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POINTS TO CONSIDER ON THE CLINICAL EVALUATION OF NEW AGENTS FOR INVASIVE FUNGAL INFECTIONS

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1. INTRODUCTION AND SCOPE

This *Points to Consider* document addresses the clinical development of new agents for the treatment and prophylaxis of invasive fungal infections.

In the EU, the majority of invasive fungal infections occur in severely debilitated and/or frankly immuno-suppressed patients who have at least one predisposing underlying illness. The range of fungal infections encountered in this patient population includes disseminated disease affecting several vital organs and deep tissues, such as may occur in invasive aspergillosis and systemic candidiasis, as well as more localised infections such as endocarditis, cryptococcal meningitis, and aspergillus infections in the lungs or sinuses. Oropharyngeal and oesophageal candidiasis are problematic superficial fungal infections in immuno-suppressed persons and should be considered to be within the scope of this document even though they are not invasive infections *per se*. However, superficial fungal infections affecting only the skin and subcutaneous tissue, hair or nails, and infections of the mucus membranes in immuno-competent patients are excluded.

Due to the range of possible infection sites and organisms, the complexities of the underlying illnesses, the variable degree and duration of immuno-suppression and its mode of management, and the incidences of concomitant infections with bacteria and viruses, these patients constitute a very heterogeneous and complex group for study. This fact has important implications for the selection of appropriate study designs to evaluate the efficacy of novel anti-fungal agents.

Although at least one randomised controlled trial (preferably double blind) to support each of the intended indications for use is always desirable, such trials are not always feasible and a consideration of alternative study designs is necessary. Therefore, this *Points to Consider* document discusses the preferred and alternative study designs that might be employed under certain circumstances. The discussion takes into account publications from professional associations of experts in the field, the types of questions that have been posed as part of requests to the CPMP for scientific advice, and recent applications for marketing authorisations for new anti-fungal agents.

There are several CPMP and ICH guidelines that are relevant to the clinical development of anti-fungal agents, which should be taken into account along with this document. In particular, reference should be made to *ICH Topic E 9* and *Topic E 11*, the *Points to consider on applications with 1. meta-analyses 2. one pivotal study (CPMP/EWP/2230/99*), and the *Note for guidance on the investigation of drug interactions (CPMP/EWP/560/95)*.

2. GENERAL CONSIDERATIONS FOR STUDY DESIGN

2.1 Randomised controlled trials

Data from at least one randomised and double blind trial that compares the novel agent with an approved anti-fungal drug(s) would normally be considered to be the minimum necessary for adequate proof of a satisfactory risk-benefit relationship for a new anti-fungal agent in any one specified indication, whether for treatment or for prophylactic use. These randomised and controlled studies should be of adequate power to demonstrate at least non-inferiority with respect to the comparative regimen(s). For non-inferiority studies, the margin of non-inferiority should be selected on a case by case basis and should be carefully justified.

Occasionally, the comparative agent(s) already approved (or sometimes not approved but widely used) for the infection under study may not be considered optimal by one or more expert professional bodies. In such cases, it may be appropriate to seek to demonstrate that the novel agent is superior to the comparative agent(s). Also, it is possible that there is no therapy (licensed or unlicensed) that is expected to be active in a particular type of infection. In most such circumstances it is very unlikely that a placebo-controlled study would be possible but the applicant should justify the lack of a comparison against placebo (see also sections 2.2 and 2.5.4).

If there are practical difficulties that would preclude a double blind design, every effort should be made to ensure that the physicians who assess the clinical responses are not aware of the patients' randomisation. Where a composite primary efficacy variable has been defined that includes the results of imaging studies or of laboratory tests (see section 2.6), all the personnel involved should be blinded as to the assigned treatment.

Alternative study designs should be used only in exceptional circumstances and must be very carefully justified. If well-founded estimates of the numbers of patients that might be recruited in a reasonable timeframe across a sufficient number of trial centres support a conclusion that an adequately powered, randomised and controlled clinical trial would not be feasible, an alternative study design might be considered. The acceptability of any alternative study design would be assessed on a case by case basis.

The optimal study design would still include a randomisation step because the availability of an internal control group makes the interpretation of the outcomes considerably more reliable than in trials that do not employ randomisation. The use of a randomised control group has the particular advantage that the patients in novel and comparative treatment groups would be enrolled across the same study sites and within the same timeframe. Thus, all patients could be expected to undergo similar concomitant therapeutic measures (both drugs and other modes of management) that might markedly affect their responses to anti-fungal therapy.

Therefore, even when enrolment is expected to be limited by patient availability, a randomised and controlled clinical trial is always preferable to an uncontrolled study or one that attempts a comparison with external or historical controls. Consideration may be given to employing unbalanced randomisation as a compromise between exposing a sufficient number of patients to the novel agent while still including an appropriate internal control group.

2.2 Other study designs

Very occasionally, there may be instances in which data from one or more prospective non-comparative trials, with or without a comparison with external or historical controls, might suffice to support an initial approval under exceptional circumstances for the use of a new anti-fungal agent in a restricted indication. It is also possible that uncontrolled data could be accepted to support a specific indication that might be granted as part of a full approval; that

is, granted along with indications for use in other types of fungal infection that are supported by randomised and controlled studies. In both instances, the adequacy of uncontrolled data can only be assessed on a case by case basis.

