only Gram-negative organisms). If all patients are to commence treatment with combination therapy, the protocol must specify if/when and under what circumstances patients may revert to monotherapy with the test antibacterial agent. Similarly, if addition or substitution of other antibacterial agents is permitted when culture and susceptibility test results become available, the protocol must specify the criteria to be met and the agents that may be used.

It may sometimes be necessary to add a second agent that overlaps in spectrum with the test agent (e.g. to cover some types of infections due to *P. aeruginosa* in line with clinical practice). If possible, the efficacy of the test antibacterial agent against the species covered by the additional agent should be assessed alone in another type of infection for which monotherapy is considered sufficient. Furthermore, the nonclinical evidence and PK-PD analyses should provide support for the efficacy of the test antibacterial agent alone if used to treat the species in question.

5.4. Efficacy trial designs

5.4.1. Non-inferiority trials

Trial designs and non-inferiority margins

A non-inferiority trial design is acceptable when there is a licensed treatment for the infection under study for which the magnitude of the treatment effect over placebo is known or can be estimated from existing data.

The selection of the non-inferiority margin should consider the need to indirectly demonstrate superiority of the test agent over no antibacterial therapy (i.e. the no-treatment effect) for the infection under study and how large a difference between the test and reference treatments could be considered clinically important. Historical data may be used to estimate the no-treatment effect but the relevance of these data to a prospective randomised trial design reflecting contemporary medical practise may be questionable. For example, general patient management may have changed to such an extent since the historical data were obtained that constancy cannot be assumed.

Section 6.1 provides guidance on the design of trials to support indications for treatment of common site-specific infections, including recommendations for non-inferiority margins. Alternative non-inferiority margins may be acceptable if adequately justified (e.g. based on different methods for estimating the no-treatment effect, which may include approaches based on pharmacometrics).

In the cases below, it is preferable to conduct randomised controlled trials even if it is not feasible to recruit the number of patients that would be required for a sample size calculated with standard levels of statistical power, nominal significance levels and a justified non-inferiority margin:

i) Treatment of infections due to specific pathogens in patients with limited treatment options (see section 6.3);

ii) Treatment of infections and/or pathogens that are rare (see section 6.4), including cases in which the test antibacterial agent has a very limited spectrum of activity confined to species or genera that are uncommon or rare.

The sample size may be driven primarily by feasibility and an estimate of accrual rates over a reasonable time frame (e.g. not exceeding approximately 2 years). There should be a justification for the trade-off proposed between statistical power, nominal significance levels and the non-inferiority margin. To illustrate the operating characteristics of the proposed trial, the NI margin, or precision of the estimated treatment effect, with 2-sided 5% significance level and the nominal significance level (Type I error) for a fully justifiable NI margin should be discussed in the trial protocol or analysis plan.

Comparative regimens

The choice of active comparative regimens, including the antibacterial agent(s), dose, dose interval and duration, is critical to the overall validity of non-inferiority trials. The regimen selected should be considered one of the best available treatments based on clinical trials, medical opinion, infection type-specific treatment guidelines and the anticipated prevalence of resistance to the comparative agent(s) at the trial sites. The use of a comparative regimen that includes an antibacterial agent and/or a dose regimen that is not licensed in some or all EU Member States may sometimes be acceptable if adequately justified.

It is generally recommended that a single comparative regimen, which may comprise more than one antibacterial agent, is used. Substitutions of antibacterial agent(s) in the comparative regimen may be allowed when culture and susceptibility testing are available based on protocol-specified criteria. The alternative agents that may be used should be listed in the protocol. If a switch from parenteral to oral therapy is considered necessary, the same criteria to be met for switching should apply to the test and comparative regimens.

5.4.2. Superiority trials

Section 6 provides guidance on infection site-specific indications for which a demonstration of superiority against placebo or against an active treatment would be required. In general, a superiority trial may be required when i) there is no licensed treatment or standard of care treatment for the infection under study or ii) the treatment effect of any licensed treatment or standard of care treatment is unknown or is considered questionable (e.g. the treatment effect has not been assessed in an adequately designed placebo-controlled trial that would meet current standards).

A demonstration of superiority over placebo should be possible and is desirable when the infection under study is usually self-limiting, is of short duration and the risk of sequelae is low. Patients randomised to placebo may be declared failures and may receive rescue therapy with an antibacterial agent if there is no improvement or worsening of protocol-specified signs and symptoms after a fixed number of days. One alternative to use of a placebo control group may be to randomise patients to a range of doses of the test agent, including one or more that is predicted (e.g. based on PK-PD analyses) likely to be insufficient.

Depending on the type of infection to be treated, it may not be possible to demonstrate superiority for the test agent based on clinical microbiological outcomes at a post-therapy test of cure (TOC) visit. There may be situations in which a demonstration of superiority based on other endpoints (e.g. time to specific clinical response measures or improvements in clinical parameters, such as lung function) could suffice. If one of these alternative endpoints is designated as primary, it is important that patients are still followed to the TOC visit.

5.4.3. Blinding

Pivotal efficacy trials should usually be double-blind. If a double-blind design is not feasible every effort must be made to ensure that the physicians who assess clinical outcomes and report adverse events remain unaware of individual patient treatment assignments. In these settings, consideration should be given to use of an independent outcome adjudication committee that is blinded to treatment assignments.

5.4.4. Withdrawal from assigned therapy

It is generally recommended that protocols should not require that patients are withdrawn from assigned therapy based on culture and susceptibility testing unless there is evidence of lack of improvement or there are reasons to consider that the patient could be at significant risk if treatment is unchanged. Whenever patients are withdrawn from therapy due to failure to improve or deterioration, there should be detailed documentation of the clinical and microbiological findings on the day of withdrawal.

