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Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections.

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This addendum complements the Guideline on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 2).

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Executive summary

During the revision of the *Guideline on evaluation of medicinal products indicated for treatment of bacterial infections* (CPMP/EWP/558/95 Rev 2) consideration was given to the need to provide recommendations for the design of clinical studies intended to support the approval of specific indications for use. During the consultation period and at a Workshop held before finalisation of the revised Guideline the CHMP was requested to provide detailed advice on several issues including patient selection criteria, primary endpoints, indications for which superiority or non-inferiority study designs would be expected and suggestions for non-inferiority margins. In addition, the CHMP was asked to suggest possible clinical development programmes for new antibacterial agents with very narrow spectra of antibacterial activity and/or with activity against multi-resistant pathogens for which there are very limited treatment options.

This addendum reiterates that the primary assessment of efficacy should usually occur at a test of cure visit that takes place within the same post-randomisation window in each treatment group and is timed to occur when a minimum numbers of days have elapsed from the last possible dose of protocol-defined treatment. With a few exceptions, it is not required that the primary assessment of efficacy should be confined to patients with a confirmed pathogen relevant to the type of infection under study.

Detailed guidance is provided for studies in five types of infection in which it is accepted that indications for use can be supported by a demonstration of non-inferiority of the test agent to an appropriate comparative regimen. Some suggestions for acceptable non-inferiority margins are provided. There is a lack of reliable evidence relevant to current clinical management practices to gauge the likely spontaneous resolution rates in the types of infection under consideration. The suggested non-inferiority margins have been selected on the basis that they are very likely to be sufficient to differentiate the treatment effect of the test agent from no antibacterial therapy and reflect a clinically acceptable difference to an appropriate active comparative regimen.

In indications for which a demonstration of superiority over placebo or an active comparative regimen could be required some suggestions are made for exploring appropriate patient populations and endpoints in the light of the current lack of data to support definitive recommendations for study design. In the specific case of acute otitis media recognition is given to accepting evidence of efficacy from non-inferiority studies subject to restriction of the study population and conduct of appropriate analyses.

Limited evidence of clinical safety and efficacy could be accepted to support an initial approval for the treatment of infections caused by multidrug-resistant (MDR) organisms for which there are few therapeutic options. Assuming that the PK/PD analyses strongly support an expectation of clinical efficacy against problematic MDR pathogens, the clinical programme should take into account the properties of the test antibacterial agent (e.g. spectrum of activity) and the unmet need it may be able to address. For example, for some agents it may be possible to conduct standard non-inferiority studies in infections not due to MDR pathogens and supplement the data with at least some clinical experience in treatment of the target MDR pathogens. Alternatively, if a study is confined to or enriched for the MDR pathogens of interest it could be randomised but not powered for inferential testing. In some cases it could be acceptable to conduct only a non-randomised study and make use of external control data to assist in interpreting the efficacy observed against the MDR pathogens of interest. Sponsors should provide a clear justification for the proposed content of the pre-approval clinical programme and consider how additional efficacy data may be generated in the post-approval period.

Limited guidance is provided regarding the clinical assessment of treatment modalities intended to exert a local antibacterial effect as a result of direct administration to the site of infection. The specific examples covered are the topical treatment of superficial skin infections, inhalational therapy (excluding patients with cystic fibrosis) and oral administration of agents intended to exert an action within the gut.

Finally, consideration is given to the assessment of efficacy to support use of an antibacterial agent for treatment of some other types of infections. These include some infections for which there are special issues to consider regarding study designs and interpretation of results.

1. Introduction (background)

It is essential that this addendum is read in conjunction with CPMP/EWP/558/95 Rev 2 in which broadly applicable general guidance is provided for the development of antibacterial agents.

CPMP/EWP/558/95 Rev 2 covers the general approach to the development of antibacterial agents. In particular, it covers matters such as microbiological investigations, study designs in treatment and prophylaxis, selection of active comparative regimens, general patient characteristics, diagnostic methods, analysis populations, primary endpoints, timing of assessment of outcomes, data analyses, studies in children and the evaluation of safety. It also addresses the development of fixed drug combinations, including antibacterial agents administered with compounds intended to inhibit a bacterial mechanism of resistance (e.g. beta-lactam agents with beta-lactamase inhibitors).

This addendum provides additional guidance on studies and clinical development programmes intended to support specific indications for use. It includes a consideration of the possible content of feasible clinical development programmes for antibacterial agents whose properties preclude their clinical evaluation along well-established lines and/or with potential for clinical activity against specific multi-resistant pathogens.

The focus of this addendum is on studies in adults and is intended to be applicable to the elderly as well as to frail, debilitated and immunocompromised patients. In particular, sponsors are encouraged to investigate pharmacokinetics and to enrol representative samples of elderly and frail patients into clinical studies.

Section 4.2.3. of CPMP/EWP/558/95 Rev 2 provides general advice on studies in children and adolescents and no specific guidance is provided in this Addendum. However some sections (such as 3.3.2. on otitis media) are of particular relevance to paediatric patients.

2. Scope

The addendum provides guidance on clinical data requirements to support:

Indications for which non-inferiority study designs are acceptable

This section considers five commonly sought indications that are supported by studies that demonstrate non-inferiority of the test regimen to an appropriate reference regimen.

Indications for which superiority study designs could be required

This section considers indications for which demonstration of superiority over placebo or over an active intervention is required for a pre-specified clinically relevant parameter(s). It also considers possible exceptions within these indications (e.g. in terms of patient and infection characteristics) for which non-inferiority study designs might be acceptable.

Circumstances in which limited clinical data may be accepted

This section considers the evaluation of efficacy of a test agent against uncommon or rarely encountered infections and pathogens that constitute an unmet clinical need. As an example, suggestions are made for collecting a body of evidence to support likely clinical efficacy against organisms that express specific types of resistance or patterns of multi-resistance that are currently uncommon or rare. Consideration is also given to the development of agents with a very narrow antibacterial spectrum of activity, including circumstances in which it will not be possible to evaluate these agents as monotherapy unless the pathogen can be determined before commencing treatment.

