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Infectious Disease Working Party (IDWP)

Concept paper on the revision of the guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease

Agreed by Infectious Disease Working Party	April 2026
Adopted by CHMP for release for consultation	15 June 2026
Start of public consultation	29 June 2026
End of consultation (deadline for comments)	30 September 2026

The proposed guideline will replace guideline on the clinical evaluation of antifungal agents intended for the treatment and prophylaxis of invasive fungal diseases (CHMP/EWP/1343/01 Rev. 1)

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Invasive fungal disease (IFD), rare IFD, emerging IFD, refractory IFD, salvage therapy, EORTC/ MSGERC Consensus Definitions of IFD, EORTC/ MSGERC response criteria for clinical studies, inhaled antifungal agents, breakthrough infection, paediatric population

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. Introduction

This concept paper proposes an update of the guideline on the clinical evaluation of antifungal agents intended for the treatment and prophylaxis of invasive fungal disease (IFD) (CHMP/EWP/1343/01). This guideline was originally adopted by CHMP in May 2003. A first revision of the guideline took place in 2009 and came into effect on the 1st of November 2010 (CHMP/EWP/1343/01 Rev. 1). This is the version in place that is proposed to be updated.

2. Problem statement

Currently there are several new antifungal agents in development that have shown activity against rare and/or emerging pathogens (e.g. *Scedosporium* spp., Mucorales and *Candida auris*). Some of them harbour activity against pathogens resistant to existing classes of antifungal agents There is a need to clarify aspects of clinical development programmes that may support regulatory claims for these agents intended for the treatment of rare and/or emerging pathogens as well as for refractory disease. Sections of the guideline addressing these two issues would benefit from a revision in terms of the minimum data package (including primary pharmacology and PK-PD translation) and/or alternative study designs to support regulatory claims for these agents.

Consensus definitions of IFD and response criteria in clinical studies have been recently updated by the scientific community and their consistency with those mentioned in the current guidance and applicability across different types of IFD should be reviewed to support consistent endpoint ascertainment and interpretation in clinical trials. A consensus definition of breakthrough infection has been developed that is missing in the current guideline.

Antifungal agents for the inhalation route of administration are being developed that are not addressed in the current guideline. The EU regulatory expectations regarding data that should be generated to support the approval of these agents, that may be specific for lung fungal diseases, will be added.

Experience has been gained with the assessment of paediatric investigation plans for antifungal agents that may enrich the information presently included in the guidance.

Other updates refer to the implementation of principles set up in other relevant guidelines such as the estimands framework (ICH E9(R1)).

Overall, considering the new developments in the field of IFD there is a need to update the current guideline, especially to reflect the new agents aimed at the treatment of rare and/or emerging pathogens as well as for refractory disease.

3. Discussion (on the problem statement)

The following elements of the current guideline need to be revised or added:

- **Rare and/or emerging fungal pathogens**

In the existing guideline, prospective, randomised and active-comparator controlled trials are recommended with the primary analysis confined to patients confirmed to have proven or probable invasive disease. For agents intended for rare and/or emerging pathogens, randomised clinical trials may be unfeasible or extremely difficult to recruit. Alternative study designs could be considered in some cases, particularly if there is (preceding or accompanying) evidence of efficacy from a randomised trial for the treatment of standard indications such as invasive candidiasis or invasive aspergillosis unless the antifungal spectrum is not appropriate. The use of larger non-inferiority margins or uncontrolled study designs will be clarified.

Given the rarity of some IFD, studies enrolling patients with different types of infections may be unavoidable raising concerns about the heterogeneity of the study population, the selection of the primary efficacy endpoint (i.e. pooled versus by type of underlying infection), and the statistical analysis of such studies. These issues will be addressed in the updated guideline.

- **Consensus definitions of IFD and response criteria in clinical studies**

The current guideline requirement is that efficacy outcomes should be assessed using the response criteria recommended by the European Organisation for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) in patients confirmed to have proven or probable invasive disease. More updated consensus definitions are presently available for IFD while response criteria that evaluate treatment success or failure based on a composite of clinical, radiological, and mycological factors need to take into consideration the advances in the field. The proposed revision will consider the applicability of the current consensus definitions of IFD and to the response criteria across different types of invasive fungal infections (including rare and/or emerging infections) and study populations (other than immunocompromised patients) in view of the advances in clinical mycology and the broadening spectrum of mould disease.

Subject to discussion with EU regulators, all-cause mortality at a predefined point in time that is relevant for the underlying IFD may be an acceptable primary endpoint provided global (clinical, mycological, and radiological) response is collected as secondary efficacy endpoint. This will be clarified in the updated guideline.

