EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2013
EMA/493109/2013
Human Medicines Development and Evaluation

Workshop on development of new antibacterial medicines

Report

25 - 26 October 2012, European Medicines Agency

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Workshop on development of new antibacterial medicines

Workshop report

Disclaimer

This workshop was organised by the European Medicines Agency in the context of the work on the Addendum to the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address indication-specific clinical data requirements. The views expressed are those of the authors and do not necessarily represent an official position of the Agency or of any of its Committees.

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Organising Committee

Prof. Eleni Giamarellou (Co-Chair), Athens, Greece

Dr. Marco Cavaleri (Co-Chair), European Medicines Agency, UK

Dr. Radu Botgros, European Medicines Agency, UK

Dr. Mair Powell, Chair - Infectious Diseases Working Party (IDWP)

Speakers

Jeff Alder, Bayer, USA

Paul Ambrose, Institute for Clinical Pharmacodynamics, USA

Keith Barker, GSK, UK

Richard Bax, Transcrip, UK

Francesco Blasi, University of Milan, Italy

Helen Boucher, IDSA, USA

Marco Cavaleri, European Medicines Agency, UK

Aaron Dane, AstraZeneca, UK

Drusano George, University of Florida, USA

Dudley Mike, Rempex, USA

Barry Eisenstein, Cubist, USA

David Friedland, Forest-Cerexa, USA

Mark Goldberger, Abbott, USA

Herman Goossens, University of Antwerp, Belgium

Jan Kluytmans, Amphia Hospital, Netherlands

Charles Knirsch, Pfizer, USA

Serge Kouzan, St Julien en Genevois Hospital, France

Michael Loebinger, Imperial College London, UK,

Mair Powell, Medicines and Healthcare Products Regulatory Agency, UK

John Rex, AstraZeneca, UK

Bart Rijnders, Erasmus MC Hospital, Netherlands

Ricardo Utili , University of Naples, Italy

Thursday 25 October 2012, 13.00pm - 18.00pm

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Objectives of the workshop

by **Radu Botgros**, European Medicines Agency, UK

The revised *Guideline on evaluation of medicinal products indicated for treatment of bacterial infections* (CPMP/EWP/558/95 rev 2) came into force in January 2012. In several places, this guideline makes reference to an *Addendum* under development. The *Addendum* provides more details on requirements for clinical trials to support individual indications for use and outlines some possible approaches to the clinical development of new agents potentially active against multidrug-resistant (MDR) pathogens. The draft *Addendum* was released for consultation on 4 July 2012 until 31 January 2013 with a plan to hold a Workshop during the consultation period attended by experts in the field and representatives from the pharmaceutical industry.

The aim of the Workshop was to obtain input on the proposals made in the *Addendum*. In particular to:

- Discuss the feasibility of the proposals made
- Discuss alternative proposals
- Identify issues not yet covered
- Identify areas requiring more detail
- Consider implications for worldwide clinical development programmes

2. Abstracts

Session 1: Introduction

"TATFAR-the EU-US forum"

Chairperson: **Marco Cavaleri**, European Medicines Agency, UK

The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was established in 2009 at the annual summit between the European Union (EU) and United States of America (US) presidencies with the aim of intensifying cooperation between the US and the EU with regard to:

1. The appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities
2. The prevention of healthcare-associated and community-associated drug-resistant infections
3. Identification of strategies to improve the pipeline of new antimicrobial agents

The first TATFAR report was issued on 22nd September 2011. It includes three Recommendations relevant to the present Workshop, along with timelines for their implementation, as follows:

- The United States Food and drug Administration (FDA) and the European Medicines Agency (EMA) should discuss ways to facilitate the conduct of antibacterial drug development programmes that satisfy regulatory requirements in both the US and EU.
- FDA and EMA should establish regular meetings to discuss common issues in the area of development and regulation of antibacterial medicinal products.

- FDA and EMA should exchange information on possible approaches to development of medicinal products for bacterial diseases where limited options are available (i.e. infections for which there are insufficient antibacterial agents available, often due to the development of antimicrobial resistance).

In response to these three Recommendations the FDA and EMA have initiated regular teleconference contact and, when possible, representative attendance at workshops and public consultations organized by each agency. The TATFAR did not expect that FDA and EMA would align regulatory requirements but it was hoped that an increase in dialogue could ultimately lead to a desirable level of convergence.

Session 2: Drugs targeting MDR pathogens

"Current Guidance"

by **Mair Powell**, Medicines and Healthcare Products Regulatory Agency, UK

The revised *Guideline on evaluation of medicinal products indicated for treatment of bacterial infections* (CPMP/EWP/558/95 rev 2) considers possible approaches to the development of new antibacterial agents expected to have efficacy against rare pathogens, including MDR pathogens (which may be extensively resistant [extensive drug resistance -XDR] or resistant to all existing antibacterial agents [pan drug resistance - PDR]).

The core *Guideline* on antibacterials recognises that it may be necessary to obtain clinical efficacy data against specific pathogens in clinical trials that enroll patients with documented infections due to the MDR pathogens of interest regardless of the body site(s) affected. Anticipating that few data can be gathered, the core guideline states that randomised trials are preferred over uncontrolled studies but if only uncontrolled trials are feasible then external controls are preferred over historical controls. The minimum number of treated cases needed to support a specific claim must be judged on a case by case basis. A pathogen-specific indication may be appropriate if an agent has been shown to have clinical efficacy against organisms that express certain types or patterns of resistance when causing infections at a range of body sites.

The draft *Addendum* aims to provide further guidance on the minimum evidence that may be expected to support approval of an antibacterial agent that addresses an unmet clinical need, using as an example a new agent that is potentially effective against MDR Gram-negative aerobes/facultative anaerobes. The focus is on the development of a robust pharmacokinetic-pharmacodynamic (PK-PD) programme to strongly support an expectation of efficacy against the MDR pathogens of interest and to consider the range of clinical trials that might be possible.

2.1. Pharmacokinetics-pharmacodynamics (PK-PD)

"Optimal dosing regimens of novel antimicrobials against MDR pathogens

by **George Drusano**, University of Florida, USA

The critical question for anti-infective drug development is the identification of the appropriate dose regimen for each mode of use. Development programmes should generate data that adequately support treatment regimens that will be efficacious and will minimise the selection of resistant organisms.

Non-clinical models are useful for setting targets but cannot be used to identify the dose to be used in humans, whereas PK-PD modeling is a valuable tool for bridging non-clinical data to the clinical setting.

Bridging non-clinical findings to man requires human pharmacokinetic (PK) data that include plasma concentrations and effect site penetration estimates. Drug penetration to a site of infection may be different in patients having an active infection vs. healthy persons so it is vital to obtain comprehensive data during clinical trials in patients to support selection of the most appropriate dose regimen.

Using the example of meropenem, reference was made to studies using the Hollow Fiber Infection (HFI) model and the murine pneumonia model, each with *P. aeruginosa* that each examined the antibacterial effect of various dose regimens and their ability to suppress selection of resistance.

The HFI model showed that, although a range of dose regimens behaved similarly over the first few hours of exposure, high doses were needed to avoid selection of resistant organisms. Using neutropenic mice, a mathematical model was applied to simultaneously examine plasma and epithelial lining fluid (ELF) meropenem concentrations and their antibacterial effects. From this, the exposure targets in ELF for cell kill and resistance suppression were calculated. Subsequently, the penetration of meropenem into ELF was measured in ventilator associated pneumonia (VAP) patients with a pathogen recovered from bronchoalveolar lavage (BAL) (> 10^4 CFU/mL). Monte Carlo simulation was used to assess variability in 2-log10 cell kill (CFU/g) and resistance suppression target attainment following a dose of 2g meropenem infused over 3 hours. The variability in effect site penetration did not provide acceptable target attainment, particularly for minimum inhibitory concentrations (MICs) higher than 1.0 mg/L.