Other indications for use that could be sought

This section includes examples of indications for which some special considerations and/or problems apply to the design of clinical studies and the interpretation of data.

This addendum does not address treatment modalities that do not exert a direct antibacterial effect. For example, agents intended to modify the course of an infectious process wholly or partly via mechanisms other than inhibition of bacterial replication.

3. Main guideline text

3.1. Introduction

The sections that follow are intended to be as broadly applicable as possible. Individual clinical development programmes may need to be tailored to fit specific circumstances.

3.2. Indications for which non-inferiority study designs are acceptable

This section considers five commonly sought indications that are supported by demonstrating non--inferiority of the test regimen to an appropriate reference regimen. The following observations are relevant in each example:

a) Non-inferiority margins

There is a lack of very reliable evidence relevant to current clinical management practices to gauge the likely spontaneous resolution rates (i.e. without specific antibacterial therapy) in the types of infection under consideration. In the examples that follow, the suggestions for appropriate non-inferiority margins are considered very likely to be sufficient to differentiate the effect of the test agent from no antibacterial treatment and take into account clinically acceptable differences for a test agent compared to an appropriate active comparative regimen. Sponsors should note that the suggested non-inferiority margins are applicable whether two pivotal studies are conducted or a single pivotal study is proposed. If a single study is proposed the sponsor should give consideration to pre-defining a smaller level of significance than is usual in such studies (e.g. 0.01 rather than 0.05). However, if a single randomised controlled pivotal study is conducted as part of the development of the types of antibacterial agents discussed in section 3.4 a level of significance at 0.05 could be acceptable subject to justification.

Sponsors may wish to propose alternative non-inferiority margins to those suggested (e.g. based on emerging methods for estimating the placebo effect). These proposals will be given due consideration according to the strength of the supportive evidence.

b) Route of administration

Patients with any of the five types of infection considered below usually require initial parenteral treatment, with or without a switch to oral therapy. For studies in patients with community acquired pneumonia or urinary tract infections using only oral treatment the inclusion criteria would require adjustment but the suggestions for the primary analysis are still applicable.

c) Pre-study antibacterial treatment

In general, up to 24 hours of prior therapy within 72 hours of enrolment may be acceptable. The protocol should specify limits for the most likely agents that would be used depending on the type of infection under study. For example, in community-acquired pneumonia (CAP) and urinary tract infection (UTI) studies the limit may be a single dose of an agent usually given once daily and 2-3 doses of agents that are routinely administered more than once a day. In intra-abdominal infections (IAI) it may be appropriate to limit prophylaxis to one pre-operative and one further dose administered during or at the conclusion of surgery. An exploratory analysis of outcomes in subgroups of patients that did and did not receive prior therapy within 72 hours for the infection under study is recommended in all studies.

Pre-study antibacterial treatment up to the time of enrolment is acceptable in a patient who has clearly failed to respond to a suitable course of antibacterial treatment (in terms of dose and duration along with documented susceptible pathogen). The protocol should specify whether prior failure includes failure to improve as well as worsening on pre-study treatment.

3.2.1. Skin and soft tissue infections (SSTI)

Patient selection criteria

Acceptable types of infection for study include cellulitis, erysipelas, wound infections (traumatic or post-surgical) and major abscesses. The extent of the infection should be documented, taking into account that the acute infection may surround a chronic lesion (e.g. a varicose ulcer) that will likely remain unchanged by systemic antibacterial therapy. A minimum area affected (e.g. area of erythema, wound dimensions) or estimated size of abscess should be stated in the protocol.

The proportion of patients enrolled with abscess should be limited (e.g. up to approximately 30% of the total patients) and the protocol should specify a time window within which drainage should occur.

Patients should demonstrate a protocol-defined minimum number of signs and symptoms associated with an ongoing acute infectious process.

If patients with infected burns are to be enrolled the maximum extent and thickness should be specified in the inclusion criteria and the protocol should set a limit on the proportion of patients with burns that are enrolled. It is preferred that efficacy in patients with diabetic foot infections is evaluated in separate dedicated studies.

Patients with suspected or confirmed osteomyelitis or septic arthritis and those with severe necrotising infections that require specific surgical and pharmacological management should be excluded.

Primary analysis

Clinical outcome documented at a test of cure (TOC) visit timed from randomisation so that it occurs within a window of approximately 7-14 days after the last day of treatment would be an acceptable primary endpoint. The suggested non-inferiority margin is -10%.

3.2.2. Community-acquired pneumonia (CAP)

Patient selection criteria

All patients must have a good quality chest radiograph obtained within 48 hours prior to enrolment that shows 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, fever, dyspnoea, tachypnoea and pleuritic chest pain as well as at least one characteristic finding on percussion and/or auscultation associated with consolidation.

Sufficient data should be collected and recorded before enrolment to assign patients within the Patient Outcomes Research Team (PORT) classification system for the purposes of stratification. When treatment is to be initiated by the intravenous route eligible patients should have a minimum PORT score of III and at least 25% (and preferably ~50%) should have a score of IV-V. It may be appropriate to exclude patients with a score of V who require immediate ICU admission. In studies that involve only treatment by the oral route patients should have PORT scores of II or III at the time of randomisation and at least 50% should have a score of III.

Protocols may also capture sufficient data to determine CURB-65 scores (i.e. a scoring system based on confusion, urea, respiratory rate and blood pressure) as part of the documentation of the baseline condition of patients.

Consideration should be given to stratification of enrolment according to age < 65 years and ≥ 65 years and no upper age limit should be set.

The sponsor may include strategies to try to enrich or to minimise the study population infected with specific pathogens, such as the use of urinary antigen tests for *S. pneumoniae* or *L. pneumophila*.

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.

Primary analysis

Clinical outcome (based on pre-defined resolution of signs and symptoms) documented at a test of cure (TOC) visit timed from randomisation so that it occurs within a window of approximately 5-10 days after the last day of treatment would be an acceptable primary endpoint. The suggested non-inferiority margin for each study is -10%.