2.2.1 Use of external or historical controls

The use of external or historical controls should be considered to be a last resort, primarily because the lack of randomisation has the potential to introduce imbalances between patient groups with respect to one or more factors that may influence patient outcomes. Because of the lack of randomisation, there are methodological concerns associated with hypothesis testing against either external or historical controls.

Comparisons between data from uncontrolled trials and outcomes observed in *external controls* are sometimes proposed. Such controls are usually selected during the period of enrolment into the uncontrolled study with the novel agent. They may be patients who are not eligible for enrolment but who have similar underlying conditions and infections or patients who might meet enrolment criteria but are managed in healthcare institutions that are not participating in the trial.

The fact that these patients are treated contemporaneously might be expected to introduce less bias into any comparison with a novel agent than in the case of historical controls. Therefore, external controls may be somewhat more relevant than, and may be preferable to, historical controls. Nevertheless, any comparison based on a group of external controls would be considered very inferior to a comparison between groups of randomised patients who are treated in the same institutions and over the same time period. In particular, it is considered that hypothesis testing of outcomes among patients who do not meet the inclusion and exclusion criteria for a study with outcomes in eligible patients is not helpful. Also, that comparisons with outcomes in patients who might meet the criteria for enrolment but who are being treated at non-study sites could be subject to bias resulting from differences that may exist between healthcare facilities in housing conditions and general management measures.

Comparisons with *historical controls* have the potential to introduce an element of bias that is in favour of the new drug. Over time, the survival rates of severely immuno-compromised patients have improved due to many factors that include the therapies available for treatment of the underlying disease and any concomitant infections, as well as general management measures such as modifications of nursing practises. Therefore, historical controls may not be appropriate for comparison with recent data from an uncontrolled study. In addition, the diagnostic criteria that were applied may have been poorly documented and/or may have been very different to current standards, so there may be uncertainty regarding the validity of the cases identified as historical controls. Therefore, where comparisons are made with historical controls, there should be a full description of the extent of any literature search and trial selection criteria used to identify cases.

2.2.2 Uncontrolled studies

An uncontrolled study should only be selected when there is no possibility of some form of prospective comparison between treatments. Such circumstances might include the treatment of very rarely encountered conditions and/or fungal species for which a specific claim of clinical efficacy is sought. Also, in the treatment of patients with infections that have been documented to be resistant to other available therapies and/or appear to be clinically refractory to other well-established anti-fungal drugs (see section 3.4.2 for a detailed discussion of this matter).

If, as a last resort, an uncontrolled study design is chosen, all possible attempts should be made to generate a precise and unbiased estimate of efficacy for the new agent in a clearly defined patient population in order to facilitate the interpretation of the data.

2.3 Patient recruitment and randomisation

Since accrual rates in the low single figures of patients per centre per year are common, large numbers of study sites are usually used so as to complete enrolment within a reasonable timeframe. It is not uncommon that many sites ultimately enrol less than 5-10 patients each so that the randomisation scheme should employ an appropriate block size. Individual sites may employ different strategies for the treatment of concomitant infections and underlying disease processes, and these may change during the duration of a study. Recruiting a small number of patients per centre has implications for the analyses of the results. These are outlined in *ICH Topic E-9*.

2.4 Definition of the patient population for study

2.4.1 Patient selection

Patients who develop invasive fungal infections usually have at least one underlying illness and take many medications that may have a considerable influence on the clinical and mycological outcomes. Even in a randomised controlled trial, the enrolment of a substantial proportion of patients with a specific underlying illness or receiving certain management strategies may positively or negatively influence the overall response rates in both treatment groups. Thus, the external validity of the study and the sensitivity of the analysis may be questionable.

In order to minimise any confounding effects of such factors, the inclusion and exclusion criteria and the list of permissible concomitant medications require careful attention in the protocol. Nevertheless, in the interests both of patient recruitment and external validity of the study data, exclusion criteria should in general be kept to a minimum. Particular consideration should be given to any restrictions that may be placed on prior systemic anti-fungal therapy as a high proportion of patients are likely to fall into this category. A balance is necessary between the purity of the data, ease of recruitment, and the wider applicability of the study conclusions to normal clinical practice.

Patients may be enrolled into studies of the treatment of fungal infections based on one or more of the clinical history and features, the results of microscopy (including possibly histology), the culture of suitable specimens, the findings on imaging studies, and antigen or nucleic acid detection tests (see 2.4.2). Diagnostic criteria should match accepted definitions of disease, such as those proposed by the EORTC and NIAID for infections in patients with cancer and stem cell transplants. The minimum criteria for eligibility should be justified according to the types of infection to be treated and, wherever possible, the protocol should require that more than one criterion should be met.

Patients may be enrolled into studies of prophylactic therapy based on the assessment of the risk of developing a life-threatening fungal infection. The risk will depend on the underlying condition, its duration and staging, and the immunosuppressive effects of the disease and of the treatments. The minimum criteria for eligibility should be justified according to the perceived risk of a life-threatening infection. It may be appropriate to stratify patients at baseline according to risk factors that may influence outcomes.