The value of combination therapy was then addressed. For example, cefepime plus tobramycin suppressed the emergence of resistant organisms *in vitro* when tested against *P. aeruginosa* producing AmpC β-lactamase when neither agent alone was able to achieve this effect. It was hypothesized that tobramycin shut down the expression of the AmpC β-lactamase.

The principles already demonstrated in experiments with meropenem and cefepime can be applied to new agents for MDR pathogens when used alone and in combination, even when they are studied only in small trials, provided that adequate and appropriate data are collected to enable PK-PD analyses. Using these techniques to identify optimal treatment regimens also has the potential to minimize the risk of selecting for resistant organisms.

“Antibiotic development for resistant bacteria: A pharmacometric-based solution”

by **Paul Ambrose**, Institute for Clinical Pharmacodynamics, USA

The use of PK-PD analyses could be expanded beyond their established role in non-clinical drug evaluation and dose regimen selection for early stage clinical development. PK-PD analyses could be used to identify the magnitude of antibacterial treatment effect, which is a critical element of non-inferiority study design, and as part of the evaluation of limited clinical data to support regulatory decisions.

For example, PK-PD analyses could be used to support the approval of a new antibacterial agent active against MDR pathogens in the setting of a single randomised clinical trial plus other clinical and non-clinical data. This approach requires i) an appropriate non-clinical model to demonstrate the effect of a specific resistance determinant on the PK-PD index required for efficacy; ii) adequate blood samples from patients treated for infections due to wild-type (i.e. data obtained during a randomised comparative trial allows evaluation of exposure-response relationships) and iii) adequate blood samples from patients infected with MDR pathogens (i.e. data mostly obtained from a smaller study, which may be uncontrolled, to allow integration of results across the clinical trials).

Data from non-clinical models have shown that the presence or absence of specific mechanism(s) of resistance does not predict outcome. Rather, it is the MIC and drug exposure indexed to the MIC that

matter. The dose may need to be increased as MIC increases and it may not be possible to overcome resistance at the highest dose that can be tolerated. A review of relevant PTA (Probability of Target Attainment) estimates reported for 20 antibacterial agents that were evaluated for use in community acquired pneumonia (CAP) and/or hospital acquired pneumonia (HAP) has demonstrated that the use of non-clinical PK-PD models and calculations of PTA have already made an impact on the likelihood of regulatory approval for use in these indications.

In the setting of a single randomised comparative study it has been demonstrated that PK-PD relationships apply equally well in man as in non-clinical models. For example, among patients enrolled in a study that compared ceftazidime with ceftobiprole for the treatment of HAP patients who had pathogens with documented MICs at baseline and adequate PK sampling, the clinical response rate correlated very well with the ceftazidime (f)T>MIC (the percentage of the dosing interval that the free drug concentration remains above the MIC of the agent for the infecting organism). In addition, PK-PD analyses in the setting of a small non-comparative study in bacteraemic patients infected with extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* and treated with various intravenous cephalosporins showed that the likelihood of clinical response correlated well with (f)T>MIC.

A pharmacologically-based package can be used to balance data quantity and quality against the unmet clinical need. By accumulating pieces of evidence as outlined, it is possible to put together a relatively robust data package to support an appropriate clinical dose regimen of a new antibacterial agent to treat organisms up to a defined MIC. These approaches can also point to the treatment effect that is achieved as the PK/PD parameter increases, from which appropriate non-inferiority margins may be deduced.

Discussion on PK-PD and Pharmacometrics

Both presentations pointed to the need to ensure that clinical trials in infected patients plan for adequate sampling for PK purposes as well as the collection of pertinent clinical data to support thorough pharmacometric analyses. It was discussed that these activities add to the complexity of clinical trials and patients may not always be willing to consent to procedures over and above those needed for routine care. However, the particular need to obtain such data in the setting of very limited clinical development programmes that might apply to new antibacterial agents active against MDR pathogens was underlined. As experience accumulates with the use of pharmacometrics in this area of drug development it may be possible to identify a minimum list of parameters that should be recorded during trials.

There are occasions when PK-PD analyses may fail to predict a reliably effective clinical dose regimen. There have been instances when it was possible to develop an exposure-response pre-clinically but not clinically even when a very high proportion of patients provided adequate plasma samples.

Due to the lack of an immune system the results of HFI models will point to the use of high doses to achieve multi-log cell kill and/or resistance suppression. Such a bias often applies, but to a lesser extent, in neutropenic animal models because granulocytes have a major role in defence against many bacteria.

There is a need to use an appropriate non-clinical model to derive a target for use of an antibacterial agent in a specific indication. The importance of taking into account infection site penetration data rather than relying solely on plasma levels is increasing in prominence along with recognition that human site penetration may be quite different from that in non-clinical models. It is also already apparent that assumptions regarding site penetration cannot be based on the drug class/sub-class to which a new agent belongs.

The feasibility of obtaining site-specific PK data other than ELF was questioned. The reliability of drug concentrations in tissue samples in which the result may be heavily influenced by the blood content was raised as an issue that may limit attempts to assess site-specific PK-PD analyses.

2.2. "Clinical trials"

"Superiority and organism-specific clinical trials of antibacterial agents"

by **Helen Boucher**, IDSA, USA

This presentation was on behalf of the Infectious Diseases Society of America (IDSA), which issued a *White Paper* during 2012 that discussed approaches to clinical trial designs, including consideration of the potential to demonstrate superiority for a new agent over best available treatment (BAT) against relevant MDR pathogens.

Guidance is needed that refers to feasible clinical programmes which, subject to satisfactory findings, can be predicted to support approvals for standard types of indications and specific indications for MDR pathogens. Development pathways should be suitable for multiple new agents over time and should take into account that any expectation of demonstrating superiority will become less as new agents are approved. However, demonstrating superiority vs. historical controls would remain a possibility provided that the controls are relevant to current clinical practise. The IDSA foresees that small studies could be sufficient to support initial approval of agents that can address an unmet clinical need, such as infections due to MDR Gram-negative bacteria.

The White Paper recognised that options could include non-inferiority trials that include sequential testing for superiority or a nested superiority design, monotherapy studies in some types of infection that aim to show superiority and uncontrolled studies where no BAT exists and a demonstration of superiority over historical controls.

The likely success of such approaches may depend on issues such as availability of rapid diagnostic techniques to detect MDR pathogens of interest and, hence, influence the final study size, adequate rescue therapies and sufficient sites known to have problems with particular pathogens that are able to conduct trials to GCP standards. There are also practical difficulties to overcome with regard to enrolling sufficient patients, pointing to the need to include patients with infections at a range of body sites and acceptance of small pre-licensure datasets and plans for post-marketing studies.

If organism-specific superiority studies are attempted, consideration should be given to endpoints other than cure and eradication and possibly composite endpoints. Demonstrating benefit vs. licensed agents in terms of safety was also recognised to be an option to explore in some cases. The comparators allowed should be stated in protocols and may need to comprise agents and/or dose regimens that are not approved for use in the US or EU.

The IDSA supports the Limited Population Antibacterial Drug (LPAD) mechanism, which has been proposed as a new development pathway based on small clinical trials in infections due to MDR pathogens. This proposal is under discussion in the US as a means of formally accepting very limited data on clinical safety and efficacy before approval for use in a very limited setting.