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

Patient selection criteria

Studies may be confined to either hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). A convincing demonstration of efficacy in VAP could support an indication that includes HAP but not vice versa. Studies that include patients with either HAP or VAP should employ stratification to ensure that representative samples of patients in each category are enrolled (e.g. it is suggested that at least 25-30% 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 suggested for CAP but not including the signs on examination and auscultation, which may be absent) plus a new infiltrate on chest radiograph. Patients who have only been assessed in an emergency care setting should be excluded in order to enhance the likelihood

that the infection is due to a pathogen highly characteristic of nosocomial infections that are commonly acquired in acute care hospitals.

In addition to clinical and radiographic features, patients with VAP should have received mechanical ventilation via an endotracheal or nasotracheal tube for at least 48 hours (i.e. the VAP population should not include patients receiving only positive pressure ventilation without intubation). Additional inclusion criteria to assist the selection of ventilated patients with an acute onset pneumonia may include documentation of the Clinical Pulmonary Infection Score (e.g. a minimum 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.

Protocols may employ other scoring systems to select for a patient population that is severely ill (e.g. in whom the mortality rate is likely to exceed 10-20%). For example, the sequential organ failure assessment (SOFA) score, the multiple organ dysfunction score (MODS) and the acute physiology and chronic health evaluation score (APACHE II).

Sponsors may include pre-enrolment rapid tests that attempt to enrich or exclude patients infected with or colonised by certain species. If sponsors choose to include specifications for respiratory secretion specimens and minimum bacterial loads (in colony forming units/mL) for classifying organisms as pathogens it is imperative that the protocol also plans for analyses in which outcomes are assessed in all patients with any positive culture of a relevant pathogen from any pre¬-treatment respiratory tract specimen.

Primary analysis

Clinical outcome documented at a TOC visit timed from randomisation so that it occurs within a window of approximately 7-14 days after the last possible day of treatment would be an acceptable primary endpoint. The secondary endpoints should include all-cause mortality (e.g. deaths that occur up to day 28 post-randomisation) and the proportions of patients that are discharged from hospital within a pre-specified post-randomisation follow-up period.

The suggested non-inferiority margin should not exceed -12.5% in studies confined to VAP or HAP or including both HAP and VAP patients.

3.2.4. Intra-abdominal infection (IAI)

Patient selection criteria

Patients should have a diagnosis of intra-abdominal infection (IAI) established during procedures such as 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. It is recommended that the proportion of patients with infections originating in the appendix should not exceed approximately 30% and that patients should be stratified at enrolment according to infection type (e.g. appendicitis-associated IAI vs. IAI secondary to other primary lesions). Patients with perforations of the stomach and small intestine should not usually be enrolled unless there is clear evidence of an established secondary infectious process within the abdominal cavity.

Primary analysis

Clinical outcome documented at a TOC visit timed from randomisation so that it occurs within a window of approximately 7-14 days after the last possible day of treatment would be an acceptable primary endpoint.

A non-inferiority margin of -12.5% is suggested.

3.2.5. Urinary tract infections (UTI)

Patient selection criteria

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 should not be enrolled. As far as is possible, patients with signs and symptoms suggesting prostatitis should not be enrolled.

Patients with acute pyelonephritis do not always require parenteral treatment and it is preferred that efficacy in acute pyelonephritis is studied separately. If a study is planned to enrol patients with any of the above conditions or acute pyelonephritis in patients considered unable to commence oral therapy there should be stratification at enrolment according to these diagnoses and it is recommended that the proportion with pyelonephritis should be limited.

The clinical picture should be consistent with an ongoing acute infectious process likely to have a primary focus within the urinary tract. For example, protocols may require that patients have a minimum number of signs of systemic upset accompanied by one or more of flank or pelvic pain, tenderness in the costo-verterbral area, fever, dysuria, frequency or urgency.

Patients may be enrolled before microbiological culture results are available on the basis of documented pyuria (≥ 10 WBCs/mm3) in suitable fresh urine samples, noting that 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 [CFU]) in urine. Based on experience and consensus it would be acceptable that patients deemed to have an infection should have > 1 x 105 CFU/mL. Some samples may not meet this cut-off with a single colony type but may have at least this number of colonies in a mixed culture based on visual inspection of morphology on an appropriate selective medium. It is recommended that the microbiologically evaluable population should be confined to those who have only a single colony type. Speciation is expected in clinical studies rather then reporting only enterobacteria or other general descriptive terms.

Primary analysis

Microbiological success should be defined as < 1 x 103 CFU/mL. The microbiological success rate, documented at a TOC visit timed from randomisation so that it occurs approximately 7 days after the last possible day of treatment, would be an acceptable primary endpoint. It is expected that a reduction of the bacterial load in urine to < 1 x 103 CFU/mL would usually be accompanied by resolution of the clinical signs and symptoms suggesting infection within the urinary tract. Patients who meet the criterion for microbiological success without clinical resolution should be fully described and investigated.

The suggested non-inferiority margin is -10%.

3.3. Indications for which superiority study designs could be required

In some types of infection and/or in subsets of patients with specific conditions that may be ascribed to bacterial infection the use of active antibacterial treatment has not been established to be superior to no treatment. The reasons include, among others, high spontaneous resolution rates in certain types of

infection, or at least in subsets of patients with such infections, and/or low likelihood that the clinical picture is due to a bacterial infection. These infections include (among others) acute bacterial maxillary sinusitis (ABS), acute bacterial exacerbations of chronic bronchitis (ABECB), acute otitis media (AOM) and superficial skin infections (such as impetigo and minor wounds). Another example is the use of inhaled antibacterial agents to prevent infective exacerbations in patients with chronic airways obstruction or bronchiectasis or as add-on therapy to systemic antibacterial regimens for the treatment of exacerbations or acute bacterial pneumonias.