5.4.5. Assessment of outcomes

The timing of the on-therapy, end of therapy (EOT), TOC and all other trial visits at which patient progress and/or outcomes are to be assessed should be selected in accordance with the type of infection under study and the PK properties of the test and comparative antibacterial agents. The TOC visit should occur within a pre-defined window of days after randomisation. The window should be selected so that the TOC visit occurs at a minimum number of days post-therapy considering the maximum possible duration of active treatment allowed in the protocol and the elimination half-lives of the test and comparative antibacterial agents. The timing of the TOC visit should also consider the possibility that for some types of infection cure rates may increase over time regardless of antibacterial therapy, which could affect the sensitivity of non-inferiority trials and reduce the chance of success in superiority trials.

In trials that allow a switch from parenteral to oral therapy (see section 5.3.2), patient outcomes at the end of parenteral therapy will reflect a combination of those cured by parenteral therapy alone, those who have improved such that they meet the protocol-defined criteria allowing a switch to oral therapy and those who failed on parenteral therapy. Later failures on treatment and post-treatment relapses will not be captured at this visit. Therefore, while outcomes at end of parenteral therapy should be secondary endpoints, the primary assessment of outcomes in trials that allow a switch should occur at a TOC visit.

Further follow-up (e.g. timed from randomisation to occur at least 1-2 weeks after TOC) is desirable, especially when the type of infection under study is associated with a substantial relapse rate.

At the TOC visit the clinical outcome should be categorised as cure, failure or indeterminate. Cure may be defined as i) complete resolution of clinical signs and symptoms and/or ii) sufficient improvement or

return to baseline status such that no further antibacterial therapy is required for the index infection. The protocol should specify the criteria that should be met to determine cure.

Microbiological documentation (as opposed to presumption based on the clinical response) of eradication or persistence of causative organisms should be attempted whenever feasible. Documentation of the microbiological outcome is required when treating urinary tract infections and uncomplicated gonorrhoea.

5.5. Analyses of efficacy

5.5.1. Primary analyses

In trials that have a clinical primary endpoint, the primary analysis should be conducted in the all randomised (ITT) population.

In trials that have a microbiological primary endpoint or a combined clinical and microbiological response primary endpoint (i.e. in which the patient must meet both clinical and microbiological outcome criteria to be considered a treatment success), the primary analysis should be conducted in the microbiological-ITT population (see sections 5.1.2 and 5.2.4). In non-inferiority trials, patients in test or control treatment groups with any baseline pathogen that is resistant to the comparative regimen should be removed from the microbiological-ITT population before unblinding of the database to treatment assignment.

In trials with antibacterial agents, patients may be withdrawn from the assigned treatment due to failure or due to adverse events (including death from the infection), may receive non-study antibacterial agents before the TOC visit and may receive other interventions that can affect outcome (such as surgical procedures and administration of concomitant medications that can affect signs and symptoms used to assess responses). Adequate sensitivity analyses should be planned to assess the effects of such events on the conclusions from the trial.

If the requirements for the primary analysis differ between regulatory authorities, protocols and statistical analysis plans should pre-define separate strategies for the statistical analyses (e.g. prioritisation of endpoints, time points or statistical technique) to meet the various requirements.

5.5.2. Secondary analyses

Secondary analyses should be conducted in:

- All randomised patients who received at least one dose of assigned treatment and the subset of this population with a relevant pathogen);
- The clinically evaluable population, including patients who meet the inclusion criteria and have adhered to the protocol and assigned treatment, and the microbiologically evaluable population (subset of the clinically evaluable population with a relevant pathogen; see section 5.2.4);
- Other pre-defined sub-populations that may be of interest.

Other secondary analyses should be conducted as appropriate to the trial design and the type of infection under study. These may include:

- Clinical and microbiological outcomes at each trial visit at which outcomes are to be assessed;
- Microbiological outcomes by pathogen (with and without excluding pathogens resistant to the comparator) and by patient subgroups with single or multiple pathogens;

- Clinical and microbiological outcomes by relevant patient sub-groups (e.g. by geographical region, age, gender, infection type and/or severity, other host factors, surgical intervention and other factors relating to patient management);
- Analyses of other measures of outcome, such as all-cause mortality;
- Clinical and microbiological outcomes for patient subsets that did and did not receive potentially active prior therapy, including prior failures (see section 5.1.3).

5.5.3. Investigation of treatment failures

Clinical trial reports should include an integrated analysis of treatment failures. These analyses should explore whether individual and combinations of host, pathogen and disease factors occur at higher rates in those who fail compared to those who do not fail. Any differences between treatment groups in factors associated with a higher risk of failure should be discussed.

An exposure-response analysis should be conducted as recommended in the *Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/456046/2015).* Also, predicted plasma exposures in those who do and do not fail should be viewed against any dose adjustments that were applied during the trials (e.g. for renal impairment) to evaluate whether these were appropriate.

Protocols should require that samples for culture are obtained whenever feasible from patients at the time of failure on-therapy or when failure is determined due to relapse or reinfection after completion of therapy. Isolates obtained from these patients should be fully characterised and, whenever possible, should be investigated to determine whether they were present at baseline (e.g. by genotyping methods). Changes in susceptibility of pathogens between baseline and the time of failure and/or appearance of pathogens not present at baseline that are resistant to the assigned treatment should be documented and presented.

5.6. Single pivotal trials

In general, if a single trial is proposed to support an indication for use, consideration should be given to the *Points to consider on application with 1. Meta-analyses 2. One pivotal study* (CPMP/EWP/2330/99). Infection site-specific indications for use may be supported by single pivotal studies with standard levels of alpha (i.e. 2-sided 0.05) under certain circumstances. For example:

i) When applications include the following combinations of infection site-specific trials that meet the requirements set out in section 6:

- Single trials in each of complicated urinary tract infections (cUTI) and uncomplicated urinary tract infection (uUTI);
- Single trials in either cUTI or uUTI and a single trial in uncomplicated gonorrhoea;
- Single trials in each of community-acquired pneumonia (CAP) and hospital acquired and/or ventilator-associated pneumonia (HAP and/or VAP).