2.4.2 Mycological confirmation of the diagnosis

In studies of the treatment of fungal infections, it is preferable that the mycological diagnosis should be confirmed by histology, culture or, at least, microscopy of an appropriate specimen before study therapy is commenced. A proposal to use the results of other tests (eg. serological studies, antigen or nucleic acid detection tests) as confirmatory evidence of a fungal infection must be justified. The choice of criteria should reflect any relevant

recommendations that have been made by expert bodies and/or expert working groups set up by professional and research associations. In studies of the prophylactic efficacy of an anti-fungal agent, it is critical that the mycological confirmation of breakthrough infections is based on similarly well founded criteria.

Mycological confirmation of the diagnosis by microscopy and culture of a suitable specimen should be straightforward in conditions such as disseminated candidiasis when accompanied by skin lesions. It should also be possible to confirm the diagnosis in all cases of suspected cryptococcal meningitis based on one or more of microscopy, culture and a positive antigen detection test.

Confirming the mycological diagnosis may be problematical in deep-seated systemic invasive fungal infections. Histological diagnosis is reliable, but this requires accurate biopsy or needle aspiration of infected tissue or fluid from normally sterile sites. Positive cultures from tissue samples, material such as bronchio-alveolar lavage or on repeated culture from blood are also confirmatory.

The results of some serological, rapid antigen or nucleic acid detection tests may be subject to caveats regarding their sensitivity and specificity. Positive serological tests may not always differentiate past exposure from ongoing active infection and, depending on the specimen, antigen or nucleic acid detection tests may not be able to differentiate infection from colonisation. Therefore, with the exception of very well validated tests, these types of tests would usually provide only supportive evidence of a clinically significant fungal infection.

The definition(s) used for the invasive fungal infection(s) under study, and the criteria for subdivision by certainty of diagnosis into *proven, probable or possible*, should be defined in the study protocol and should be as objective as possible. It is preferable to use criteria for which scientific consensus is established, such as those proposed by the mycoses study groups of the EORTC and NIAID. It is recommended that an expert panel that is preferably independent of the study or, at least, is kept unaware of treatment assignments should assess the certainty of diagnosis in individual patients. .

2.5 Treatment regimens

2.5.1 Dose regimen(s) of the novel anti-fungal agent

Before commencing large clinical trials, it would be expected that the anti-fungal activity of the novel agent would have been characterised *in vitro.* The range of species studied, the numbers of isolates and their geographic origin should be relevant to the indications sought. An assessment of efficacy in animal models may also be appropriate. Such studies may assist in the assessment of the pharmacokinetic/pharmacodynamic relationship and, thus, contribute to the selection of doses for study in man. The possible mechanism(s) of resistance to the novel anti-fungal agent and the potential for cross-resistance within and between anti-fungal drug classes should be explored.

2.5.1.1 Treatment

The proposed regimen(s) must ensure adequate exposure in all patients treated. Dose selection for the Phase III confirmatory trials of efficacy should be based on the considerations outlined above, and should be preceded by at least limited dose-ranging studies. More extensive dose ranging studies should be conducted in those types of fungal infections that are not immediately life threatening. These studies should include patients with the same diagnosis/es, based on the same criteria, that are to be used in the various Phase III studies. The extrapolation of such dose-response data to less common conditions may be accepted provided that this can be justified from all the other relevant information.

However, the Phase II data may not be wholly conclusive due to the complex nature of the patients, their ongoing diseases and their concomitant medications. Therefore, it may be appropriate or even necessary to proceed to Phase III with a plan for an evaluation of population pharmacokinetics during confirmatory efficacy trials so as to evaluate further any demonstrable relationship between exposure to drug, clinical and mycological outcomes, and adverse events. Such data may also aid the assessment of the clinical significance of any potential drug interactions, and may help identify appropriate dose adjustments for patients with renal or hepatic insufficiency.

If the spectrum of activity of the novel agent is limited, it may be considered desirable, or even necessary, to study it in combination with another antifungal agent in one or more of the indications sought. Combination therapy may also be needed for the treatment of certain very severe fungal infections and/or when single agent therapy provides limited efficacy. In such cases, the need for and choice of the second agent must be fully justified. Whenever circumstances permit, studies should compare the combination with both the novel and the second agent alone. Such a study design not only allows for an assessment of any additive or synergistic effect of combining the two drugs, but also facilitates the interpretation of the safety data. If a comparison with either drug alone cannot be performed because it might put patients at unacceptable risk, the reasons for the omission of such a study should be carefully explained. The results of, and conclusions drawn from, such investigations must be reflected in the SPC.

2.5.1.2 Prophylaxis

The optimal dose for treatment may be very different to that necessary for prophylactic use in at-risk patients. The choice of the dose to be studied will likely have to be based on any available experience in the treatment of invasive fungal infections, and all the information available on the safety profile of the drug. For these reasons, the evaluation of a drug for prophylaxis is usually sequential to major trials of efficacy in the treatment of fungal disease (see section 3.3).