In these instances the clinical benefit of a test agent cannot be assessed with confidence in a non¬-inferiority study vs. an antibacterial agent that has been approved in the past for the type(s) of infection under consideration. Therefore, efficacy should be evaluated in studies that are designed to demonstrate superiority of the test agent compared to placebo or, possibly, compared to active comparative therapy for a pre-specified clinically important endpoint. It is not possible to provide definitive recommendations for clinical development programmes in these circumstances but some suggestions are provided for consideration.

3.3.1. Study designs

In several types of infection discussed in the following sections, demonstrating superiority of the test agent over placebo or over an active comparator based on clinical cure rates at a TOC visit is unlikely to be a feasible objective. To assist in selecting appropriate patient populations for study and endpoints for evaluation it is suggested that at least one exploratory study is conducted before proceeding to pivotal studies with pre-defined objectives. These exploratory studies could serve to identify potentially clinically important endpoints for which there is some likelihood that the test agent would demonstrate superiority in an adequately powered study in a carefully selected patient population. Before embarking on pivotal studies it is recommended that study designs and efficacy endpoints are discussed with EU Regulators.

For example, in studies in which patients are randomised to commence either the test agent or placebo from the outset it may be that a benefit for active treatment is demonstrated only during and/or at end of treatment i.e. active treatment speeds up resolution of the infection but it does not significantly affect cure rates assessed at a post-therapy TOC visit. An effect of active treatment on time to resolution of an infection might be regarded as clinically important if it is of sufficient magnitude. This situation is especially likely to be encountered in studies involving topical treatments for impetigo or superficial wounds. It may also apply in subsets of patients with AOM, ABS and ABECB.

One possible alternative to a study against placebo is to randomise patients either to a full course of the test agent that is commenced at study entry or to commence with placebo for a specified number of days (e.g. 48-72 hours) followed by a full course of an appropriate licensed agent. If the test agent has a safety profile that allows for a wide range of doses and if PK/PD suggests the strong possibility of a clear dose-response relationship these features could allow for a further alternative study design that avoids a placebo group. Thus, all patients could be randomised to one of several dose regimens of the test agent starting from the minimum that might be clinically active at least against some potential pathogens based on PK/PD considerations.

In each of these examples the final wording of the indication would reflect the clinical benefit that was actually demonstrated.

3.3.2. Acute otitis media

It is considered that published data support a specific exception to the general requirement for a superiority study against placebo in AOM. Based on the findings reported by Tähtinen et al. (2011) and

Hoberman et al. (2011) a placebo-controlled study is not required in adequately diagnosed AOM in children aged from 6 months up to 3 years. Nevertheless, the available data do not provide an unequivocal indication of the primary endpoint and non-inferiority margin to apply.

An acceptable non-inferiority study in AOM must employ strict inclusion criteria. It is recommended that all eligible children should present with acute onset (within 48 hours) otalgia and a bulging tympanic membrane on otoscopy as a minimum. AOM may be unilateral or bilateral and stratification is suggested. All signs and symptoms compatible with an ongoing acute infection should be documented and the use of a scoring system is recommended. Based on the two published studies the comparative regimen should be oral amoxicillin-clavulanate administered at the highest dose that is approved for treatment of AOM in this age group across the study sites and for at least 7 days.

Clinical success should require resolution of abnormalities on repeat otoscopy (in both ears if AOM was bilateral) and resolution of otalgia. There should also be resolution of signs and symptoms of an ongoing acute infectious process that were present at baseline. A demonstration of non-inferiority could be based on comparison of clinical success rates at a visit timed from randomisation to occur at 1-2 days post-therapy. It is suggested that the pre-defined non-inferiority margin should be less than -10%. There should also be a comparison of sustained success rates at approximately 14-21 days post-randomisation, depending on the length of treatment and timing of the TOC visit.

At the current time an approval for treatment of AOM in other age groups and in populations that do not meet these diagnostic criteria is not possible based solely on non-inferiority studies.

3.3.3. Acute bacterial sinusitis

An approval based solely on non-inferiority studies is not currently acceptable. There is a need for further clinical data in adequately diagnosed and well-characterised patient populations before definitive suggestions for clinical studies that could support approval for use in ABS can be made.

3.3.4. Acute bacterial exacerbations of chronic bronchitis

An approval for the treatment of infective exacerbations of chronic bronchitis based solely on non-inferiority studies is not currently acceptable. Studies are hampered by a lack of consensus on the criteria that constitute an exacerbation and the criteria that should determine the need for specific antibacterial therapy in addition to other treatment modalities. Nevertheless, if sponsors wish to conduct studies in such patients it could be acceptable to use criteria to identify exacerbations that might benefit from antibacterial therapy suggested by at least one professional body including experts in the field.

The judgment of clinical success is also not straightforward when a return to pre-exacerbation status is likely the best that can be achieved and when each exacerbation may result in some further deterioration. All of these issues underline the need for high quality placebo-controlled studies in well-defined patient populations.

3.3.5. Inhalational antibacterial regimens in non cystic fibrosis patients

Sponsors may wish to assess the potential for an inhaled antibacterial regimen to prevent infective exacerbations of underlying conditions such as chronic bronchitis or bronchiectasis and/or to assess inhalational treatment of acute bacterial pneumonia or acute exacerbations in addition to a systemic regimen. Currently the efficacy of these possible uses of inhalational antibacterial therapy has not been established and a demonstration of superiority for the test regimen over placebo is required. In addition, since the relationship between demonstrating an effect on bacterial loads in respiratory

secretions and a documented clinical benefit has not been established in any of these conditions the primary analysis must be based on an appropriate clinical endpoint. The use of disease-specific validated instruments to assess outcomes is currently viewed as exploratory although this situation may change in future in accordance with available data and experience gained. Similar considerations currently apply to instruments that measure improvements in chronic baseline symptoms and instruments that detect acute changes in symptoms during exacerbations.