Applications based on other combinations of single infection site-specific trials may be acceptable subject to adequate justification that evidence of efficacy at one body site is relevant to efficacy at another body site.

ii) When the test antibacterial agent addresses an unmet need. In these cases, if the CHMP considers that the total evidence (nonclinical and clinical) is sufficient to support a pathogen-specific indication in

patients with limited treatment options, additional infection-site specific indications may be granted based on a single pivotal trial per indication provided they meet the requirements set out in section 6.

5.7. Combinations of licensed beta-lactam agents with beta-lactamase inhibitors

There are some specific considerations for trials required to support infection site-specific indications when a licensed BL is to be used with a BLI with which it has not previously been co-formulated in a licensed product or licensed for co-administration. The BLI may be previously unlicensed or licensed for use in combination with other BLs. In all cases it is essential that the clinical microbiology studies and the PK-PD analyses provide robust evidence that using the BL and BLI together at the recommended doses can be expected to maintain the efficacy of the BL against pathogens expressing beta-lactamases within the inhibitory range of the BLI. See section 4.1.3.

Regardless of whether the BL/BLI is expected to address an unmet need, it is recommended that at least one randomised controlled trial is conducted in patients with one type of site-specific infection already approved for the BL alone. It is not expected that the trial will enrol sufficient organisms that are resistant to the BL but susceptible to the BL/BLI to demonstrate the clinical benefit of adding the BLI and/or substantiate the adequacy of the BLI dose regimen. The trial will provide important comparative safety data and patient PK data, which can be used to update the population PK model and re-estimate the PTA to support the BLI dose regimen.

The trial would not have to meet the usual requirements for non-inferiority margins set out in section 6 to support an infection site-specific indication. Nevertheless, clinical outcomes should be determined and reported in the usual way. Considerations for the size of the trial may include its contribution to the total safety database and the need to obtain sufficient PK data to adequately assess inter-patient variability.

If the total daily dose of the BL exceeds the maximum daily dose approved (i.e. excluding situations in which the BL dose regimen is within the approved total daily dose but is used with modified frequency and/or infusion time) and/or the BLI is previously unlicensed, it may be necessary to adjust the trial size and/or conduct additional trials to provide an adequate safety database.

On a case by case basis, indications for use of the BL alone other than the one selected for the clinical trial may be applied to the BL/BLI based on relevant pharmacokinetic data. For example, if the BL is approved for treating CAP and/or HAP/VAP, a study of BL and BLI concentrations in lung epithelial lining fluid (ELF) in healthy subjects and/or infected patients could be conducted. The study should generate sufficient data points to be able to estimate the plasma/ELF ratios for unbound BL and BLI concentrations. If a PDT has been established for ELF, this should be used to estimate the PTA.

6. Clinical studies to support specific indications

6.1. Non-inferiority trials to support infection site-specific indications

This section considers trials that aim to demonstrate non-inferiority of the test regimen to an appropriate reference regimen to support infection type-specific indications. The following sections should be read in conjunction with the general guidance provided in section 5.

6.1.1. Acute bacterial skin and skin structure infections (ABSSSI)

Patient selection: Acceptable types of infection for study include cellulitis, erysipelas, wound infections (traumatic or post-surgical) and major abscesses. If patients with infected burns are included, limits

should be placed on the burn area and thickness. A minimum area of infection (e.g. area of erythema, wound dimensions) or estimated size of abscess should be stated in the protocol. The proportion of patients enrolled with abscesses should be limited (e.g. up to approximately 30% of the total patients) and the protocol should specify a window (e.g. 24-48 h) around the time of randomisation within which surgical or percutaneous drainage should occur if this is necessary. Patients with suspected or confirmed osteomyelitis or septic arthritis and those with severe necrotising infections should be excluded. It is preferred that separate trials are conducted to support treatment of diabetic foot infections.

Primary analysis: Clinical outcome in the ITT population at the TOC visit using a non-inferiority margin of -10%.

6.1.2. Community-acquired pneumonia (CAP)

Patient selection: A chest radiograph obtained within 48 hours prior to enrolment should show new infiltrates in a lobar or multilobar distribution. Patients should demonstrate a protocol-defined minimum number (e.g. at least 3-4) of new onset cough, purulent sputum, dyspnoea, tachypnoea and pleuritic chest pain as well as at least one characteristic finding on percussion and/or auscultation associated with consolidation. Patients suspected of having pneumonia that is secondary to aspiration or a specific obstruction (e.g. malignancy and inhaled foreign body) and those with cystic fibrosis should not be enrolled.

Patients should be assigned to a class within the Patient Outcomes Research Team (PORT) system to determine eligibility for the trial and to allow stratification at randomisation. When treatment is to be initiated by the intravenous route patients should have a minimum PORT score of III and at least 25% should have a score >III. It is acceptable to exclude patients with a score of V who require immediate ICU admission. When treatment is to be initiated by the oral route patients should have PORT scores of II or III and at least 50% should have a score of III. The baseline condition of patients may also be described based on other scoring schemes (e.g. CURB-65 scores). Consideration should be given to stratification according to age < 65 years and ≥ 65 years.

Primary analysis: Clinical outcome in the ITT population at the TOC visit using a non-inferiority margin of -10%.

6.1.3. Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)

Patient selection: Trials may be confined to HAP or VAP. A convincing demonstration of efficacy in VAP could support an indication that includes HAP but not vice versa. In trials that include patients with HAP or VAP, ~30% of patients as a minimum should have VAP.