"Treatment of serious infections due to MDR Acinetobacter baumannii. Presentation of a multicenter randomized clinical trial"

By **Ricardo Utili**, University of Naples, Italy

In a randomised open-label study[1] conducted during 2008-2011 at 5 sites in Italy, colistin was compared with colistin + rifampicin for the treatment of 210 patients infected with XDR *A. baumannii* and managed in ICUs. The range of infections included HAP, VAP (the majority; 69%), bacteraemia and intra-abdominal infections. Randomisation was stratified by centre and SAPS II scores < 40 or ≥ 40. Treatment was with 2MU colistin q8h with or without rifampicin 600 mg q12h for 10-21 days. The sample size was based on the objective to show an absolute reduction in day 30 mortality of 20% assuming an actual rate of 60% in the colistin only group.

"Discussion"

Issues regarding the IDSA White paper and the proposals made for development programmes were taken up under the main discussion (see below).

The study in patients with *A. baumannii* illustrated many of the issues that can be anticipated to affect the design and findings of studies in patients infected with XDR/MDR pathogens. The study stretched over 2-3 years but it did enrol 210 patients with XDR organisms of a single species causing infections at a range of body sites. There was debate regarding the dose of colistin that was used and adjustments made for renal function. The regimen used reflected the prescribing information but the optimal regimen and schema for adjustments remains to be identified. Nevertheless, currently 3 megaunits thrice daily is more widely used. In this regard, no patient PK data were obtained during the study in *A. baumannii* infections but prior in-vitro data had supported the use of colistin plus rifampicin in combination.

"Drugs for MDR pathogens - Issues in development"

by **Mark Goldberger**, Abbott, USA

An overview was presented of the European Federation of Pharmaceutical Industries and Associations (EFPIA) Working Group's proposal for an expedited approach to the development of new antibacterial agents potentially active against MDR pathogens, whether they have a broad or narrow spectrum of antibacterial activity. The underlying premise is that the potential for a new agent to address an unmet need justifies acceptance of greater uncertainties regarding safety and efficacy compared to routine development programmes. The proposal is based on programmes that provide some degree of clinical evidence of efficacy but, depending on the properties of each agent, this is expected to be markedly less extensive than is usually provided in the more standard types of indications for use. Initial applications for marketing authorisation will rely to a considerable extent on support from PK-PD analyses. The resulting prescribing information will reflect the uncertainties.

Building on observations made regarding PK-PD, any clinical data obtained from patients infected with wild-type organisms would be informative.

Gathering clinical experience in treating MDR organisms may need to encompass patients with all types of infection. Pooling of data across infections at a range of body sites needs support from detailed knowledge of PK-PD properties of the agent and the range of species known or most likely to be causing the infections. While a randomised design has the advantage of a control group that has similar characteristics to the group that receives the test agent this may not always be feasible, taking

[1] Since the Workshop this study has been published in Clin Infect Dis. 2013 Aug;57(3):349-58

into account patient numbers and the heterogeneity of comparative regimens that is likely to be needed.

If the data are obtained from a non-randomised study the interpretation of the data could be facilitated by the use of external controls from which sufficient details are obtained to substantiate the relevance of the clinical success rates to those observed with new agents.

Once there is at least one agent approved for treatment of a particular type of MDR pathogen, the unmet need cannot be viewed as addressed. Having more than one option available may provide efficacy when there is resistance to or intolerance of the first agent. Nevertheless, demonstrating superiority for each sequential agent over the first approved agent(s) is not likely to be feasible based on endpoints such as cure and eradication and may not be possible based on alternative exploratory endpoints. Therefore, acceptance of a non-inferiority approach is considered essential.

It was pointed out that patients who are not necessarily severely ill at presentation may be at high risk of progression to the more severe end of the spectrum if not managed appropriately from the start. Therefore, demanding that patients enrolled into studies with new agents should meet pre-defined criteria that may equate with likely more severe infections is not necessarily appropriate and requires careful consideration. In the case of studies in population infected with MDR pathogens, the most important criterion is that patients have or have a very high likelihood of harbouring the type of pathogen of interest.

Finally, there is a need for regulatory bodies to agree on the basic components of programmes that could suffice to achieve approval of new agents active against MDR pathogens. In addition, Regulators should reach agreement on issues such as acceptable comparators and the construct of external control cohorts.

2.2.1. Example scenarios: outline proposals of possible development programmes for specific types of products:

"Issues to address for a new active substance (NAS) with fairly broad spectrum that will include one or more MDR/XDR pathogens"

by **Barry Eisenstein**, Cubist, USA

Building on an extensive PK-PD evaluation, a clinical programme to evaluate efficacy was proposed to consist of one randomised comparative study in a single infection type with a standard non-inferiority design. The study would not plan to enrol pre-specified numbers infected with the MDR pathogens of interest. The study would be accompanied by an uncontrolled study in patients infected with the MDR pathogen of interest at a range of body sites (including the type of infection selected for the comparative study). Proposals were made for the possible content of the prescribing information that would result from a limited programme along these lines.

"Issues to address for a NAS with narrow/very narrow spectrum that will include one or more MDR/XDR pathogens"

by **Aaron Dane,** AstraZeneca, UK

Consideration was given to the clinical programme for an antibacterial agent when the conduct of an adequately powered non-inferiority study may not be feasible.

One possible approach could include a randomised study that compared the new agent to BAT for treatment of infections at multiple body sites. The study could be conducted at centres where the MDR

pathogens of interest are known to be a problem but having such an infection would not be a strict requirement for eligibility. The randomised study could be accompanied by an uncontrolled study in infections due to MDR pathogens for which there is no BAT (i.e. in a salvage population) and an observational study to collect external control data in patients that inadvertently receive ineffective treatment for the MDR pathogen of interest.

Another approach might be to conduct a randomised study in a single infection type that enrols numbers that would not be sufficient for an evaluation of non-inferiority, at least not using the usual non-inferiority margins and level of alpha. This would have the strengths of providing a randomised comparison and it could enrol patients infected with wild-type and MDR pathogens of interest. Such a study could be analysed using alternative approaches and explore comparisons based on alternative endpoints, for which some suggestions were made. Since infections at different sites may yield different response rates both rank order and examination of the magnitude of responses across indications may assist in analysing small datasets.

Proposals made for the analysis of such a study included pre-defining a wider than usual non-inferiority margin or an alternative level of alpha (e.g. 5 or 10%), taking into account acceptance of a greater degree of uncertainty regarding the treatment effect for a new agent that may address and unmet need. Examples illustrating the effect on the sample size calculation were presented. The use of Bayesian priors was proposed as another possible approach provided that there are sufficient and relevant historical data to draw from. Reasons why demonstrating superiority for a new agent over BAT is very unlikely to be feasible within a randomised study were presented.

For some new agents the options for clinical study design will be even more limited. A very small prospective randomised study could be considered but this would not permit inferential testing. It may be that an uncontrolled study that enrols patients with infections due to the MDR pathogens of interest at a range of body sites is all that is feasible for some new agents. The use of relevant external controls could assist in interpreting such data. Pooling data across body sites needs to take into account the possibility of different primary endpoints and variable response rates.