- **Salvage therapy in refractory disease**

Salvage therapy is considered in situations where standard antifungal therapy is insufficient or not possible, including refractory disease, intolerance, organ dysfunction, and/or failure to achieve sufficient plasma levels. It is generally recommended that distinction is made between patients with drug intolerance as compared to those with refractory disease if both are enrolled in the same study. Focusing on refractory disease, the current recommendation is that the clinical development of antifungal agents intended to support this indication is approached from the standpoint of establishing the minimum data package that would be acceptable for a new antifungal agent of a new class that does not show cross- resistance to licensed antifungal agents in other classes. Only in those cases where efficacy cannot be initially assessed in one or more specific types of IFD such as invasive aspergillosis or invasive candidiasis, alternative data packages and/or study designs could be discussed. In addition, consideration should be given to studies on combination therapy as salvage therapy and to the clinical pharmacology programme that is needed to support this approach (combination therapy is presently only discussed as primary treatment of IFD).

- **Breakthrough infection**

Consensus criteria for defining breakthrough IFD are missing in the current guidance. As these have been developed by the Mycoses Study Group Education and Research Consortium (MSG-ERC) and the European Confederation of Medical Mycology (ECMM) to support the design of clinical trials and epidemiological research in clinical mycology, references will be added.

- **Inhaled antifungal agents**

Routes of administration other than intravenous or oral may require to be addressed such as inhalation given the global health issue that fungal lung disease represents in terms of burden, morbidity and mortality. The clinical development of inhaled antifungal agents requires specific consideration given that they are expected to be administered as add-on to standard systemic antifungal agents. The expectations in terms of efficacy demonstration will be clarified.

- **Paediatric population**

Extrapolation of efficacy based on exposure-matching is considered an acceptable approach. Therefore, single arm paediatric PK and safety studies are considered appropriate. In recent regulatory procedures, proposals have been made to perform these studies in paediatric patients at high risk of IFD, i.e. in the prophylaxis setting regardless of whether the target adult indication is for treatment or for prophylaxis of IFD. Clarification will be provided in this respect.

Clinical studies in children are primarily PK studies. Despite that, and for the purpose of safety assessment, these studies are expected to also provide reassurance about the safety profile in the target paediatric population with respect to adult/older patients. This would be particularly relevant if there are paediatric-specific concerns emerging from the available non-clinical and/or adult safety that, in principle, do not prevent the paediatric development.

Specific considerations will be made in the updated guideline for (term and preterm) neonates and very young children, including references to non-clinical models of fungal infection that are particularly relevant for IFD occurring in this age group.

- **Estimand framework and other applicable recommendations for the statistical analysis**

The guideline should be updated to align with most recent guidance regarding the estimand framework and statistical analyses.

- **Considerations for the SmPC**

Similarly to what has been discussed and agreed for the Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev 3), guidance for sections 4.1 and 5,1 of the SmPC of antifungal agents will likely be updated on inclusion of a standard sentence in relation to the use of antifungal agents according to official guidance and with respect to the EUCAST breakpoints, respectively.

- **Editorial changes**

Structural changes to improve readability as needed.

4. Recommendation

The IDWP recommends revising the existing EMA guideline on the clinical evaluation of antifungal agents intended for the treatment and prophylaxis of fungal invasive disease (CHMP/EWP/1343/01 Rev. 1), considering the issues identified above.

5. Proposed timetable

Timetable for the concept paper is the following:

Discussion at IDWP: January 2026

Adoption by CHMP: June 2026

Released for public consultation: TBD

Adoption and publication of the final version: TBD

6. Resource requirements for preparation

The update of the guideline will be carried out by the IDWP, in co-operation with the ETF and the CHMP. A drafting group of 3-5 members will be constituted. The IDWP will appoint a rapporteur among its members who will lead the drafting group and the discussion at IDWP during the development of the guideline.

CHMP will discuss and adopt the concept paper, the draft guideline before external consultation and the finalised guideline before publication.

7. Impact assessment (anticipated)

The most important impact is expected to be on:

- clinical development programmes to support applications for antifungal agents intended for the treatment or prophylaxis of IFD due to rare and/or emerging pathogens as well as for the treatment of refractory disease.
- the content of scientific advice

8. Interested parties

EMA: PDCO, ETF, MWP, CTCG, consultation with other working parties or committees will be initiated as appropriate.

External parties: European learned societies and scientific organisations (e.g. European Confederation of Medical Mycology, Mycoses Study Group Education and Research Consortium), EU/EEA Regulatory authorities, patient representatives and Pharmaceutical Industry.

9. References to literature, guidelines, etc.

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