In the case of treatment or prophylactic regimens in patients with chronic bronchitis or bronchiectasis it is essential that there are adequate pre-study investigations to fully document the presence and severity of the underlying lung condition. A major issue for the conduct and interpretation of these studies is the lack of consensus regarding the definition of an acute bacterial exacerbation. Rational criteria for the definition need to be proposed (e.g. taking into account definitions proposed by professional associations of pulmonologists) and justified in protocols.

In studies that assess the effect of single or multiple courses of an inhaled antibacterial agent on preventing bacterial exacerbations an appropriate primary endpoint could be time to exacerbation assessed over 12 months after completion of an initial or first course of the test agent (depending on the regimen under evaluation). It is expected that studies of the treatment of acute bacterial exacerbations of underlying conditions or of acute pneumonias will involve addition of the test and placebo inhaled regimens to a standard systemic antibacterial regimen. In such cases it could be acceptable that the study demonstrates superiority for the test inhaled regimen over inhalation of a placebo based on one or more pre-specified clinical criteria (e.g. time to resolution of clinical signs and symptoms, return to baseline status).

In the case of treatment of pneumonia, subsequent to compelling results from adequate exploratory studies, sponsors may wish to demonstrate non-inferiority of an inhalational therapy alone compared to an appropriate systemic antibacterial treatment in terms of cure rates. In this instance the suggestions made in sections 3.2.2 and 3.2.3 would apply.

3.3.6. Superficial skin infections

An approval based solely on non-inferiority studies is not currently acceptable. Placebo-controlled studies in patients with impetigo, superficial wound infections and some types of secondary infected dermatoses are feasible. These should be studied separately and with appropriate limitations placed on the use of adjunctive therapies, including the use of antiseptics.

It would be acceptable if the test agent was shown to be superior to placebo based on time to resolution of the infection, which could be assessed at end of treatment. Clinical resolution should also be assessed at post-therapy visits to document relapse rates. Organisms within the two major pathogenic species (*S. aureus* and *S. pyogenes*) may manufacture a range of toxins, some of which could have a negative impact on the success of oral or topical antibacterial treatment. It is recommended that pathogens recovered from infections that have not resolved by end of treatment or which relapse should be investigated for production of toxins.

In studies in impetigo the number of lesions should be counted and an estimate made of the total body surface affected. Protocols may set limitations on numbers and/or surface area, especially if treatment is topical. The protocol may designate treatment of only the single largest lesion, a specific number of lesions or all lesions present to be treated. Depending on the strategy adopted, pre-defined additional analyses may be needed according to lesion numbers or area since untreated neighbouring lesions can affect the likelihood of clinical success at treated lesions.

The design of studies in secondary infected dermatoses should take into account the possibility of stratifying according to the underlying diagnosis, the need for ongoing topical steroid treatment and the use of occlusion.

3.4. Circumstances in which limited clinical data may be accepted

3.4.1. Introduction

The justification for seeking initial approval based on limited clinical safety and efficacy data should be based on the ability of an antibacterial agent to address an unmet clinical need. This situation includes, among others, antibacterial agents with potential to treat infections due to multidrug-resistant (MDR) organisms that are currently uncommon or rare and for which there are few remaining therapeutic options. The possible acceptance of a limited pre-licensure clinical development programme should be discussed and agreed with EU Regulators at an early stage. For example, discussions could be initiated as soon as there are sufficient PK/PD data to indicate a strong possibility that the test antibacterial agent would address an unmet clinical need.

No or very few patients who are infected with such organisms are likely to be enrolled in efficacy studies in commonly sought indications as described in section 3.2. Thus, alternative approaches are needed to accumulate evidence to support a specific endorsement for treatment of MDR pathogens that are susceptible to few licensed antibacterial agents.

There is a range of possible approaches that could be taken to the initial clinical programme and only some of the possible options are outlined in this section. Additional modification and tailoring of programmes could be considered in certain scenarios (e.g. if an established antibacterial agent were to be co-administered with a new beta-lactamase inhibitor or *vice versa*).

3.4.2. Justification for a limited initial clinical development programme

A new antibacterial agent that belongs to a new class that has a unique mechanism of action can be assumed to be a candidate to address an unmet clinical need. Nevertheless, it is important to evaluate whether its utility could be severely impacted by mechanisms that can confer resistance to multiple classes of antibacterial agents. For example, (impermeability of the outer membrane and/or the presence of efflux pumps, both of which can lead to resistance to several classes of agents).

New agents of existing classes that are active against organisms resistant to other members of the same class are also potential candidates for approval based on a limited initial development programme. These could be standalone agents or they may be presented in combination with a molecule (e.g. beta-lactam drug plus beta-lactamase inhibitor) that protects them against one or more bacterial mechanisms of resistance.

If the spectrum of activity of the new agent is very limited (e.g. to a single genus or species) then there should be adequate justification that the organism(s) within its range are clinically problematical.

There is a need to consider what happens once a new agent that addresses a specific unmet need has been approved based on limited clinical data. A second (or sequential) agent that may address the same types of pathogens could also be considered for an initial approval based on limited data taking into account that having a choice of agents available has several obvious benefits. In these situations it becomes even more important that the justification for a limited development programme leading to first approval is agreed with EU Regulators as early as possible.

3.4.3. Content of the development programme

General considerations

It is expected that an adequate pre-licensure pharmacokinetic assessment will be conducted to support use of the antibacterial agent to treat systemic bacterial infections in the intended target population. For example, there would need to be sufficient data on the effects of hepato-renal impairment and on the potential for drug-drug-interactions to occur.

In addition, there would need to be sufficient PK data in the target population or, at least, in patients with a similar degree of infection-associated systemic disturbance as a result of an ongoing acute infectious process, to support robust PK/PD analyses. This is considered to be essential since it is expected that in these situations the PK/PD analyses will form a major part of the justification for the dose regimen and the expectation of clinical activity against the target pathogens.

There is a need to consider whether the new antibacterial agent can be evaluated as monotherapy and in which indications this could be possible to provide a clear picture of safety as well as efficacy. In studies that are confined to or enriched for infections due to the target pathogens of interest current clinical practise may preclude monotherapy with the new agent whenever there is at least one licensed agent to which the pathogen is susceptible.