"Considerations in the development of beta-lactamase inhibitor combination products for MDR pathogens"

By **Mike Dudley**, Rempex, USA

For the beta-lactam + beta-lactamase inhibitor (BL/BLI) combinations already available, non-clinical information on inhibition of beta-lactamases and restoration of beta-lactam activity has been shown to correlate with clinical efficacy. Products currently in development for treating MDR pathogens include existing BLs paired with new BLIs and a wholly new BL/BLI combination. In the former type of product the existing experience with the BL provides important background safety and efficacy data that can be built on during development of the combination, with implications for the total programme content.

Non-clinical studies, including use of HFI models, can demonstrate the effect of the BLI in restoring the activity of the BL in terms of reducing MICs to within the range observed for wild-types of the same species. In this way the PK-PD index can be identified for the BL and BLI. Using these data, it is not necessary to enroll large numbers of patients infected with BL-resistant, BL/BLI-susceptible organisms to confirm the efficacy of the combination.

Pharmacometric analyses of patient data derived from treatment of organisms susceptible to the BL and organisms resistant to the BL but susceptible to the BL/BLI can assist in quantifying the effect of the inhibitor. These analyses can be applied in the setting of randomised controlled studies or uncontrolled studies that employ comparisons to external controls. In each setting data obtained from

patients infected with BL-susceptible strains can serve as an internal control for the data obtained from the BL-resistant BL/BLI-susceptible strains.

Discussion of clinical trials for antibacterial agents with activity against MDR pathogens

General observations

For many of the types of new agents with potential activity against MDR pathogens the conduct of adequately powered randomised controlled trials in specific indications will not be feasible. For new agents that could be studied based on a conventional type of clinical development programme, the implications for the time taken to first authorisation have to be taken into account. To make these new agents available as soon as possible will not only mean that initial applications would provide limited clinical efficacy data but also that the safety databases will be much smaller than is usually expected. Hence, an acceptance of greater uncertainty regarding both safety and efficacy is inevitable to make potentially valuable new agents available in a reasonable time frame. The concept of a restricted evidence base for an initial regulatory decision is relatively novel for antibacterial agents but there is considerable regulatory experience across other therapeutic areas.

Content of development programmes

The examples outlined in the draft *Addendum* to the core antibacterial guideline and the additional proposals made during the presentations are not expected to cover all possible scenarios and sponsors may suggest alternative strategies.

In the case of new agents with a broad antibacterial spectrum some of the options include conduct of standard non-inferiority trials, each in a single indication, with addition of a supplementary trial in MDR pathogens of interest. This programme could result in standard indication(s) for use as well as a restricted indication for use against MDR pathogens. Supplementary trials could be conducted in a range of infection types including those not selected for the standard non-inferiority trial(s) and could be confined to or at least enriched for the MDR pathogen(s) of interest. A randomised study in one or more types of infection that is not of a size to support a demonstration of non-inferiority could support use for treating MDR pathogens but would not be sufficient to support a standard indication for use.

Opinion was expressed that the use of intensified data collection in a small randomised study and the application of pharmacometrics potentially could yield more relevant information for treatment of MDR pathogens than would be obtained from one or two standard non-inferiority studies.

Regarding the clinical development of sequential new agents that address the same type of MDR pathogen(s), there was recognition of the need to have several new agents available to provide choice. Thus, having one new agent approved to address a specific unmet need should not prevent the approval of others that can address the same problem. It could be argued that there is particular benefit in these settings to have multiple drugs licensed to avoid loss of chance to the patient. Nevertheless, the availability of a suitable active comparator has inevitable implications for the design of subsequent clinical trials and the content of clinical programmes. Obtaining clinical experience in the treatment of MDR pathogens of interest will still be difficult but the feasibility of conducting small randomised studies will be enhanced.

In the post-approval period some of the new agents may be studied in standard randomised controlled studies to support additional indications for use but for some agents (e.g. those active against a single species) adequately powered randomised trials may not be feasible. Such studies would provide an important addition to the safety database. In the post-approval period it will be especially important to

identify ways to collect additional information on efficacy against MDR pathogens of interest and to assess the risk of selecting for resistant organisms.

Trial designs

In situations where considerations of feasibility dictate that a conventional level of evidence will not be available for regulatory decision making, a number of compromises were discussed including uncontrolled trials, the use of external or historical controls, the application of Bayesian methods and placing increased weight on modelling and simulation to support decision making.

Non-inferiority trials

The possibility of conducting feasible non-inferiority trials included consideration of the selection of non-inferiority margins since this directly influences the sample size calculation. A non-inferiority trial that aims to show (indirectly) only that the experimental regimen is superior to placebo may be able to justify use of a larger non-inferiority margin than a trial that additionally tries to quantify differences between active regimens, more commonly with the aim of excluding any differences in effect that are deemed to be of clinical relevance.

Superiority trials

The potential to demonstrate superiority of a new agent over a designated comparator, over best available therapy (BAT) or over external or historical controls infected with similar MDR pathogens was debated. Whilst a demonstration of superiority would be viewed as a desirable finding there is low feasibility for showing superiority based on cure or eradication. The likelihood of demonstrating an added benefit for the new agent based on any endpoint will vary according to the type of MDR pathogen of interest and the content of the BAT applied within a randomised study or in external controls. As new agents are approved there is even less likelihood that later products will be able to demonstrate superiority for any endpoint.

An exploration of superiority in terms of endpoints other than cure or eradication (e.g. time to resolution, mortality and safety parameters) could be performed but failure to show any superiority was not viewed as a reason to preclude approval. A trial with the aim of showing superiority on parameters not usually considered to be primary variables (e.g. safety) may well incorporate a non-inferiority hypothesis on the usual primary (efficacy) variable to exclude any important loss of effect.

The proposal to use an 'inflated alpha' for assessment in a superiority trial could be discussed with regulators in situations where it is not feasible to recruit a sufficient number of patients for a conventionally powered trial. However, a statistically significant hypothesis test (measured against an artificially inflated nominal significance level), which appears to drive the desire to use an inflated alpha level, might not necessarily represent the most critical factor for a positive regulatory decision.

Uncontrolled trials

The potential problems associated with the use of historical controls or external controls rather than concurrent, randomised control groups were appreciated. The recognised benefits of having a randomisation step even when a fully powered controlled trial may not be feasible means that reliance on historical or external controls requires considerable justification. The use of historical controls would have to be underpinned by identification of representative well-conducted trials in which the patient populations and standards of care remain relevant to current practise and where the methods of data collection, synthesis and analysis were similar to those proposed for the prospective, uncontrolled study. In addition, it would be preferable that consistent results have been reported across multiple

historical datasets. If external controls are used, collection of relevant data could commence in the period before the study is initiated as well as during enrolment to provide recent data highly relevant to the patients who receive the new agent.

Bayesian methods

Experience with the use of Bayesian methods in confirmatory analyses of primary endpoints of clinical trials is presently sparse. It may seem attractive to use a Bayesian approach with informative prior in situations where a fully powered randomised controlled trial is not feasible, so that prior information combined with the 'likelihood' from the underpowered trial gives a level of evidence that meets conventional standards.

Alternatively a Bayesian approach may seem attractive as a quantitative approach to pool multiple sources of evidence, either relating to the control group of a prospective trial (in this case issues relevant to 'historical controls' need to be addressed) or to the experimental agent, combining information from non-clinical models and PK/PD analyses.

The use of non-clinical models and pharmacometric models can be of particular relevance for this type of drug development and would make a good topic for broader discussion between industry and regulators considering how to construct prior distributions, how to validate the assumptions underpinning the model and what should be the minimum contribution of the data from the prospective trial to the overall evidence base (analogously the weight of the prior information in the Bayesian model).