2.5.2 Duration of therapy

The normal minimum and maximum duration of treatment with study medication, and the timing of on-therapy and post-therapy assessments should be pre-defined in the study protocol. It is inevitable that the minimum duration of treatment that is selected will, to some considerable extent, be based on the experience with established anti-fungal drugs. The maximal duration will likely be left more open to the investigator, according to the disease and the patient response. However, in protocols aimed at specific types of fungal infections, it may be appropriate to set a maximal duration after which a patient who has not met the response criteria may be considered to have failed therapy.

On occasion, it may be appropriate for the protocol to allow for continuation of the novel drug after an apparently successful course of treatment (*i.e.* suppressive therapy). It is essential that the protocol lists clear and justifiable criteria that must be met before therapy may be prolonged in an individual patient. The total duration of therapy allowed should be based on laboratory parameters related to the achievement of immune recovery and on any safety concerns regarding prolonged exposure to drug.

In trials that evaluate the prophylactic use of an anti-fungal agent, the duration of therapy should be based on the degree of ongoing risk of the patient to develop an invasive infection. Therapy should be stopped when the patient meets protocol-specified criteria for low risk, such as recovery of the neutrophil count.

2.5.3 Parenteral and oral formulations and switching

If parenteral and oral formulations of the new drug are available, studies may allow for one route of administration throughout or a switch from parenteral to oral therapy when protocol-specified criteria are met, depending on the types of infections that are to be treated.

When a study allows a switch from parenteral to oral therapy with the new anti-fungal agent, it is preferable that both parenteral and oral formulations of the chosen comparative drug are also available. Thus, patients in each treatment group may receive a single anti-fungal agent throughout the study, and may switch from parenteral to oral therapy using identical criteria. In such studies, it should be possible to maintain a double blind design.

The timing of the switch, and the doses of the oral formulations of the new and reference therapies, should be justified according to the absolute bioavailability of each of the active substances from the oral preparations. That is, consideration should be given as to whether the change to oral therapy represents a simple switch or whether the change also represents a "step-down" in the dose. Provided that all these matters are taken into account, the interpretation of the results of such studies should be relatively straightforward.

However, difficulties may arise when either the new or comparative agent can be given by only one route, but a switch to oral therapy is desirable for routine patient management. For example, when:

- There is no oral formulation of the new agent, but the comparative agent is available for both parenteral and oral administration or *vice versa*
- There is only one possible route of administration for the new agent, but it is preferable or necessary to commence the comparative therapy *via* a different route or *vice versa*

In all such instances, it may be difficult to employ a double blind study design and special measures may be needed in order to ensure that those who assess patient outcomes remain blinded as to the treatment assignment.

Whether the switch to a different follow-on therapy occurs in one or both treatment groups, a minimum duration of prior parenteral therapy should be set. In all cases, the choice of oral therapy will require careful justification. Consideration should be given to switching to an oral drug that is from the same class. If both the new and comparative agents are from the same class, it may or may not be appropriate to switch to the same oral agent in both treatment groups. However, it will be necessary to consider these issues on a case by case basis.

2.5.4 Choice of comparator in randomised controlled trials

The active comparative therapy should, where possible, be a single designated agent and should be used at the recommended dose regimen. The comparative regimen that is selected should be that considered to be the best therapy, or among the optimal available therapies, for the condition being treated in all patients eligible for the study, whether or not it is actually approved for that condition. Allowing the investigators some choice with regard to the comparative regimen may be justifiable within limits.

2.6 Outcomes and efficacy variables

2.6.1 Outcomes

The clinical outcome should be assessed in all randomised and all treated patients. In studies of treatment of fungal infections, the judgement of clinical outcome may be based on whether

or not the patient meets one or more pre-defined criteria and/or a composite score derived from the resolution of defined signs, symptoms and features of relevant imaging tests.

The mycological outcome should be assessed (either documented or presumed from the clinical outcome) in all treated patients with a confirmed mycological diagnosis (see section 2.4.2). In studies of prophylactic efficacy, the occurrence of breakthrough infections must be based on pre-defined clinical and mycological criteria.

Clinical and mycological outcomes should be presented for all treated patients and also for all sub-populations that may be pre-defined in the protocol, including the clinically evaluable and the mycologically evaluable populations. It is recommended that, even in double blind or evaluator-blinded studies, there is a plan for a secondary assessment of clinical and mycological outcomes. If possible, this should be conducted by an independent blinded panel of experts. If it is necessary that investigators make up some or all of the panel, a secondary numbering system should be applied to the data before review so that physicians cannot easily determine where each patient was recruited or identify an individual patient. It is particularly important to make every effort to prevent investigators recognising their own patients when the number of patients enrolled at least in some study centres is small. While the data analysis plans should define whether the investigator or panel judgements of outcome will be considered primary, analyses of both datasets should be presented in the study reports.

2.6.2 Efficacy variables and primary populations

In indications in which confirmatory evidence of fungal infection may be difficult to obtain and/or it is difficult to differentiate between infection and colonisation at baseline or at follow-up, the primary efficacy variable should be the clinical outcome. The mycological outcome will be a secondary efficacy variable and, in the majority of patients, will likely have to be presumed from the clinical response.