Additional difficulties apply to the clinical evaluation of antibacterial agents that have a very limited spectrum of activity. Monotherapy may be feasible only in types of infection that are commonly due to a single species and when there are rapid diagnostic tests available (these could be commercially available or developed in parallel with the antibacterial agent). If the only feasible monotherapy study is in patients with UTI and the pharmacokinetic data show very high concentrations of the test agent within the urinary tract then further cautionary wording might be needed regarding a claim for treating other types of infection, as discussed in section 3.4.4.

For clinical development programmes in which most or all of the clinical data are obtained from patients receiving more than one potentially active antibacterial agent the role of the PK/PD analyses becomes even more important to support the likely efficacy of the selected dose regimen.

At the time of initial approval it will be important to evaluate the content of the post-licensure programme to further substantiate safety and efficacy. In some cases and subject to the properties of the new antibacterial agent sponsors may plan to conduct randomised controlled studies in standard indications along the lines described in section 3.2, which will further support the safety and efficacy of the dosing regimen. Additional data on use against target pathogens could be obtained by means of prospective uncontrolled studies, registries and/or other types of observational studies depending on the research questions. Sponsors should have clear proposals for post-approval data collection at the time of submitting the initial application.

Examples of clinical programmes

Building on the general guidance provided in CHMP/EWP/558/95 Rev 2, some possibilities for demonstrating efficacy and accumulating adequate safety data to support claims for use against multi-resistant organisms could include (but are not limited to) development programmes along the lines suggested below.

In all cases it is essential to accumulate evidence to support a strong prediction of efficacy in the intended use(s) from PK/PD analyses that are founded on a thorough documentation of in-vitro activity, non-clinical evidence of efficacy and relevant human PK data, which should include adequate PK data obtained from patients who are systemically ill with a range of types of infection in which the sponsor expects the new agent will need to be used. For example, patients infected with MDR

pathogens may have received several prior courses of antibacterial agents, been hospitalised for some time, be debilitated and have a range of underlying chronic conditions and it is important that the study population is representative of this population. There should be adequate PK sampling to detect any possible effects of infection-associated systemic upset or specific type of infection/treatment on plasma concentrations and, as may be needed, additional PK/PD analyses.

The PK/PD analyses should address the likelihood that the test agent will be clinically active against organisms for which there is an unmet clinical need. In the sections that follow these organisms are referred to as the target organisms expected to respond to treatment with the new agent and for which there are few remaining treatment options. Since several different mechanisms of resistance could co-exist in these organisms and any one new agent may not be active in all cases it is essential that these issues are fully explored. For example, a new beta-lactamase inhibitor may prevent hydrolysis of a partner beta-lactam agent by the majority of the extended spectrum beta-lactamases (ESBLs) and serine-based carbapenemases but the in-vitro activity of the combination may be considerably reduced (and it may not be clinically active) in the presence of one or more of other types of beta-lactamases, impermeability of the outer membrane or an efficient efflux pump.

Some options for clinical programmes that would, as a minimum, allow for an initial indication for use in patients for whom there are few remaining treatment options, are provided in points i., ii. and iii. Sponsors should note that in each case it is expected that every effort will be made to collect information on safety and efficacy in patients who are infected with the target organisms. The minimum number of patients infected with target organisms will inevitably depend on their prevalence and sponsors are advised to discuss and seek agreement on their expectations for numbers of treated cases with EU Regulators.

i) If the antibacterial spectrum and pharmacokinetics of the test agent permit, the sponsor may choose to conduct at least one randomised and active¬ controlled study in a specific type of infection. For example, if the test agent is expected to be active against MDR Gram-negative aerobes/facultative anaerobes it could be studied for efficacy in HAP/VAP or IAI since many of the patients will be infected by organisms of relevant genera/species. If the test agent is expected to be active against MDR Gram-positive pathogens such as glycopeptide-resistant staphylococci it could be studied for efficacy in HAP/VAP or SSTI. A study in UTI would require a careful justification to support extrapolation of the data to other body sites depending on the PK properties of the new agent. These studies are not expected to enrol sufficient numbers of patients infected with the target organisms to allow for an assessment of efficacy in this subset, although any cases that are enrolled should be carefully scrutinised for outcomes. Their purpose is to provide data to support the safety and efficacy of the selected dose regimen for species within the spectrum of activity of the test agent.

To support a companion claim for clinical efficacy against target organisms an additional study should provide some pre-approval evidence of efficacy. These data could come from a study in which data on well-documented infections due to the target organisms are treated, which may be confined to or enriched for these pathogens. The types of infections treated could be restricted or could include all types that the sponsor feels could be supported by the PK data, noting that infections such as meningitis, endocarditis and osteomyelitis would likely be excluded at least from an initial study due to the special considerations required.

These data specific to the target organisms might come from a small randomised study that is not powered for inferential testing or from an uncontrolled study, with or without the generation of external control data (see further comments on these options in ii. and iii. below).

In this setting of a development programme for an antibacterial agent for which the sponsor intends to seek an indication for use in patients with few remaining treatment options it may be possible to grant

an additional indication for use based on a single accompanying randomised controlled study. Specifically in such cases the demonstration of efficacy in the type of infection that was studied could be less precise than would usually be expected for single pivotal studies (i.e. the usual non-inferiority margin recommended for the type of infection under study and level of alpha could be acceptable; see section 3.2). Hence, provided that non-inferiority is convincingly demonstrated for the test product compared to the active comparator and provided that the indication for use in patients with limited therapeutic options is considered to be soundly supported, the data from a single pivotal study could suffice to support a standard claim for efficacy in the indication studied.

ii) If the sponsor seeks only an indication for treatment of the target organisms (i.e. to address an unmet clinical need) at the time of initial approval then one option would be to conduct a prospective randomised study of the new antibacterial agent vs. best-available treatment (BAT). The study could be confined to or enriched for infections due to the target organisms. If it is not feasible to confine the BAT to a single regimen then a protocol that provides a hierarchical preference would be preferred if at all possible. Similarly, if combination therapy is necessary for both treatment groups then it is preferable that the additional agents that are allowed are standardised in accordance with protocol-defined criteria. Sponsors could limit the types of infection studied or effectively allow all-comers (with the few exceptions suggested above).