Monotherapy vs. combination therapy

It may not be possible to evaluate new agents as monotherapy in trials that are confined to or enriched for MDR pathogens except, perhaps, in urinary tract infections (UTI), including complicated urinary tract infections (cUTI) and pyelonephritis. Otherwise, assuming that an individual pathogen is susceptible to at least one authorised agent, investigators may not be willing to risk monotherapy even when *P. aeruginosa* is not the pathogen being treated because such patients may already be very ill and may have an enhanced high risk of failure when treated with a single active agent.

Double-blind studies

The feasibility of conducting double-blind trials in these settings was considered to be low, with the exception of a programme in which one standard non-inferiority trial is performed in a specific indication. In other settings the need for tailored combination therapy and for allowing a range of comparators would seem to rule out a double-blind design. There is also the possibility that within a comparative study there could be instances in which the protocol allows switching patients in the comparative arm to the new agent if there is no BAT available for their pathogen.

Clinical efficacy by indication and by body site

Pooling data across types of infection may be problematical, especially if PK-PD analyses point to the use of different dose regimens according to body site and there are reasons to avoid using a single maximal regimen in all instances. In addition, in a trial that enrols patients with infections of many types it may be necessary to plan for a range of endpoints and comparative regimens. There could be concern if the actual results suggest that a new agent might not be as good as comparative treatment or falls below response rates observed in external controls when treating infections at any one site.

The extrapolation of results obtained in one type of infection to infections at other body sites raises some concerns, in particular if a randomised comparative study is confined to patients with cUTI and the agent in question reaches relatively high concentrations in the urine. However, it may be that for

some agents a prospective randomised comparison is only feasible in patients with cUTI and, subject to careful evaluation of PK and PK-PD relevant to other sites, such data could be deemed valuable. Also, it appears that UTI due to MDR pathogens is a real clinical problem so that such patients may be readily available for study. For example, such patients (who may have indwelling catheters) may have recovered from the illness that caused hospitalisation and may have been discharged but cannot clear the organism.

In trials that allow enrolment of patients infected with specific MDR pathogens regardless of site it is possible that patients who only have the organism in blood cultures (i.e. no primary focus of infection identified) could be enrolled. If there is doubt that the new agent and/or the dose regimen are suitable for infections at certain body sites it might be prudent not to include cases of primary bacteraemia at least until there has been some clinical experience gained in the treatment of a range of infection types.

Other issues

The use of mortality as an efficacy endpoint was discussed. Early mortality (e.g. at 14 days) could be included as a secondary endpoint. Later mortality (e.g. at 28 days) was not viewed as a sensitive endpoint due to the many non-treatment-related causes of death that might apply and which confound this endpoint. It was also noted that targets obtained from non-clinical studies that are used to derive dose regimens are not based on mortality but on the early microbiological response to treatment.

The potential ecological effect of new agents on selection of resistance was also debated. Generally, it was not considered fruitful to evaluate the effect of new agents on the normal flora during clinical trials. The selection of potentially pathogenic species within the normal flora that are resistant to the new agent may occur during treatment without any impact on patient outcome. The risk could be greater if resistant sub-populations become well established, which may occur especially during prolonged therapy. This possibility has implications for the duration of treatment and mandating potentially unnecessarily long durations of treatment in protocols should be avoided.

The collection of appropriate PK data needs to be balanced against the clinical status of patients and the fact that sites that are selected for their rates of MDR pathogens may not be the most experienced at collecting and handling samples. If detailed PK data are limited it may still be possible to obtain sparse PK data to enrich the population PK model.

Discussion on regulatory interactions

The EU regulatory system welcomes discussion on novel methodological approaches to drug development. The qualification process can be used to discuss biomarkers, methodological approaches, or any other scientific questions outside the context of a particular drug development programme.

These pathways compliment the formal Scientific Advice / Protocol Assistance process offered by EMA / CHMP and by individual National Competent Authorities. EMA / CHMP Scientific Advice can be conducted as Parallel Scientific Advice, i.e. a tripartite interaction involving regulators from both EU and FDA.

Session 3: Companion diagnostics for the rapid diagnosis of MDR pathogens

"Challenges to develop diagnostics for treatment of MDR pathogens"

by **Herman Goossens**, University of Antwerp, Belgium

The technology exists (e.g. on chip bacterial lysis and DNA purification/amplification is now a possibility) but to develop feasible rapid diagnostics that are highly relevant to patient management cannot be achieved by either industry or academia alone and this is an area in which public-private partnerships may be particularly fruitful. In this way, platforms can be developed that will ultimately lend themselves to many possible specific uses. Alongside the technical issues are the regulatory factors relating to in-vitro diagnostic devices (currently undergoing revision in the EU) and the eventual acceptance of rapid diagnostics by clinicians engaged in routine patient management.

For each potential rapid diagnostic test there is a need to identify the optimum biological material on which to perform the test (including sample preparation) and to assess its potential to differentiate colonisation from infection. It is already possible to detect species and resistance mechanisms in a single test that also provides some degree of quantification but in reality it may be that not all these functions are strictly necessary depending on the intended mode of use of the test. In particular, depending on the intended use there is a need to decide whether speciation is mandatory and how many types of resistance should be sought in order to guide initial treatment.

As an example, there are several issues surrounding detection of particular types of beta-lactamases in terms of the very large number of variants that can occur. It is possible to produce tests that detect widely shared sequences although this will not inform regarding the level of expression. The information that is needed to select treatment is not the same as that which would be required for epidemiological and infection control purposes.

"Diagnostics: A focus on use in development of drugs for MDR pathogens"

by **John Rex,** AstraZeneca, UK

New diagnostics need to be simple to use and provide rapid results. In the setting of clinical trials diagnostics can help overcome the low sensitivity of classical culture techniques, the variability of sampling methods and transportation issues for viability and, ideally, problems distinguishing colonisation from infection. What is really needed are predictive diagnostics (i.e. that predict the result of culture and/or susceptibility) to enhance patient selection for receipt of a new agent during a clinical trial and subsequently optimise the appropriate use of a new antibacterial agent during routine clinical use.

The acceptable sensitivity and specificity of rapid diagnostic tests used in these settings should take into account how they will be used to enhance treatment selection rather than provide definitive diagnoses. For example, any rapid test that surpasses the performance of routine culture by providing a reasonably reliable result within a short timeframe has potential to enhance the stewardship and cost-effectiveness of antibacterial agents. At the same time, the cost of the test requires consideration. It may be anticipated that some platforms are going to be too expensive for routine use but could be wholly viable for use in clinical trials since the cost of the test would be balanced against the cost of enrolling non-evaluable patients.

Rapidity is of particular relevance to clinical trials with antibacterial agents since a test result could minimise the need for pre-study treatments and at the same time enhance the inclusion of eligible patients, resulting in a final study population that includes a high percentage of clinically and microbiologically evaluable patients. Nevertheless, rapid tests may not always be similarly informative as positive cultures, especially taking into account the fact that they may be picking up unknown quantities of live vs. dead bacteria that may reflect the efficiency of the patient's immune response with attendant implications for prognosis. In contrast cultures reveal only the live bacterial burden not dealt with by the immune system.

Issues that require further consideration include the regulatory approach to predictive rather than definitive diagnostics and concerns that the use of a predictive diagnostic during clinical trials might result in a direct link to its use after licensure of the antibacterial agent. This then raises issues regarding test development and approval timelines quite separate to those for the antibacterial agent itself.