In studies that aim to show non-inferiority between novel and established agents for the treatment of fungal infections, the primary analysis of clinical outcomes should be performed on data from the clinically evaluable population. This population should be confined to those patients who meet the criteria for *proven* or *probable* invasive infections before the end of the study (see 2.4.3). Data from those patients with only *possible* invasive infection at the time of study completion would be considered to be only supportive. In studies that aim to show superiority of the novel treatment, the primary analysis should be conducted in the full analysis set. In all cases, whichever population is designated primary, results for all other defined populations should be presented and reviewed for consistency.

Nevertheless, documented mycological outcomes provide an objective measure of anti-fungal activity *in vivo*. In instances where the mycological diagnosis is likely to be confirmed in the majority of patients and the mycological response can be documented or can be very reliably discerned from the clinical outcome (as in cryptococcal meningitis), the mycological outcome among the mycologically evaluable patients should be the designated primary efficacy variable. However, documented eradication of the fungus may not always correlate with a favourable clinical outcome and *vice versa*. Therefore, any discrepancies between clinical and mycological outcomes in individual patients should be investigated.

Other secondary efficacy variables may be proposed provided that the correlation between these observations and resolution of the initial fungal infection can be justified. For example, mortality, both overall and that attributed to the acute fungal infection, may be a particularly important efficacy variable in large studies in invasive systemic fungal infections that carry a high mortality in the short term. All clinical and laboratory parameters that may be relevant to the patient and the condition under treatment should be considered as potential secondary

efficacy variables. Whether or not these parameters are designated as efficacy variables in the analysis plan, they should be documented and presented in the study report.

2.6.3 Timing of assessments

Efficacy evaluations should be performed at regular intervals up to the end of treatment, with an initial assessment of efficacy within 4-5 days of the commencement of therapy. The timing of the *test of cure* assessment should be based on the fungal infection and its clinical form. It should also take into account the terminal elimination half-life and tissue distribution of the drug. It may also be appropriate to take into consideration the nature and likely course of the underlying illness(es) and time to immune recovery in the eligible patient population.

The final study visit should be timed not only so as to provide information on delayed adverse events but also to document recrudescent or novel fungal infections. In some populations, it may also be appropriate that this visit is timed to fall before, during or after recovery of neutrophil counts. Preferably, the total period of follow-up after cessation of treatment of a fungal infection should be three months but may justifiably be shorter in specific types of patients (such as those with severe underlying diseases) or infections (such as oesophageal candidiasis).

Whenever the protocol allows for continuation of the novel drug after an apparently successful course of treatment (i.e. suppressive therapy), and in studies of prophylactic efficacy, patients should be assessed after achieving sufficient immune recovery such that anti-fungal drugs have been stopped. Clear criteria for stopping therapy must be laid down, and the total duration of sequential follow-up must be carefully justified.

3. CONSIDERATIONS FOR SPECIFIC TYPES OF STUDIES

3.1 Treatment of established fungal infections

Clinical trials that evaluate new anti-fungal agents for the treatment of established infections should aim to enrol patients in whom the mycological diagnosis is already confirmed.

3.1.1 Consideration of the spectrum of anti-fungal activity

Anti-fungal agents that are active against a limited range of genera and/or species of fungi will necessarily be evaluated for efficacy in infections that are caused by a limited range of organisms. Even when the novel anti-fungal agent is active against a very wide range of fungi, applicants may sometimes choose to evaluate its efficacy against a limited range of organisms (as above), at least initially.

When the indication(s) sought is/are to be genus-specific, such as treatment of *invasive aspergillosis* or *oesophageal candidiasis*, adequate trials (see section 2.1) are required to support each indication. However, the majority of causative pathogens that are actually identified in such studies will likely be limited to a few species within the chosen genus. Also, the drug may not show potentially useful activity *in vitro* against all the species within a single genus. Therefore, although the in-vitro and clinical data combined may support a genus-specific indication (such as *treatment of invasive aspergillosis*), in reality clinical efficacy can be assessed in only a small number of the total possibly pathogenic species within that genus.

In order to reflect both the range of species that were actually successfully treated and any differences in the activity of the anti-fungal agent against various species within a genus, genus-specific indications should make reference to section 5.1. Here the activity of the anti-fungal agent against the various species in each genus relevant to the indications should be

described, particularly noting any species that are inherently drug-resistant. Also, the species that predominated among the clinical isolates should be mentioned.

In the case of anti-fungal agents that are active against most or all of the genera and species that are commonly pathogenic in man, an alternative approach to the clinical development programme may be considered. As in the development of broad-spectrum antibacterial agents, it may be justifiable to perform clinical trials that aim to evaluate the new agent in certain types of infection rather than restrict enrolment to patients infected with only certain types of fungi. For example, patients with any documented systemic invasive infection might be enrolled provided that the causative organism(s) is/are known or expected to be susceptible. However, this approach may lead to trials in which certain types of fungi may be insufficiently represented.