It is not expected that such a study would be powered for inferential testing. There is no rationale for determining a non-inferiority margin based on clinical success rates. In addition, it is not expected to be feasible to demonstrate superiority for the new agent over BAT based on the usual endpoints that would be applied to each type of infection. However, an exploratory comparison of success rates within the sub-population proven to be infected with the target organisms should be planned. Sponsors are also encouraged to evaluate the potential for superiority of the new agent based on a range of clinically relevant endpoints, which could include time to resolution of specific features of infection or overall survival.

iii) In cases where the numbers of infections due to target organisms is very limited, it may be considered acceptable to conduct an uncontrolled study that employs either recent historical controls or, preferably, external controls. Such a study should be confined to or heavily enriched for patients infected with the target multi-resistant organisms.

3.4.4. Reflecting the evidence in the Summary of Product Characteristics (SmPC)

There are several possible options regarding reflection of the evidence for efficacy in the SmPC and the final wording can only be decided after a full review of the data. The following proposals should be viewed as preliminary suggestions.

The availability of approved rapid diagnostic tests that can detect specific pathogens and/or specific mechanisms of resistance could have an important influence on the wording of indications. In the absence of any approved relevant rapid tests an approach that is clinically practical needs to be considered.

In addition to the standard sentence in section 4.1 regarding the advice *Consideration should be given to official guidance on the appropriate use of antibacterial agents* it is proposed that section 4.2 should contain as an initial statement the following:

It is recommended that {agent 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.

For new agents active against only one genus or species that have been studied along the lines suggested in sections ii. or iii. a possible indication could be: *For the treatment of infections due to {genus or species} in patients with limited treatment options.*

There would have to be a cross reference to section 4.4, where the limitations of the clinical data would need to be mentioned, and to section 5.1, where the actual organisms treated and the data on lack of cross-resistance / potential for co-resistance would be stated.

For new agents that have a broader spectrum of activity it is unlikely to be feasible or appropriate to specify use of the agent only to address the unmet clinical need that justified the acceptance of limited clinical data. In many cases the new agent will be commenced based on a suspicion of the presence of target MDR organisms. Therefore an appropriate indication could be: *For the treatment of infections due to [some types of] pathogens in patients with limited treatment options.*

The specification of types of pathogens could be as broad as aerobic Gram-negative or enterobacterial or similar, depending on the unmet need that is to be addressed and the activity of the individual antibacterial agent. The same approach to cross-referencing would be needed as for an agent with a very narrow spectrum.

In some instances it may be considered necessary to qualify these indications by site of infection due to the pharmacokinetic properties of the test agent and/or any concerns that may arise from the available data on safety or efficacy. If there is no clear rationale to restrict the indications the limitations of the evidence would be reflected elsewhere in the prescribing information as described above.

For some agents consideration may be given to advising stopping the agent in cases where the susceptibility testing results (which could take 48 h) indicate the lack of target MDR pathogens. However, if the agent has a reasonably good safety profile, is active in vitro against the actual pathogens and the patient is showing clear signs of improvement it could be inappropriate to mandate a change in treatment and the decision may be left to the specialist in infectious diseases who is managing or advising on the individual patient.

3.5. Other indications for use that could be sought

3.5.1. Bacteraemia

Non-pathogen-specific

It may be possible to accumulate sufficient clinical data to support an indication for use of an antibacterial agent in the treatment of bacteraemia that is associated with specific types of infection, with or without restriction to certain pathogens. For example, in the case of agents that have been in use for many years and are indicated for use in a broad range of infections the total evidence may be considered sufficient for an indication that reads *Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above* (i.e. referring to the list of indications approved).

It is likely that at the time of first approval there will be very little clinical experience with an antibacterial agent in the treatment of bacteraemic patients. If no concern arises from review of the subset with accompanying bacteraemia then no statement is made about use in such patients in the SmPC except to mention the limited experience. If the antibacterial agent has been evaluated in several indications and the total number of bacteraemic patients treated across these indications is deemed sufficient (e.g. ~50 or more) to support a conclusion that efficacy is comparable to that in other patients or, at least, comparable to that of other treatments, then the addition of the sentence

above could be considered appropriate.

Pathogen-specific

Studies that enrol patients with bacteraemia due to a specific pathogen but regardless of the underlying infection are not usually considered sufficient to support a pathogen-specific indication without additional qualification because this would imply that the test agent could be used to treat such cases regardless of the location of the primary focus/foci of infection (which will anyway be unknown in a proportion of cases). An exception to this approach could apply to agents that are expected to be clinically active against uncommon or rare pathogens and/or multi-resistant pathogens for which there are few treatment options. In such cases, depending on the level of evidence that can be provided, an indication that includes bacteraemic patients regardless of the focus of infection might be considered possible in patients with limited therapeutic options as described in section 3.4.

3.5.2. Treatment of acute bacterial infections in neutropenic patients

The institution of an antibacterial agent prior to or at the time of onset of expected neutropenia is now a common practise in some patient populations and centres so that rates of breakthrough infections may be low compared to other patient groups. The study population actually enrolled with acute bacterial infections during neutropenia will comprise some ratio of patients with breakthrough infections despite prophylaxis and patients who have not received routine prophylaxis. The two sub-groups may be substantially different in terms of their underlying conditions and are likely to be enrolled at different centres with variable routine management protocols. On this basis stratification according to prior or no prophylaxis may be appropriate. The protocol should provide clear criteria to be met in terms of neutropenia (cut-off and expected duration). The definition of fever will also require alignment across sites.