Patients with HAP should have been hospitalised for at least 48 hours before onset of the first signs or symptoms or these should occur within 7 days of hospital discharge. Patients should present with a minimum number of clinical features (as for CAP but signs on examination and auscultation are not required) plus a new infiltrate on chest radiograph. Patients who have only been assessed in an emergency care setting should be excluded.

Patients with VAP should have received mechanical ventilation via an endotracheal or nasotracheal tube for at least 48 hours (i.e. not including patients receiving only positive pressure ventilation without intubation). Additional selection criteria may include a minimum Clinical Pulmonary Infection Score (CPIS) of ~6, partial pressure of oxygen < 60 mm Hg in arterial blood (on room air), oxygen saturation < 90% (on room air) and worsening of the PaO2/FiO2 ratio. Baseline lower and upper limits

in other scoring systems may be applied, such as the sequential organ failure assessment (SOFA) score, the multiple organ dysfunction score (MODS) and the acute physiology and chronic health evaluation score (APACHE II).

Primary analysis: Clinical outcome in the ITT population at the TOC visit using a non-inferiority margin of -12.5%.

6.1.4. Complicated intra-abdominal infection (cIAI)

Patient selection: Evidence of cIAI should be documented during laparotomy, laparoscopy or percutaneous drainage. Suitable diagnoses include (but are not limited to) perforations of the gall bladder, a diverticulum or the appendix, established peritonitis secondary to trauma and abscesses associated with any of these conditions. The proportion of patients with infections originating in the appendix should not exceed 50% and stratification at randomisation according to appendix and non-appendix associated cIAI is recommended. Patients with perforations of the stomach and small intestine should not be enrolled unless there is evidence of an established secondary infectious process within the abdominal cavity.

Primary analysis: Clinical outcome in the microbiological-ITT population at the TOC visit using a non-inferiority margin of -10.

6.1.5. Complicated urinary tract infections (cUTI) and acute pyelonephritis (AP)

Patient selection: Patients should have at least one of indwelling urethral (i.e. not percutaneous) catheter, urinary retention, urinary obstruction or neurogenic bladder. Patients with ileal loops or vesico-ureteric reflux and patients with signs and symptoms suggesting prostatitis should not be enrolled. If patients with AP are to be enrolled in the same study as patients with cUTI it is recommended that at least 30% of the total enrolled should have cUTI and at least 30% should have AP. Protocols should require the presence of a minimum number of signs and/or symptoms compatible with an ongoing infectious process in the urinary tract such as flank or pelvic pain, tenderness in the costo-verterbral area, dysuria, frequency or urgency.

Patients may be enrolled before microbiological culture results are available based on documented pyuria ($\geq$ 10 WBCs/mm3) in suitable fresh urine samples. Specimens from urine collection bags are not acceptable. If a mid-stream or clean catch specimen is not possible it is preferred that patients with indwelling catheters have the catheter replaced before the sample is obtained.

It is essential that the culture methods allow for an estimation of the bacterial load (expressed in colony forming units per millilitre [CFU/mL]) in urine. Patients eligible for the microbiological-ITT population should have $> 1 \times 10^5$ CFU/mL of a single, or no more than two relevant pathogens in the baseline urine sample. Pathogens should be identified to species level.

Primary analysis: Combined clinical and microbiological (defined as $< 1 \times 10^3$ CFU/mL in urine obtained at TOC visit) success rate (i.e. in which the patient must meet both clinical and microbiological outcome criteria to be considered a treatment success) in the microbiological-ITT population at TOC using a non-inferiority margin of -10%.

6.1.6. Uncomplicated urinary tract infections (uUTI)

Patient selection: Female patients with acute cystitis should have a minimum number of symptoms such as frequency, urgency and dysuria. Patients may be enrolled before microbiological culture results are available based on documented pyuria (≥ 10 WBCs/mm3) in a mid-stream specimen.

Patients eligible for the microbiological-MITT population should have > 1 x 10^5 CFU/mL of a single relevant pathogen in the baseline urine sample. Pathogens should be identified to species level in clinical trials.

Primary analysis: Combined clinical and microbiological success (defined as for cUTI) in the microbiological-ITT population at TOC using a non-inferiority margin of -10%.

6.1.7. Uncomplicated gonorrhoea

Patient selection: Patients should have evidence of gonococcal cervicitis or urethritis at enrolment based on finding characteristic Gram-negative diplococci in urethral or cervical pus or swabs. If patients with evidence of rectal or pharyngeal gonorrhoea are enrolled, alone or in conjunction with urethral or cervical infection, it is recommended that there is stratification by infection site at randomisation. The TOC visit may be conducted within one week (e.g. 3-4 days) after treatment to maximise the proportion with documented eradication. A late follow-up visit should be planned to capture late relapses, re-infections or new infections.

Patients eligible for the microbiological-MITT population should have a positive culture result for *N. gonorrhoeae*.

Primary analysis: Microbiological eradication in the microbiological-ITT population at TOC using a non-inferiority margin of -10%.

6.2. Superiority trials to support infection site-specific indications

This section considers trials that aim to demonstrate superiority of the test regimen over placebo or over an active comparator to support infection type-specific indications.

6.2.1. Acute otitis media (AOM)

Trials in AOM media are feasible only in children. Sponsors should consult specific CHMP guidance.

6.2.2. Acute bacterial sinusitis (ABS)

There is a need for further clinical data in adequately diagnosed and well-characterised patient populations before guidance can be provided on the requirements for clinical trials to support treatment of ABS.

Meanwhile, it is recommended that at least one trial should be conducted in patients with maxillary sinusitis diagnosed by imaging studies who undergo microbiological documentation by culture of samples obtained by antral puncture. The primary analysis should be conducted in patients with a relevant baseline pathogen (the microbiological-ITT population) and the measurable outcome of interest is resolution of clinical signs and symptoms at a TOC visit.