In this type of study, the investigative sites should be chosen according to their likely ability to enrol patients with a range of fungal pathogens. Nevertheless, as in studies that are restricted to the treatment of infections due to a single genus, the majority of causative organisms will likely belong to a small number of species from a few genera. However, just as in genus-specific indications, this need not necessarily preclude granting the indication provided that adequate information is made available to prescribers.

In some instances, the anti-fungal properties of the novel agent may suggest that it would be useful for the treatment of infections due to certain species that are rarely encountered in clinical practice. Clearly, organism-specific studies will not be feasible, and so the data that might support a mention of utility against these species must be collected by other means. If the novel agent has been evaluated in studies that enrol patients by clinical condition rather than by pre-determined pathogen, a small number of patients infected with rare species may have been included. Additional information may be obtained from patients to whom the drug has been made available outside of a formal clinical trial setting, provided that there is sufficient documentation of each case to be able to assess the anti-fungal effect.

Nevertheless, the total numbers of patients who have been treated for infections with rare species will always be small and how the information should best be reflected in the SPC would have to be considered on a case by case basis. If an indication for the treatment of *systemic invasive fungal infections* is considered to be possible, then the rare species and numbers treated could simply be described in the SPC. Alternatively, a species-specific indication for use might be possible, but this should always be accompanied by a mention of the clinical experience and in-vitro activity in section 5.1 of the SPC.

3.1.2 Consideration of the pharmacokinetic properties

Depending on the pharmacokinetic properties of the novel agent, especially its ability to penetrate certain body compartments, it may be appropriate to evaluate efficacy in site-specific infections. In some instances, it may be appropriate and/or necessary that a site-specific indication is limited by mention of the fungal genus/species. For example, if the inclusion criteria have restricted enrolment such that the infections treated are both site-specific and organism-specific, as in *cryptococcal meningitis*, then the indication must inevitably reflect this. Alternatively, if the inclusion criteria did not limit the range of organisms, then there are considerations for inserting relevant details in the SPC as outlined in 3.1.1 above.

3.2 Empirical treatment of fungal infections

Anti-fungal agents are commonly commenced at the first suspicion of a potentially life-threatening fungal infection. The choice of therapy is made from among those agents that have already been shown to be efficacious in the treatment of the clinical condition and which are usually active against the putative pathogen(s). A particularly common scenario involves

the empiric therapy of presumptive fungal infections in neutropenic patients in whom an invasive systemic fungal infection is usually suspected solely on the basis of a continuing fever despite a defined period of therapy to cover other likely pathogens. Should an Applicant seek a specific indication for use in such instances, there are some very important considerations for the design of trials that are intended to support such an indication. In all such cases, the applicant is advised to seek advice from EU regulators.

Firstly, only those anti-fungal drugs with an appropriately broad spectrum of activity are suitable for study due to the possible range of causative organisms.

Secondly, studies should be sequential to confirmatory trials of efficacy in the treatment of systemic invasive fungal infections. Since the patients in the confirmatory efficacy studies will have been very predominantly neutropenic, the need for any further studies in those with presumptive rather than proven infections has to be questioned.

Thirdly, although many cultures are usually obtained before adding an anti-fungal agent to the other therapies, it is likely that confirmatory evidence of a pre-treatment fungal infection may be obtained in less than 5% of the total number enrolled.

Fourthly, in the past, such trials have sometimes wholly or primarily depended on the resolution of fever for the assessment of efficacy. However, patients may become afebrile as a result of concomitant successful therapy for a non-fungal infection, since other therapies may be changed or added at the same time as or after the anti-fungal drug is commenced. Also, an afebrile state may be due to resolution of a drug-induced fever, recovery of the neutrophil count, and success of other management strategies aimed at the underlying illness. Therefore, a judgement of efficacy in such patients that is wholly or primarily based on resolution of fever is untenable.

Studies in which the primary endpoint is composite and includes breakthrough infection rates and resolution of fever as well as treatment of any documented baseline infections provide an idea of the overall utility of the drug in febrile neutropenic patients. However, they cannot be used to assess the efficacy of *empiric therapy* since, strictly speaking, such an indication should be based solely on the successful treatment of any fungal infections documented from examination of specimens taken just before adding the anti-fungal agent. This is because confirmation of a fungal infection from post-baseline specimens only might represent failure to treat an infection that was present, but not confirmed, before initiation of therapy or, albeit less likely, a failure of prophylaxis. Thus, the two possible roles of the drug cannot be differentiated. However, if such a study were to demonstrate superiority over the comparative regimen, it might be considered possible to grant an indication that reflected the overall utility of the drug in this type of clinical situation. Companies who are considering performing such a study for regulatory purposes should seek scientific advice from EU regulators at an early stage.

3.3 Prophylaxis in at-risk patient populations

The principles outlined in respect of the design of trials that evaluate new drugs for treatment of established infections are also relevant to studies in prophylaxis. An uncontrolled prospective trial that uses historical or external control data to estimate the expected incidence of fungal infections in the absence of prophylaxis is open to all the caveats regarding interpretation of the data that have been expressed in section 2. Therefore, at least one randomised, comparative trial with sufficient statistical power to demonstrate superiority or exclude inferiority would be necessary in order to support the use of an anti-fungal agent for prophylaxis against fungal infections in at-risk patients.