Discussion

Developing a rapid diagnostic test and obtaining regulatory approval for routine use in parallel with developing a new antibacterial agent is potentially problematical and very labour intensive. The Companies developing new antibacterial agents may not have the required infrastructure and/or capacity to develop new diagnostic tests in parallel, hence the value of public-private partnerships.

Several different platforms now seem to be possible for rapid diagnostic tests. Each type of platform, taking into account ease of use (e.g. can the test be performed by the physician or would trained laboratory staff be needed) and cost, may have potential for clinical trial patient selection but may not be equally suited for use as a routine point of care diagnostic test. The ideal features of a test may also differ according to clinical trial or routine use. While a desirable timeframe for obtaining a result would likely be < 2 h in either case the requirements for sensitivity and specificity may not necessarily be the same. In addition, in routine use there is more potential that the test would be used to guide changes to therapy, in which case perhaps the time to obtain a result is not so critical.

The use of rapid diagnostic tests alone, including unapproved tests, to qualify patients for inclusion in the microbiological ITT and evaluable populations requires further consideration depending on the features of the test and accompanying documentation. At present the use of such tests to guide enrolment is acknowledged but only urinary antigen detection tests for *S. pneumoniae* and *L. pneumophila* have been accepted in the EU *in lieu* of positive cultures to establish the causative pathogen.

Session 4: Discussion on specific indications

"Regulatory status"

by **Mair Powell**, Medicines and Healthcare Products Regulatory Agency, UK

The approach that has been taken in the draft *Addendum* to the *Guideline on evaluation of medicinal products indicated for treatment of bacterial infections* (CPMP/EWP/558/95 rev 2) is to consider clinical trials to support five major indications that are commonly sought and then to discuss trials for some other types of indications that have been the subject of requests for scientific advice. The draft *Addendum* reiterates the focus on clinical and/or microbiological primary endpoints assessed at post-therapy test of cure (TOC) visits. The suggested non-inferiority margins have taken into account their perceived ability to differentiate the treatment effect from placebo, an acceptable difference with SOC and also to some extent the feasibility of recruitment. Specific recommendations for patient selection

criteria have been kept to the minimum considered to be crucial since it was considered that making very detailed recommendations increased the potential for conflict with the requirements of other regulatory authorities, which could hinder the use of trials to support global submissions for marketing authorisation.

"Hospital-acquired and ventilator-associated pneumonia (HAP/VAP)"

By **Serge Kouzan,** St Julien en Genevois Hospital, France

A comparison was made between the guidance provided in the draft *Addendum* and the corresponding draft FDA guidance document. Whereas there seems to be balance between flexibility and specificity of the enrolment criteria suggested in the draft *Addendum* it was proposed that there should be more specificity on several issues that are considered to be most important for patient selection and management. Some of the discrepancies between guidance documents were questioned because the rationale is not clear (e.g. the lack of a statement on physical signs, elderly patients and patients with renal insufficiency in the draft *Addendum*).

The draft *Addendum* states that patients with VAP should be intubated but it was pointed out that patients receiving non-invasive ventilation (NIV) are actually at greatest risk of mortality and should not be excluded from trials. The exclusion of patients who have only attended a hospital emergency department requires clarification to allow enrolment of those who may have stayed at least 48 h in an emergency care ward or developed pneumonia within 7 days of discharge from such a facility.

The draft *Addendum* also makes reference to the anticipated overall mortality rate in such studies and recommends the use of various scoring systems but there is no definitive guidance provided except that the Clinical Pulmonary Infection Score (CPIS) ≥ 6 was suggested as a requirement for eligibility, which will likely exclude about 25% of potential patients from trials. It was proposed that the focus should rather be on enhancing the proportion with a documented pathogen and thereby minimising the difference between the intention-to-treat (ITT) population and the population comprising all patients with a pathogen.

Overall, there was concern that the lack of detail in the draft *Addendum* could result in a trial population with relatively less severe infections associated with a low mortality rate and make it difficult to detect real differences between regimens. Separate HAP and VAP studies are preferred to avoid any possible dilution effects (i.e. allowing a mixed study provided that a minimum of 30% of patients have VAP was not supported) along with more detailed recommendations that minimise the risk that sub-optimal agents and/or dose regimens could be approved. In particular, it was proposed that the FDA and EU requirements should be more closely aligned and that the focus should be on the adequate assessment of new agents suitable to treat the ESKAPE pathogens (*E. faecium*, *S. aureus, K. pneumoniae, A. baumanii, P. aeruginosa* and *Enterobacter* species).

"HAP-VAP"

by **David Friedland**, Forest-Cerexa, USA

With regard to the suggestions made in the draft *Addendum*, the allowance for up to 24 hours prior antibacterial treatment before randomisation and designation of the ITT and clinically evaluable (CE) populations as co-primary were considered acceptable. In a mixed HAP/VAP study the requirement that at least 30% should have VAP may not be practical due to decreasing incidence of VAP as preventative measures improve and 25% was suggested to be appropriate. CPIS ≥ 6 should not be a requirement for eligibility. A non-inferiority margin of 12.5% is appropriate if a single pivotal study is conducted and would require approximately 970 subjects based on standard assumptions and 45%

clinical evaluability. It was proposed that Day 14 rather than Day 28 mortality should be included among the secondary endpoints since Day 14 rates give a better measure of efficacy while day 28 rates are more relevant to the safety assessment. Addition of antibacterial agents to provide dual therapy for *P. aeruginosa* or to cover pathogens not within the test agent spectrum should not affect evaluability.

In addition to the suggestions made in the draft *Addendum*, and in light of the perceived slow enrolment and low percentage of MDR pathogens of interest that could be expected, it was questioned whether a qualified indication for use in HAP/VAP for a new agent expected to be active against MDR pathogens could be based on provision of at least one standard pivotal trial in another major indication accompanied by a relatively small randomised study in HAP/VAP (i.e. not powered to demonstrate non-inferiority).

Discussion

It was pointed out that failure of an antibacterial agent to provide suitable efficacy in HAP/VAP has been evident from some recent trials despite the difficulties in interpreting the data (e.g. due to allowances for additional antibacterial agents). Enrolling sufficient patients into HAP/VAP trials in a reasonable time frame to provide an adequately powered assessment of non-inferiority was viewed as a major hindrance and alternative means to obtain the requisite clinical experience to support an indication for use are needed. Allowing patients to be enrolled based only on prior residence at a chronic healthcare facility (i.e. not specifically a hospital) would assist enrolment.

There was some support for BAL and/or "mini-BAL" techniques to improve pathogen recovery but others considered that their use has not been demonstrated to be superior to other specimens in this respect. The use of quantitative culture poses several problems not only regarding the methodology used for quantification but also the lack of experience by routine (trial site) diagnostic laboratories. The use of centralised laboratories to perform quantitative cultures was not considered to be a feasible solution because specimen transportation studies using controlled conditions and time lines have demonstrated very considerable loss of viable organisms. Importantly, there is no consensus on the cut-offs that should be applied to quantitative culture results to determine a possible causative role of the organisms rather than colonisation.

Session 5: Discussion on specific indications: Community acquired pneumonia (CAP) (PORT III and IV)

"Clinical trials in CAP"

by **Francesco Blasi**, University of Milan, Italy

The location in which the patient with CAP is treated has commonly been inextricably linked to the severity of the pneumonia, the benefit that may be obtained from specific or supportive treatment and probability of morbidity and mortality. The mortality in HCAP approximates to that in HAP. The risk of a causative MDR pathogen is higher in the HCAP population (based on one of several possible definitions) vs. those with spontaneously occurring CAP in the absence of any contact with a healthcare facility. In particular, MDR pathogens are more likely to occur in those who reside in a healthcare facility, have been hospitalised for a least 2days within the prior 90 days and/or have chronic renal failure.