6.2.3. Acute bacterial exacerbations of chronic bronchitis (ABECB) or non-cystic fibrosis bronchiectasis (NCFBE)

Eligible patients should have exacerbations requiring antibacterial therapy that meet a set of criteria widely-recommended by appropriate professional bodies. The primary analysis should be based on clinical success in the ITT population. Clinical success may be defined as resolution of the signs and symptoms of the exacerbation and/or return to baseline status.

6.2.4. Superficial skin infections

The following considerations for trials in the treatment of superficial skin infections are applicable to antibacterial agents formulated for systemic administration or for topical administration to skin. Generally, it is expected that trials will be designed to show superiority over a placebo.

Separate trials should be conducted in specific types of infection, such as impetigo, superficial wound infections and infected dermatoses. Moreover, due to differences in the pathogenesis and the treatment of various dermatoses, it is recommended that conditions such as infected atopic eczema and infected psoriasis should be studied in separate trials.

There should be appropriate limitations placed on the use of adjunctive therapies, including the use of antiseptics and topical corticosteroids, depending on the underlying condition.

The primary endpoint should usually be resolution of signs and symptoms of infection at a TOC visit in the microbiological-ITT population. Time to resolution of the infection, which could be assessed at end of treatment, may be an acceptable primary endpoint when treating infections with high spontaneous resolution rates, such as infected superficial wounds. It is recommended that pathogens recovered at baseline and from infections that have not resolved by end of treatment or which relapse should be investigated for genes encoding major toxins and/or for toxin production.

6.3. Pathogen-specific indications in patients with limited treatment options

This section considers clinical programmes for test antibacterial agents or combinations expected to be clinically active against multidrug-resistant organisms for which there are limited licensed treatment options. Subject to establishing eligibility, this section may be applicable to:

- Unlicensed antibacterial agents;
- Combinations of antibacterial agents, one or both of which may be previously unlicensed, to be co-formulated or co-administered;
- Products consisting of an unlicensed BL co-formulated or co-administered with a BLI;
- Products consisting of a licensed BL co-formulated or co-administered with a BLI (in which case section 5.6.2 should be read in conjunction with this section).

6.3.1. Establishing eligibility

<u>In vitro studies</u>

- If the test antibacterial agent is of a new class, in vitro studies should demonstrate that MICs are unaffected or affected to an unimportant extent against species within its spectrum of activity that are resistant to most or all licensed antibacterial agents;

- If the test antibacterial agent is of an existing class, in vitro studies should show no appreciable difference in MICs between organisms that do and do not express resistance to most or all other agents of the same class;
- In both cases it is important that MICs are determined against organisms that demonstrate resistance to multiple classes of antibacterial agents (see section 4.1.4).

PK considerations and PK-PD analyses

There may be instances in which the PK properties of the test antibacterial agent indicate that a pathogen-specific indication cannot be granted without qualification by site of infection. For example, if the spectrum of activity includes multidrug-resistant Gram-negative organisms but there is insufficient distribution of the test antibacterial agent or the BLI into urine or ELF to support an expectation of clinical efficacy in urinary tract or nosocomial lung infections, respectively.

The PK-PD analyses are critically important to support a conclusion that the clinical dose regimen is sufficient to treat the target multidrug-resistant organisms. It is essential that PK data from infected patients enrolled in clinical efficacy trials are used to update the population PK model and re-estimate the PTA to substantiate the adequacy of the proposed dose regimen in the application dossier. The *Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products (EMA/CHMP/594085/2015)* should be consulted.

Multiple agents that address the same target multidrug-resistant organisms

As new antibacterial products are approved it is possible that some types of multidrug resistance will no longer be considered to constitute an unmet need because a range of treatments that address the same problematic resistant organisms has become available. Therefore, the eligibility of an antibacterial product for a pathogen-specific indication in patients with limited treatment options should be discussed before embarking on clinical efficacy trials.

6.3.2. Clinical trials

It is recommended that at least one randomised comparative trial is conducted. Whenever possible each trial should be conducted in a single type of infection that is appropriate to the spectrum of activity and PK of the test antibacterial product. If the spectrum of activity of the test agent is confined to uncommon or rare pathogen(s), it may be justifiable to enrol patients with infections at different body sites where the pathogen(s) is/are particularly likely to be causative (see also section 6.4). In either case, the guidance on patient selection provided in section 6.1 that is relevant to the type(s) of infection(s) selected for study should be followed.

Whenever possible, the site-specific infection(s) selected for study should enable the test antibacterial agent to be evaluated as monotherapy against species within its antibacterial spectrum of activity.

To enable use of a single comparative regimen, trials may enrol a typical patient population with the selected type of infection for study, i.e. without enrichment for the target multidrug-resistant pathogens for the test agent. However, if there is a licensed comparative agent available that would cover the target multidrug-resistant organisms for the test antibacterial agent, the trial could be enriched for patients infected with such organisms (e.g. by selecting trial sites where such organisms are known to occur and/or using RDTs for patient selection purposes).

If the trial is intended to support only a pathogen-specific indication in patients with limited treatment options, it does not need to comply with the guidance on non-inferiority margins provided in section 6.1. The statistical issues discussed in section 5.4.1 are applicable and should be considered.

If the trial is intended to support a standard infection site-specific indication (i.e. in addition to a pathogen-specific indication confined to patients with limited treatment options), the guidance provided in section 6.1 on the primary analysis should be followed and the recommended non-inferiority margin for the type of infection under study must be met.