In most cases, it would be anticipated that the aim would be demonstrate prevention of systemic invasive fungal infections in patient groups known to be at high or at least moderate

risk. Current trends in clinical practise make it unlikely that placebo-controlled studies could be performed in the majority of types of patients who at risk of invasive fungal infections. Therefore, an appropriate comparative regimen(s) must be identified along the lines already discussed. It is essential that the criteria by which patients are defined as being at risk of an invasive fungal infection, with categorisation of patients according to the degree of risk, should be clearly specified in the protocol and documented in the study report. It may be appropriate to plan for stratification of patients according to risk categories at baseline. Every effort must be made to establish that patients do not already have an established infection at baseline.

The primary efficacy variable in such a study would be the incidence of proven or probable invasive fungal infections. Whether or not *any* such infection would be counted in the primary analysis of efficacy, or those due *only* to certain species, would depend on the spectrum of activity of the drug *i.e.* what it might be expected to prevent. However, all fungal infections (invasive or otherwise) must be documented, and must be included in the intent to treat analysis. Consideration should be given to denoting time to breakthrough infection as a secondary efficacy variable.

Depending on the choice of the clinically significant difference, and due to the low anticipated fungal infection rates on any active therapy, the projected size of adequately controlled trials may make them unfeasible. In such cases, other study designs, including the use of unbalanced randomisation, may provide an acceptable compromise between exposing a sufficient number of patients to the novel agent and yet, in the same trial, including a control group to aid interpretation of the results of the study.

3.4 Salvage therapy in refractory cases

If the new anti-fungal drug shows potentially useful activity *in vitro* against fungi that demonstrate resistance to one or more other anti-fungal agents, it may be appropriate to evaluate it for the treatment of patients who have already failed therapy with another anti-fungal drug or drugs. These patients may be described as *refractory cases* and the switch to the new agent may be referred to as *salvage therapy*. The aim, then, of a clinical trial is to demonstrate satisfactory efficacy following a switch to the new agent.

Considerations for the evaluation of a new drug in so-called refractory cases and for the resulting indication for use include (i) the possible reason(s) for failure to respond to other drug(s) that have been previously administered, (ii) the definition of failure on previous therapy(ies), (iii) the specific anti-fungal agents that have been tried already, and (iv) the general study design.

(i) Failure of a patient to respond to an anti-fungal agent(s) may be due to one or more of:

- Drug-resistant fungal pathogen(s)
- The nature of the underlying disease
- Concomitant non-fungal infections
- Insufficient drug concentrations achieved and/or maintained at the site(s) of infection

Therefore, the patients who may be defined as *refractory cases* are potentially a very heterogeneous group, and it may not be possible to determine the most important reason(s) for failure of prior therapy in many cases. In addition, patients who have failed on more than one past treatment for the same infection might have underlying factors that make it far less likely that they will respond to any anti-fungal agent.

(ii) While the working definition of failure of prior therapy will likely have to be based on a combination of features, evidence is required that the same fungal infection as initially

discovered has persisted or even progressed despite previous treatment, and the in-vitro susceptibility of the pathogen(s) must be documented. This means that all the patients enrolled into such studies should usually have a *proven* fungal infection. However, in those types of infections where a proven diagnosis is difficult to obtain, patients with probable infections may be enrolled.

There must be complete documentation of the administration of prior anti-fungal therapy(ies) at an appropriate dose regimen(s). The duration of exposure before a judgement of failure is made must be justified. An independent expert evaluation of each case may be appropriate, but this type of *Post hoc* assessment cannot take the place of well-defined inclusion criteria.

(iii) An unqualified indication for the treatment of *patients who are refractory to other anti-fungal agents* is not tenable. This wording would imply that the drug has been demonstrated to be effective in patients who have failed on *any other anti-fungal agent*. Such an indication gives an erroneous message that the drug should be useful in cases that have failed on *all* those anti-fungal agents that are already licensed when the new agent is approved, which is an extremely unlikely scenario. It would also wrongly imply that the drug would treat patients who may fail therapy with *all* those anti-fungal agents that may be licensed in the future. Therefore, the wording of any such indication for use would have to reflect the individual anti-fungal agents or, if mycologically appropriate, the class(es) of drugs, that the patients to be enrolled into such a trial had previously received for their ongoing infections.

(iv) The mycological spectrum of activity of the new anti-fungal agent should assist in the development of appropriate inclusion and exclusion criteria. Firstly, those cases known to be due to pathogens that are not inherently susceptible to the drug would necessarily be excluded. Secondly, the existence or the lack of cross-resistance between the new agent and specific drugs of the same or of another class at least against some species should be reflected in the inclusion criteria.

It is also possible that failure has occurred on other drug(s) without demonstrable anti-fungal drug-resistance. Therefore, every effort should be made to define the patients who are suitable for enrolment based on a consideration of the other possible reasons as to why they might have failed prior therapy(ies) yet might still be expected to respond to the novel agent.