If the test agent must be co-administered due to its spectrum of activity then the additional agent(s) should be specified, including dose regimen and any dose adjustments. If possible the range of agents allowed should be standardised. The protocol should include clear criteria for stopping therapy in terms of susceptibility data, clinical progress, culture results and recovery of the granulocyte count. It is critical that the criteria for failure are very carefully specified (e.g. persistence of the baseline pathogen beyond ~48 hours of treatment).

The most objective basis for the assessment of efficacy would be the comparison of bacterial eradication rates in the subset of patients with a positive blood culture pre-treatment between the test and comparative regimens. Patients with an obvious primary focus should also have a resolution of infection. Due to the complex nature of these patients, difficulties in ascertaining the range of co-existing pathogens and lack of clear distinction between the treatment and prophylactic role of antibacterial agents (even in the subset with a documented bacterial pathogen) the resulting indication would likely reflect the utility of the agent in the overall management of such patients rather than specifying use in the treatment of bacterial infections.

3.5.3. Eradication of carriage

Indications that relate to the reduction or eradication of a pathogen from a specified body site are not acceptable unless the microbiological effect of active treatment has been shown to result in a measurable clinical benefit. In the absence of adequate data to support such a link, the clinical benefit associated with the effect of treatment on carriage should be demonstrated in a placebo-controlled study with a primary clinical endpoint.

A demonstration of efficacy based on a primary microbiological endpoint and an indication that reflects

the observed effect on carriage would only be acceptable if current clinical opinion (e.g. supported by published literature and/or evidence-based recommendations of professional bodies) considers that eradication of carriage in the specific circumstance studied is well established to be clinically beneficial and is widely recommended.

Possible examples in which studies with primary microbiological endpoints could be acceptable include (but are not limited to) the use of oral treatment regimens to eradicate carriage of meningococci from the nasopharyngeal area of contacts of cases and the eradication of *S. pyogenes* in order to reduce the risk of post-streptococcal syndromes (e.g. rheumatic fever and glomerulonephritis). In these examples a study of the test agent against placebo/vehicle is not feasible. Pivotal studies would have to demonstrate non-inferiority for the test agent regimens against recommended regimens based on microbiological eradication rates.

In addition, sponsors may be able to justify that eradication of *S. aureus* carriage at some body sites (such as the anterior nares) prior to specific types of surgical procedures can be expected to reduce the rate of post-operative infections. Pivotal studies to support this use should aim to demonstrate superiority of the test agent compared to placebo/vehicle in terms of microbiological eradication rates in subjects who are not in imminent need of the treatment. If there is an approved comparator, this could be included as a third arm in a placebo-controlled study and/or a separate comparative study could be performed (which could include subjects with imminent need of eradication).

The clinical studies should incorporate an assessment of the treatment duration required to achieve the required effect and the risk of, and time to, re-colonisation. This requires that there are adequate means available for differentiating re-growth of initial strains from new colonisation events. Organisms recovered from patients who fail to achieve eradication or who show a very slow response to treatment, rapid re-growth or re-colonisation should be fully characterised in terms of susceptibility, mechanisms of resistance and, as may be appropriate to the species, other features such as sub-type and toxin encoding genes/toxin production.

Microbiological culture techniques cannot demonstrate absolute eradication since there will always be a minimum number of organisms that cannot be detected. In reality, only a *reduction in numbers* (within a range that can be differentiated by culture) or *apparent eradication* (i.e. negative cultures) can be demonstrated. In cases that involve topical applications there is also the issue of a carry over effect from residual active agent at the sampling site influencing the numbers of organisms cultured, which may give a falsely optimistic view of the real effect. For all these reasons it is essential that there is an extensive documentation of the detection limits of the sampling and culture methodologies applied in pivotal studies. 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.

3.5.4. Oral treatment intended to exert an action within the gut

Currently, antibacterial regimens intended to exert an action within the gut (some of which are and some not absorbed systemically to any potentially clinically useful extent) have been approved for the treatment of *C. difficile* infections producing diarrhoea and for the treatment of travellers' diarrhoea (with variably specified usages according to genera).

The systemic absorption of agents intended for these uses should be adequately characterised and an appropriate range of pharmacokinetic studies should be conducted accordingly. The implications of any systemic absorption for selection of drug-resistant organisms colonising body sites other than the gut should be discussed. In these types of indications PK/PD analyses do not assist in predicting an effective dose and adequate dose-finding studies are needed.

For treatment of *C. difficile* associated diarrhoea a demonstration of non-inferiority of the test agent compared to a licensed agent would be acceptable. The patient population should have carefully documented changes in bowel habit within a pre-defined pre-study period accompanied by detection of toxin (A or B) in stools. An established *C. difficile* infection (CDI) severity index should be applied within the inclusion criteria. The primary efficacy endpoint should be the cure rate using a definition of cure that encompasses resolution of symptoms and no requirement for further antibacterial treatment. The suggested non-inferiority margin is 10%.

There should be sufficient follow-up to document sustained cures and clinical relapse rates. For example, patients should be followed for at least one month after completion of treatment.

In the case of travellers' diarrhoea the rate and rapidity of spontaneous resolution varies according to the pathogen. In a population presenting with recent onset travellers' diarrhoea that is not associated with any features suggestive of the presence of an invasive pathogen it is expected that the test agent is shown to be superior to placebo. A third treatment arm in which subjects receive an antibacterial agent approved for use in this setting could be included for assay sensitivity purposes. Protocols should make adequate provision for subject management when a pathogen that requires specific treatment is detected after enrolment and/or there is rapid worsening (e.g. onset of blood in stool) during the study period.

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. The recommended primary endpoint is time to last unformed stool (TLUS).

Suitable test agents should at least demonstrate in-vitro activity against *E. coli*. The risk of encountering organisms of this and other species that are unlikely to be susceptible to the test agent at concentrations expected within the gut should be taken into account in the study design and may influence the geographical location of study sites. It is particularly important that the identity and in-vitro susceptibility of pathogens recovered from subjects who do not respond to the test agent are fully documented since the clinical effect of test agents within the gut may differ from expectations based solely on in-vitro and PK data.