6.4. Rare pathogens and rare infections

For very rare pathogens and infections (e.g. anthrax and listeriosis), it may not be feasible to conduct a clinical trial. In these cases, it may be possible to obtain an indication for use based on in vitro data, efficacy in nonclinical models, human PK data and any relevant clinical experience (e.g. for inhalational anthrax a demonstration of efficacy in one or more types of pneumonia would be supportive).

When it is possible to obtain limited clinical efficacy data the following considerations apply:

- For uncommon or rare infections (e.g.as osteomyelitis or infective endocarditis) or pathogens the considerations stated in section 5.4.1 are applicable;
- For some uncommon or rare pathogens, it may be justifiable to conduct a trial that enrols patients with infections at different body sites where the pathogen(s) is/are particularly likely to be causative. This consideration also applies when the test antibacterial agent has a very limited spectrum of antibacterial activity. See sections 5.4.1 and 6.3;
- For relatively rare pathogens that can cause common types of infections it may be possible to obtain some clinical efficacy data from patient subsets enrolled into infection site-specific randomised controlled trials (e.g. community-acquired pneumonia due to Legionella spp.).

In each of the situations described above, the total nonclinical and clinical data required to support an indication for use must be addressed on a case by case basis.

6.5. Other infections

6.5.1. Bacteraemia

Non-pathogen-specific: It may be possible to accumulate sufficient clinical evidence from trials and/or routine clinical use to support use of an antibacterial agent to treat patients with bacteraemia that occurs in association with, or is suspected to be associated with, the licensed indication(s). For example, an endorsement for use in the licensed indication(s) regardless of bacteraemia may be possible when the antibacterial agent has been evaluated in several infection site-specific clinical trials and data indicate that efficacy is broadly similar between bacteraemic and non-bacteraemic subsets. Generally, it would be expected that data are available for 50 or more bacteraemic patients.

Pathogen-specific: It is not considered that an indication for treatment of bacteraemia can be substantiated by a trial that enrols patients with bacteraemia due to a specific pathogen regardless of the primary focus of infection. Such trials are not recommended because i) most patients will be treated for a site-specific infection, whether known or unknown, with associated bacteraemia and the outcome will be related to source control and ii) the trial will not be designed or powered to assess efficacy in sub-groups defined by primary foci or unknown source.

6.5.2. Eradication of carriage

Trials with a microbiological primary endpoint

A primary endpoint based on the reduction or eradication of a pathogen from a specified body site is

not acceptable unless it has been soundly established that the microbiological effect results in a clinically important benefit, such as a reduction in the rate of post-procedure infections. The evidence to support a link between microbiological effect and clinical benefit for any one type of usage (e.g. eradication of one or more pathogenic species from a specific body site) should come from well-conducted clinical trials with other antibacterial agents reported in the literature.

If the evidence is considered acceptable, test antibacterial agents may be approved for the same usage based on randomised clinical trials with a primary microbiological endpoint. These trials should demonstrate superiority of the test agent over placebo unless eradication of carriage is the established standard of care in the patient population under study, in which case trials may be designed to show non-inferiority compared to an active control.

Examples in which studies with primary microbiological endpoints could be acceptable include:

- Eradication of nasopharyngeal carriage of meningococci from contacts of cases of invasive meningococcal infections;
- Eradication of S. pyogenes to reduce the risk of post-streptococcal syndromes (e.g. rheumatic fever and glomerulonephritis);
- Eradication of S. aureus carriage at some body sites (such as the anterior nares) prior to specific types of surgical procedures to reduce the rate of post-operative infections.

It is particularly important that detailed information is available on the microbiological methods used to sample treated sites and recover any residual live organisms in prior and prospective trials. Sampling and culture methods have variable detection limits so that no growth from a specimen does not necessarily mean that there are no live organisms remaining. Other detection methods, such as PCR, cannot differentiate live from dead organisms and data obtained from these methods should not be used for the primary assessment of efficacy.

Trials with a clinical primary endpoint

If evidence to support a link between microbiological effect and clinical benefit for any one type of usage is lacking or is considered inadequate, the clinical benefit of achieving microbiological eradication with test antibacterial agents should be demonstrated.

6.5.3. Oral treatment to exert an action within the gut

The systemic absorption of antibacterial agents intended for these uses should be adequately characterised using the formulation to be used in clinical efficacy trials. In these types of indications PK-PD analyses do not assist in predicting an effective dose and clinical dose-finding trials are required. Human challenge studies may be appropriate for dose regimen selection for travellers' diarrhoea.

Treatment of C. difficile associated diarrhoea

Eligible patients should have documented changes in bowel habit within a pre-defined pre-study period accompanied by detection of toxin (A or B) in stools. Diarrhoea should be defined by number of unformed stools (≥3) and/or volume of liquid stool within a 24-hour period. Patients should be categorised by baseline *C. difficile* infection (CDI) severity index. It may be appropriate to stratify patients by age (≤65 and >65 years) and number of prior relapses.

The primary efficacy endpoint should be the cure rate using a definition of cure that encompasses resolution of diarrhoea (using maximum number of stools per day and stool form criteria) at a TOC visit that should be timed to occur at least 48 hours after the last dose of study therapy. Absence of toxin in stools is not required for patients to be considered cured but the presence of toxin should be

documented and should be considered when comparing relapse rates between treatment groups. The primary analysis should demonstrate non-inferiority of the test agent compared to a licensed agent for cure rate at TOC in the ITT population using a non-inferiority margin of -10%. There should be a late follow-up visit at approximately 40 days post-randomisation to document sustained cures and early clinical relapse rates.

Treatment of travellers' diarrhoea

In clinical efficacy trials, eligible subjects should have an acute onset of diarrhoea within a defined number of days before enrolment that is characterised by a minimum number of unformed stools per day. Depending on the expected spectrum of activity and mucosal penetration of the test antibacterial agent it may be appropriate to exclude subjects with visible blood in stool and any signs of invasive infection beyond the gut wall.