In addition, patients who have failed to respond to an adequate course(s) and regimen(s) of anti-fungal therapy may also have been intolerant of one or more of the anti-fungal drugs that were administered previously. These patients may be enrolled into studies that aim to evaluate the new agent in those who have a persistent infection despite prior therapy provided that they clearly satisfy the inclusion criteria for the study. In particular, only those patients who have clearly failed on prior therapy should be included in the primary analysis of efficacy.

Whether or not a randomised-controlled trial is feasible will depend on the definition of refractory cases that is employed, which, in turn, depends on the properties of the new anti-fungal agent. For example, if the mycological activity of the new anti-fungal drug suggests that it might be useful in aspergillus infections that have not responded to a potentially active triazole, patients could be randomised either to the novel agent or to a licensed amphotericin formulation. However, if the protocol stipulates that patients must have failed on at least one drug from each class of anti-fungal agents known to be inherently active against the pathogen, an uncontrolled trial might be inevitable.

If an uncontrolled trial were proposed, there would have to be some estimate made, and preferably specified in the protocol, of the expected recovery rates in the absence of specific treatment. Given the varied causes of refractoriness to treatment, it is considered that it would likely be impossible to make a sufficiently reliable estimate of such rates in conditions where improvement might occur in the absence of a potentially active anti-fungal agent. Thus, a

non-comparative study design might provide adequate evidence of efficacy only in the treatment of fungal disease processes that are known to inevitably progress without adequate treatment.

3.5 Studies in children and adolescents

Serious invasive fungal infections can occur at any age, including the very premature. In accordance with *ICH E 11*, it is expected that plans should be made for the early development of suitable dose sizes and, if the novel agent is orally available, paediatric formulations.

When sufficient pre-clinical and adult data are available to identify a likely suitable dose range for children, studies should aim to evaluate the pharmacokinetics and safety of the novel agent in different age groups while patients are undergoing treatment for documented fungal infections. Eventually, data should usually be obtained across the entire range 0-18 years.

It is accepted that these trials will likely be uncontrolled studies that enrol at least sufficient numbers so as to establish appropriate dose recommendations. Although the collection of information on the clinical and mycological outcomes in these children is also important, the efficacy that might be expected in different age groups will likely be extrapolated from the confirmatory studies in adults.

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

4. ASSESSMENT OF SAFETY

4.1 Assessment of the safety profile

The evaluation of the safety of a novel anti-fungal agent under the conditions of use that have been discussed in the above sections is fraught with difficulty. The most important limiting factors for the assessment of the safety profile are the serious underlying disease processes and the large number of concomitant medications that are inevitably present in the types of patients who will be at risk of invasive fungal infections. Thus, both the characterisation of the safety profile of a novel anti-fungal drug and, especially, the categorisation of events according to drug-relatedness are very difficult. Investigators, company personnel and regulatory authorities alike experience such difficulties of interpretation.

The provision of safety data derived from comparative trials is to be preferred since it provides some indication of the "background noise" that is much more likely to be due to the patients' other diseases and treatments than the anti-fungal drugs. However, even comparative data cannot entirely resolve the problem. Therefore, every effort must be made to provide adequate narratives for patients who were withdrawn from therapy due to adverse events, and for those who experienced serious adverse events and/or died, regardless of the causality assessments. The tabulations should include rates of events in patients who were taking certain concomitant medications, whether or not there is any known likelihood of clinically significant drug interactions.

Additional difficulties arise if the novel agent is to be given in combination with a well-established anti-fungal agent either as a routinely or, at least, in specified circumstances. Although it is preferable to compare the combination with each of the two drugs alone during the clinical development programme, this may not be possible if mono-therapy with either drug might pose an unacceptable risk to patients. If a comparison of separate and combined

administrations has not been possible, the adverse reactions attributable to the novel agent may not be distinguishable from those already known to be associated with the other drug. In addition, it would not be possible to identify unwanted effects that occur more commonly, or are more severe, with combined therapy than with either drug alone. These issues have implications for the adverse reactions and frequencies that appear in the SPC.

4.2 Size of the database

The extent of the clinical safety database that would be required before an initial marketing authorisation might be granted must be considered on a case by case basis, and will partly depend on the preclinical evidence and on past experience with any similar compounds of the same drug class.

Should it be proposed that an initial approval under exceptional circumstances might be justified due to the properties of the novel agent, the number of patients exposed will necessarily be relatively small. However, a limited safety database might be considered acceptable where the observed safety profile is such that the risk-benefit is considered to be favourable. In such circumstances, it would be anticipated that more safety data would be forthcoming as additional trials are completed, and it would be usual for the applicant to provide approximate timeframes for the provision of such information.

Even when a full approval is granted initially, the total number of patients that have been exposed within formal trials or during any pre-licensure drug access programme is still very likely to be relatively small in comparison with most other new drugs. Therefore, it is likely that there may be concerns raised over events that may well not be drug-related, and it may be considered necessary to make mention of at least some of these in the initial SPC, along with those events that are very likely to represent adverse reactions.

Whatever the conditions of the initial approval, supplementation of routine post-marketing safety update reports with specific studies that are designed to evaluate particular issues raised by the pre-authorisation data may be deemed necessary.