The PSI and CURB scores have utility in selecting low risk patients suitable for outpatient treatment but are not so good at predicting which patients will require ICU management. In particular, they may over-estimate severity in older patients and those with chronic organ dysfunction and under-estimate severity in younger patients.

"Community-acquired pneumonia (CAP)"

by **Keith Barker**, GSK, UK

Many suggestions made in the draft *Addendum* for trials in CAP were supported but there were some concerns expressed. In particular, HCAP patients are excluded from both the CAP and HAP trial populations in the current draft *Addendum*. HCAP represents an intermediate group between CAP and HAP in terms of morbidity and mortality and risk of MDR causative pathogens so that excluding such patients reduces the chance of enrolling cases due to MDR pathogens.

It is considered essential to allow transition from intravenous to oral treatment based on protocol-defined criteria but a minimum duration of initial intravenous therapy is not considered necessary if the oral regimen is with the same agent and provides comparable plasma exposures to parenteral therapy. It was also proposed that adjunctive treatment for atypical pneumonia should be allowed at study entry when the test agent is not suitably active, even when the additional agent likely provides overlapping cover for standard CAP pathogens (in particular for *S. pneumoniae*).

Typically the microbiological evaluability rate in CAP studies is only about 30% of the total enrolled. It was proposed that the results of rapid diagnostic tests other than those already accepted by CHMP in prior submissions should be sufficient for patients to be counted among those with a pathogen.

The final *Addendum* should clarify the acceptability of pooling data across single Phase 3 studies in each of CAP and HAP/VAP, the alpha level that would be required for a single pivotal study and whether provision of a much larger ME population than has hitherto been the case could support a larger non-inferiority margin.

Discussion

There was some debate regarding the need for and allowance of routine or optional adjunctive treatment for atypical pneumonia, mainly due to the potential that this treatment would also provide activity against pneumococci. However, certainly at some trial sites there may be high rates of resistance to macrolides among pneumococci so their use in conjunction with a test agent would not impact on the efficacy observed. Some considered that trials would not be feasible unless they allowed additional agents to cover atypical pneumonia while others considered that cover was not urgent if the urinary antigen test for *L. pneumophila* was negative (although it was pointed out that the test does not pick up all cases nor does it detect all *Legionellae* of concern).

A proposal was made that unapproved rapid diagnostic tests could be considered sufficient for inclusion among all patients with a pathogen.

There was some support for the proposal that a single CAP and single HAP study could be mutually supportive but the differences in pathogens and in patient characteristics (e.g. rates of underlying and predisposing conditions) could be problematical.

Session 6: Discussion on specific indications: Urinary tract infections (UTI), intra-abdominal infections (IAI), skin and soft tissue infections (SSTI)

Most of the discussion focused on studies in various types of UTI. Several commentators had pointed out that there is a particular problem with chronic UTI caused by MDR pathogens that were acquired during hospitalisation. This occurs not only in patients after discharge but also in hospitalised patients who were infected during prior ICU residence. While these patients represent a not insignificant population with MDR pathogens available for study there were some concerns expressed regarding

pivotal trials with agents suitable for MDR/XDR in chronic UTI. On the other hand, there was some opinion that any experience in treatment of target pathogens, wherever the site of infection, would be important.

"Bacteraemia"

by **Bart Rijnders,** Erasmus MC Hospital, Netherlands

The proportion of patients with documented bacteraemia in pre-licensure indication-specific trials is usually very low so that collecting useful information on outcomes in bacteraemic cases requires a large study population. Nevertheless, sufficiently large studies have been conducted and the available data have underlined the beneficial effect of administering an adequate antibacterial regimen as early as possible. There is a particular need to study new agents in populations with primary bacteraemia to enhance evidence-based management.

The draft *Addendum* suggests an approach for accumulating evidence of use of an agent to treat bacteraemia across trials in several different indications, potentially leading to an indication for treating bacteraemia known or suspected to be associated with one of the approved specific indications for use.

In contrast, the draft *Addendum* indicates that an unqualified indication for pathogen-specific bacteraemia (i.e. not linked to the approved indications) is problematical since the wording would imply an anticipation of efficacy regardless of the site of the primary focus/foci of infection. Currently there is an exception made for antibacterial agents with activity against uncommon and/or MDR pathogens for which there are few treatment options. In these specific cases it is stated that, depending on the level of evidence, an indication for use in bacteraemia regardless of the focus of infection might be considered but with adequate qualification of the circumstances of use (i.e. few treatment options).

It was proposed that an indication for treatment of pathogen-specific bacteraemia without qualification by site should be possible provided that an agent has been adequately assessed in bacteraemic patients, regardless of known or unknown infection foci. Patients presenting with any bacteraemia due to likely susceptible pathogens could be enrolled with a switch to alternative agents allowed as/when there is identification of the underlying focus/foci. In the case of some species (such as *S. aureus*) about one third will never have an identified focus. In the specific case of *S. aureus* it was proposed that patients with catheter-related bacteraemia could be enrolled provided that protocols mandate catheter removal.

There appears to be something of a contradiction between the section in the draft *Addendum* on acute bacterial infections in neutropenic patients, in which a comparison of eradication rates in the subset with proven bacteraemia is suggested, and the statements made regarding primary bacteraemia. A similar approach to the two situations was advocated.

Development of drugs for bacteraemia

By **Charles Knirsch**, Pfizer, USA

It was proposed that a special case should be made for considering *S. aureus* bacteraemia (SAB) as an entity regardless of any known underling focus of infection. The optimal management of SAB requires exploration in trials but these will not be done unless there is a regulatory pathway towards SAB as an indication. The same considerations for clinical development should then apply to bacteraemia due to MDR Gram-negative organisms.

SAB represents a cluster of syndromes among which mortality is highest when there is no focus of infection identified. Due to the diversity of patients with SAB there is no obvious single primary endpoint that could be applicable in all instances and there seems to be a need to develop some sort of composite endpoint to make trials feasible.

Suggestions were made to improve the precision and analysis of trials in patients with SAB regardless of known foci of infection. For example, the analysis could take into account baseline factors (e.g. presence of endocarditis or a removable focus) and a composite endpoint could incorporate time to negative cultures and/or resolution of other parameters and the overall clinical response.

Discussion

In general there has been a longstanding avoidance of trials aimed at bacteraemia, catheter-related infections and neutropenic patients with bacteraemia at least in part because they are not easy to perform or interpret and due to lack of feasible regulatory pathways to obtain indications for use. The availability of rapid diagnostic tests could enhance the feasibility of these studies.

Regarding studies in any patients vs. neutropenic patients with bacteraemia it was observed that finding a pathogen in the blood of an immunocompromised patient is usually highly significant even though there is little chance of finding a source. On this basis, observing that treatment eradicates the organisms from subsequent cultures in this population is rather a hard endpoint. The situation could be viewed as somewhat different in a very mixed population in which transient bacteraemia may occur and when the documentation of a primary focus depends to some considerable extent on the range of investigations undertaken.

With regard to evaluating the potential for new agents to treat MDR pathogens causing bacteraemia the non-clinical data could provide information on treatment of infections at a range of body sites. Collecting clinical data in bacteraemic patients could occur during any of the planned clinical studies but there was concern regarding enrolment of bacteraemic patients with any known/unknown primary focus/foci of infection unless there was already substantial PK data and at least some clinical experience to support use of a new agent in patients with limited treatment options. There was also some concern that bacteraemia in ICU patients often originates from the gut (so no primary focus is actually obvious) and this patient subset constitute a special prognostic group that is especially difficult to manage.