A baseline (pre-treatment) stool sample should be obtained to identify potential causative pathogens in as many trial subjects as possible using culture and/or RDTs, including tests that can detect bacterial enterotoxins if available. If the test agent is proposed only for treatment of specific pathogens (e.g. enterotoxigenic *E. coli*) the use of appropriate RDTs becomes essential.

The susceptibility of baseline pathogens cannot be based on interpretive criteria applicable to systemic use (if these have been established for the test antibacterial agent). Nevertheless, MICs of the test antibacterial agent for baseline pathogens and for pathogens recovered from subjects who do not respond to treatment should be documented and explored for any relationship to efficacy parameters.

The recommended primary endpoint is time to last unformed stool (TLUS). The test antibacterial regimen should be shown to be superior to placebo in the microbiological-ITT population, i.e. there should be shortening of the TLUS with active treatment by a margin that is considered beneficial in all subjects with evidence of a known causative pathogen. Secondary analyses should be conducted in the ITT population and in subgroups by baseline pathogen.

7. Prophylaxis trials

- If the role of prophylaxis has not been established and is not standard of care under the circumstances proposed for study, a placebo-controlled trial is required to demonstrate superiority of active treatment;
- If the role of antibacterial agents in preventing a specific type of infection in defined clinical circumstances is already established and is standard of care, a comparative study against a licensed therapy is acceptable if a non-inferiority margin can be justified (e.g. using data from prior placebo-controlled trials with the active comparator);
- 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. In vitro pharmacodynamic models may be useful for dose regimen selection in this setting;
- Protocols must provide definitions for cases of the infections to be prevented, including clinical and microbiological criteria to be met as appropriate. If applicable, the criteria suggested for patient selection in treatment trials could be used, with or without some modification. There should also be a time window after the intervention within which cases are captured, depending on whether the trial examines peri-procedural prophylaxis or long-term prophylaxis in subjects with chronic risk factors.

8. Safety

8.1. Size of the safety database

The size of the safety database that could be accepted to support an initial marketing authorisation will depend on factors that include the anticipated benefit, the ability of the antibacterial agent to address an unmet need and the actual safety profile that is observed. The Risk Management Plan should reflect the uncertainties regarding the safety profile due to limited numbers exposed pre-licensure.

8.2. Assessment of safety

The assessment of the safety of an antibacterial agent commonly relies wholly or mainly on comparisons with licensed antibacterial agents. If the test antibacterial agent is of a class for which certain types of adverse reactions may be anticipated, the selection of comparative regimens should consider whether use of agents from the same or different classes as the test antibacterial agent could facilitate the assessment of safety.

Furthermore, 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 (e.g. renal toxicity of the test antibacterial agent may be confused with worsening renal function resulting from a severe urinary tract infection and/or systemic under-perfusion). In such situations, especially if treatment was stopped early because of the event, it may not be possible to discern the relationship between the test agent and the event. Such events should be identified for careful review in the Risk Management Plan.

In most trials patients will be treated for less than two weeks and are unlikely to be followed for more than 4-6 weeks from randomisation. Longer-term safety monitoring may be appropriate if there is a possibility that late onset adverse reactions could occur or to document resolution or persistence of earlier onset adverse reactions (e.g. ototoxicity).

8.3. Presentation of the safety data

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.

9. Summary of product characteristics

In addition to the CHMP guidance, which should be followed, there are some special considerations for presentation of the indications and the critical data, including the microbiological data, in SmPCs for antibacterial agents as follows.

Section 4.1 Therapeutic indications

Standard indications for use should be listed as follows:

{Product name} is indicated for the treatment of the following infections in {adults or adults and adolescents/children from the age of x years} (see section 5.1):

- *(e.g.) Complicated urinary tract infections*

- *(e.g.) Complicated intra-abdominal infections*

There should be a cross-reference to section 5.1 inserted as a routine. Additional cross-references to sections 4.2 and 4.4 may be required in some cases.

Pathogen-specific indications for use should follow any standard indications and, if there are no other indications, should include the age range for use. On occasion, pathogen-specific indications may also be limited by body site (see section 6.3.1). Cross-references should be included. The following format should be used:

{Product name} is {also} indicated for the treatment of infections due to {pathogen – species, genus or general term such as aerobic Gram-negative organisms} in patients with limited treatment options. *See sections 4.2, 4.4 and 5.1.*

In all cases the listed indications must be followed by the following statement:

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

In specific cases it is possible that indications may be restricted by pathogen and/or population due to concerns over safety and/or efficacy.

Section 4.2 Posology and method of administration

If a pathogen-specific indication for use in patients with limited treatment options is listed in section 4.1, section 4.2 should commence with the following statement:

It is recommended that {Product name} should be used to treat patients that have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases.

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 studied.

Section 4.4 Special warnings and precautions for use

Limitations of the clinical data

Standard indications

In most cases, if the guidance in section 6 has been followed, no statement on limitations of the clinical trial database is necessary in section 4.4. On occasion, a warning may be considered necessary if there are concerns regarding efficacy in an important subset of patients (e.g. if there was a higher failure or death rate in bacteraemic patients or patients with renal impairment compared with the rest of the patient population that is unexplained).

For standard indications granted to products comprising a licensed BL and a licensed or unlicensed BLI there should be a statement to advise users that approval was based on the known efficacy of the BL and PK-PD analyses to support the BLI dose.

If the clinical trial data indicate that the test antibacterial agent has poor clinical efficacy against a species/genus relevant to the indications for which clinical efficacy was predicted, this should be stated.

If the test antibacterial agent has been shown not to have acceptable efficacy in an infection type-specific trial this should be stated (e.g. the antibacterial agent is approved for cIAI but was also

evaluated for cUTI and the trial failed to demonstrate non-inferiority) to alert users to the need to consider additional or alternative treatments in patients with co-existing infections.