Session 7: Eradication of carriage

"Eradication of Carriage"

by **Jan Kluytmans**, Amphia Hospital, Netherlands

The design of rational clinical trials is complicated by the fact that carriage of specific pathogens only increases the risk of disease and that carriers can transmit to non-carriers. There are some examples in which effects of interventions of carriage and the link to clinical benefit have been systematically studied.

In the case of *S. aureus* carriage the associated risk for post-operative infections (Relative Risk~10) and the effects of eradication of nasal carriage on infection rates (Risk Reduction~60%) and on post-cardiothoracic surgery mortality rates (p=0.04) have been well documented in a double-blind setting.

An open-label clustered group randomised study has been conducted in the setting of selective decontamination of the digestive tract (SDD) in ICU patients using a combination of three oral agents not absorbed from the gut with (SDD) or without (SOD) one parenteral agent versus standard of care (SOC). In a random-effects logistic-regression model adjusted for age, sex, APACHE II score, intubation status, medical specialty, study site and study period the odds ratios for death during the first 28 days vs. SOC group were 0.86 (95% CI 0.74 to 0.99; P=0.045) and 0.83 (95% CI 0.72 to 0.97; P=0.02), respectively. The use of SDD was not associated with increased risk of developing bacteraemia or respiratory tract colonisation due to organisms not susceptible to the antimicrobial agents used in the regimen.

It was concluded that eradication of carriage can be demonstrated to have a substantial impact on clinically meaningful endpoints and there is a need for new agents to be developed for such uses.

"Development of drugs for eradication of nasal carriage of *S.aureus* to reduce *S.aureus* infections in vulnerable surgical patients"

by **Richard Bax**, Transcrip, UK

Focussing on the development of agents to eradicate nasal carriage of *S. aureus* with the aim of preventing post-operative infections the numbers required for trials based on clinical endpoints make them not feasible. There is a need for validation of microbiological techniques to fully assess colonisation, eradication (e.g. taking into account issues such as sampling, carry-over effects on cultures, reproducibility and organism replacement or resistance) and duration of the treatment effect. There is also the need for in-depth literature reviews to establish existing links between effects on carriage and clinically relevant benefits.

Discussion

New and better products that achieve "apparent eradication" as referred to the draft *Addendum* were recognised to have merit. For some types of products it seemed likely that an approval for individual patient prophylaxis would result in outbreak interventional uses even though this mode of use is unlikely to have been assessed. The need to link the microbiological effect to clinical benefit was acknowledged. In addition to the effect of topical agents on carriage of *S. aureus* there are several other examples for which linkage to clinical benefit has been demonstrated and/or is widely accepted to apply. There is a need to increase the available treatments (e.g. there is some resistance to mupirocin) and a clear regulatory pathway is needed.

At the same time, concern was expressed regarding the risk of selecting for resistance in the target pathogens and/or for potentially pathogenic replacement flora. In particular, some were concerned regarding the possible development of new antibacterial agents for this type of use while others considered that the risk might be very small. It might not be possible to determine the real risk in pre-licensure trials.

Session 8: Inhaled drugs for non-CF indications

"Inhaled antibiotics in non-CF bronchiectasis"

by **Michael Loebinger**, Imperial College London, UK,

One of the main areas under investigation is the use of inhaled antibacterial agents in patients with non-CF-related bronchiectasis. Following on from the success of inhaled treatments in CF patients, there is much interest in chronic suppressive therapy to reduce infection and inflammation-related tissue damage and in the treatment of acute exacerbations in non-CF bronchiectasis.

Thus far there are limited clinical trial data with nebulised colistin, tobramycin and gentamicin, most of which have been uncontrolled. Some have suggested a benefit but microbiological effects do not necessarily correlate with clinical benefits, which may be difficult to assess. There have also been concerns regarding side effects on selection of drug resistance. There is an ongoing randomised study with nebulised colistin vs. placebo with a primary endpoint of time to exacerbation and there are several new formulations/presentations of existing antibacterial agents currently under evaluation. Nevertheless, it remains unclear which patient populations are the most suitable for study/most likely to derive a benefit and what could be expected in terms of duration of benefit in relation to the treatment regimen. In addition, there are several issues regarding identification of optimal regimens for acute exacerbations or chronic suppressive therapy and assessing the possible clinical relevance of eradication, replacement and selection of organisms with reduced susceptibility.

"Inhalational antibacterial regimens in non-cystic fibrosis patients"

by **Jeff Alder**, Bayer, USA

Among possible modes of use, two areas of clinical use are of major interest – adjunctive therapy of HAP/VAP and monotherapy for long-term suppressive therapy in non-CF bronchiectasis or COPD. Since the benefit of inhaled antibacterial agents has not been established in these settings, trials seek to demonstrate superiority for the test treatment vs. placebo against background SOC. However, there remain uncertainties regarding several features of study design, including the selection and definition of primary endpoints (e.g. definitions of exacerbations).

In the case of HAP/VAP the local concentrations that can be achieved at the infection site with improved technology could overcome issues of systemic drug penetration and selection of resistance or failure to eradicate less susceptible pathogens. A mortality endpoint is not feasible in the setting of add-on treatment due to the numbers that would be required to detect a benefit. Since the trials will aim to show superiority the use of other endpoints of clinical relevance (such as early improvement or overall clinical response or a composite of the two) could be valid and trials offer the potential to explore the correlation between early response criteria and clinical outcome.

In the case of long-term suppressive treatment regimens consideration could be given to enrolment of patients with daily symptoms, those who have frequent exacerbations and those who have both. Thus far several studies have demonstrated high lung concentrations and effects on bacterial colonisation but there is no established link between these effects and clinically measurable improvements.

Nevertheless, the hypothesis remains that a clinical benefit should be possible with long-term reduction in the bacterial burden, which raises several questions regarding the appropriate duration of studies.

In light of the CF experience several products are under evaluation as cyclical regimens although there is no clear evidence to support this approach over alternatives. The primary endpoints most often proposed have been time to and number of exacerbations (based on protocol-defined criteria for exacerbation), with or without PROs (which may be the most appropriate way to capture changes in daily signs and symptoms). However, the most appropriate endpoint may differ between bronchiectatic and COPD populations and require validation in these different populations during the course of placebo-controlled superiority trials.

Discussion

As with eradication of carriage, these types of trials require very careful validation of sampling and microbiological techniques and the availability of local laboratories able to follow standard protocols for specimen processing. While evaluation of MIC during trials continues to be a routine to document any shifts, thus far these have not occurred at high rates with cyclical regimens in CF patients and there are no relevant breakpoints for inhalational use since the relationship between MIC and clinical effects is not known.

The optimal design and duration of studies remains unclear although at least 6 and commonly 12 months are employed. A more standard expectation for pivotal trial design would be helpful but this may not be possible until more placebo-controlled trials have been reported.

The preference for time to exacerbation vs. number of exacerbations within a defined period is not aligned between regulatory bodies. However, as has occurred in studies in other indications, preference for different primary endpoints does not preclude the possibility that a single trial design can provide satisfactory evidence to regulators from more than one region, possibly using multiple Statistical Analysis Plans.

3. Summary and next steps

Following the end of the consultation period for the *Addendum* it is intended that a final version may be developed and adopted by CHMP by the end of 2013.