Pathogen-specific indications in patients with limited treatment options

There should be a statement on the limited clinical trial data and the use of PK-PD analyses to substantiate the adequacy of the dose regimen to cover the target resistant pathogens.

Limitations of the spectrum of antibacterial activity

This section is not routinely required since all antibacterial agents have some limitations to their spectrum of activity, which will be reflected in section 5.1. There should be a statement when the antibacterial agent has a very limited spectrum (e.g. single species or genus) or there is an important omission in its spectrum of high importance to the indications for use (e.g. an antibacterial agent indicated for treatment of ABSSSI has no activity against methicillin-resistant staphylococci).

For BLIs, there should be a statement to convey which beta-lactamase classes fall within the inhibitory spectrum with mention of specific enzymes that are not inhibited if this is appropriate to the indication(s). For example, if the BL/BLI has a pathogen-specific indication relating to infections caused by aerobic Gram-negative organisms it would be important to state whether the BLI inhibits Class B enzymes (metallo-enzymes) and Class D carbapenemases.

Section 5.1 Pharmacodynamic properties

The following recommended format for section 5.1 should be implemented prospectively at the time of first approval of new antibacterial agents, including combinations of licensed BLs with licensed or unlicensed BLIs, or when revising the SmPC for licensed antibacterial agents for which there are sufficient data available to apply the format.

ATC classification

Mechanism of action

This section must be confined to what is known about how the antibacterial agent exerts its effect. For BLIs the type and mechanism of inhibition and the presence or absence of any inherent antibacterial activity should be stated.

Resistance

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 that organisms resistant to antibacterial agents of other drug classes may be resistant to the test antibacterial agent due to mechanisms such as multidrug efflux pumps or impermeability of the outer membrane in Gram-negative species and/or due to co-transference of resistance determinants (e.g. when genes encoding resistance to the test antibacterial agent are linked to genes encoding resistance to other classes of antibacterial agents);
- Lack of effect of specific 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. Data on laboratory-determined rates

for the selection of resistant organisms should not appear unless this occurs at an unusually high rate (e.g. by means of a single mutational event);

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

Antibacterial activity in combination with other antibacterial agents

Lack of antagonism in in vitro studies may be stated here for other antibacterial agents that are very likely to be co-administered with the test antibacterial agent when treating some of the indicated infections. Claims for synergy should not be included.

Susceptibility testing interpretive criteria

If there are EUCAST-recommended interpretive criteria available, those which are applicable to pathogens relevant to the indications will be listed on the EMA website and a link to this part of the website should be included in the SmPC. General interpretive criteria not relevant to the indications will not be listed on the EMA website.

If there are no EUCAST-recommended interpretive criteria, this section should be omitted.

For antibacterial agents or specific formulations that are anticipated to have only a local antibacterial action, this section should appear and should state that there are no interpretive criteria.

PK-PD relationship

This section should describe the major features of the PK-PD relationship, including the PK-PD index. It may be appropriate to mention the PDT(s) for certain important pathogens. Details of estimated PTA should be described in the EPAR and should not be reported in this section.

Clinical efficacy against specific pathogens

The introduction to the first sub-section should state that:

Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to {active substance(s)} 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. Generally, at least 10 patients infected with a listed species or other acceptable grouping (e.g. *A. baumannii* complex) should have been treated with the test antibacterial agent and, as far as can be judged from small denominators, the results should not give cause for concern.

If the pathogens are the same for one or more of the indications, they may be listed under a single joint heading.

Listed organisms should not be qualified by any type of resistance shown. Lack of effect of other resistance mechanisms on the in vitro activity of the test antibacterial agent will be stated under *Resistance* (see above). Very pertinent information on clinical efficacy against organisms resistant to certain other agents may be included in the section on *Clinical trials* (see below).

The introduction to the second sub-section should state that:

Clinical efficacy has not been established against the following pathogens that are relevant to the approved indications although in vitro studies suggest that they would be susceptible to {active substance(s)} in the absence of acquired mechanisms of resistance.

This section will not always be considered appropriate. If it appears, the list of organisms should be confined to those species of most importance to the indications.

The introduction to the third sub-section should state that:

In vitro data indicate that the following species are not susceptible to {active substance(s)}:

Inherently non-susceptible species of relevance to the indications should be stated. For example, if the test antibacterial agent is indicated for treatment of cIAI but has no activity against anaerobes this should be stated. This section is not needed if the test antibacterial agent has a very narrow spectrum of activity that is already explained in the prior sub-sections. This section should not mention acquired resistance to the test antibacterial agent.

Clinical trials

The clinical data from the efficacy studies will be presented in detail in the EPAR. This sub-section in the SmPC should be very short. It should include:

- A summary statement of the clinical efficacy trials relevant to the indications including, if appropriate, a statement on the types of infections treated (e.g. percentages of patients with cUTI or acute pyelonephritis);
- For trials that were designed for statistical testing the results of the primary analysis/es should be presented in a table;
- For trials that were not designed for statistical testing a description of the outcomes should be included;
- Secondary analyses should not usually be included unless the information is of high importance to guide usage (e.g. it may be acceptable to state the all-cause mortality rates in a HAP/VAP trial);
- For antibacterial agents indicated for use against specific pathogens in patients with limited treatment options, if there are clinical efficacy data available for target multidrug-resistant organisms it may sometimes be considered appropriate to mention the data here;
- Trials conducted with BL/BLI combinations where the BL was previously licensed will not be described in section 5.1 unless it was possible to enrol a substantial proportion of patients infected with BL-resistant, BLI-susceptible organisms.

The standard section on the Paediatric population should appear at the end of the section.