EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EU Regulatory Considerations for Development of Antifungal Medicines

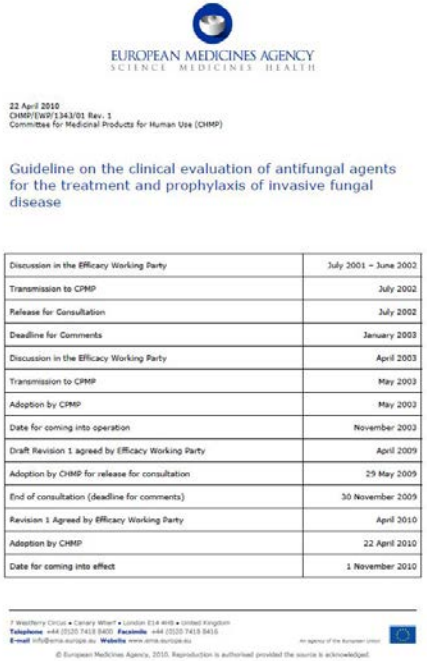
FDA Public Workshop: **Development Considerations of Antifungal Drugs to Address Unmet Medical Need**

Presented by Dr Radu Botgros on 4 August 2020

An agency of the European Union

EMA/CHMP Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease (IFD) *CHMP/EWP/1343/01 Rev. 1*

- first guidance in 2003, in response to repeated applications or SA proposals to seek approval
  - based on non-randomised studies
  - with or without external or historical controls,
  - often in patients who had failed and/or were intolerant of initial antifungal treatments
- 2010 revision updated the guidance in line with CHMP scientific advice and approvals between 2003-2010; this version is still the current one
- reflects revised EORTC-MSG recommendations and categorisations



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22 April 2010
CHMP/EWP/1343/01 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

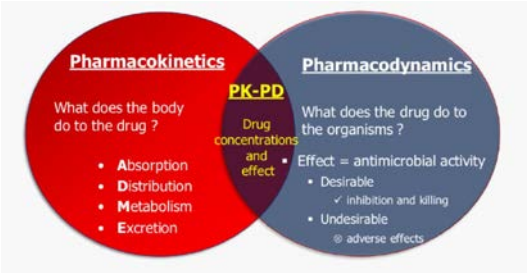
Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease

Discussion in the Efficacy Working Party	July 2001 – June 2002
Transmission to CPMP	July 2002
Release for Consultation	July 2002
Deadline for Comments	January 2003
Discussion in the Efficacy Working Party	April 2003
Transmission to CPMP	May 2003
Adoption by CPMP	May 2003
Date for coming into operation	November 2003
Draft Revision 1 agreed by Efficacy Working Party	April 2009
Adoption by CHMP for release for consultation	29 May 2009
End of consultation (deadline for comments)	30 November 2009
Revision 1 Agreed by Efficacy Working Party	April 2010
Adoption by CHMP	22 April 2010
Date for coming into effect	1 November 2010

Dose regimens for the treatment of invasive fungal disease

- **CHMP/EWP/1343/01 Rev. 1** :

  The selection of proposed regimen(s) to be studied in confirmatory studies of clinical efficacy should be based on all the available non-clinical data, human pharmacokinetic data and exploration of the PK-PD relationship



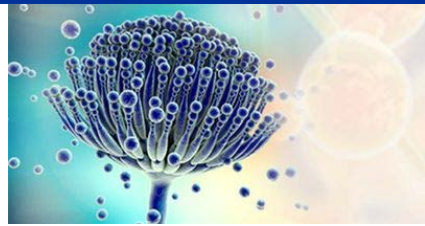
From clsi.org

- **The PK-PD guideline** (EMA/CHMP/594085/2015) states:

  This Guideline is intended to be applicable to systemically active antibacterial agents, antimycobacterial agents and antifungal agents.

- Experience using PK-PD to select doses for anti-fungal agents is accumulating

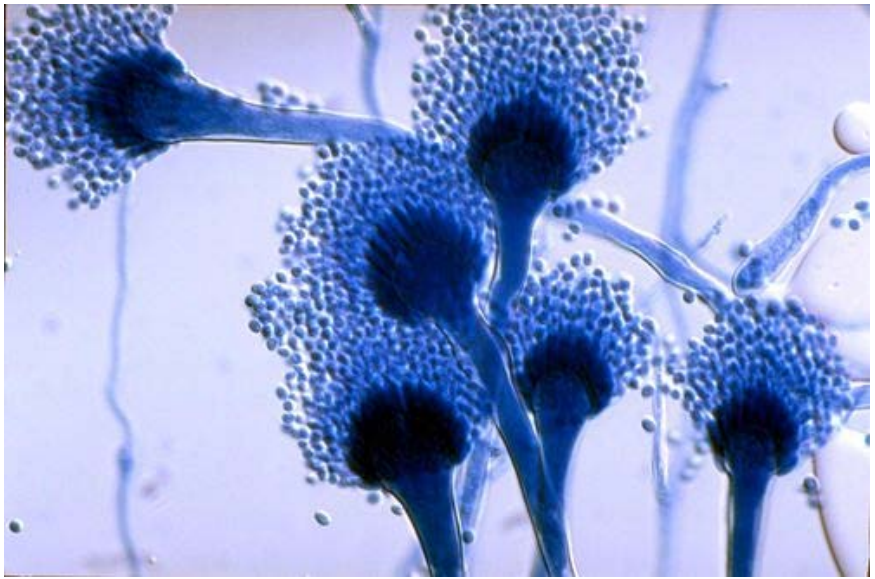
Treatment of invasive fungal disease produced by Candida or Aspergillus



- Prospective, randomised and active controlled trials recommended
- Single pivotal trials acceptable
- primary analysis: in patients confirmed to have proven or probable IFD
- Preferably single comparative agent allowed; if not possible, restrict choices
- recommends independent adjudication committee blinded to treatment assignment to determine eligibility and outcomes
- fungaemia should be investigated for identifiable primary foci and should persist after removal of known/suspected catheter sources
- Patients with persistent fungaemia and/or established primary foci can be counted in primary analyses to support indications for invasive aspergillosis

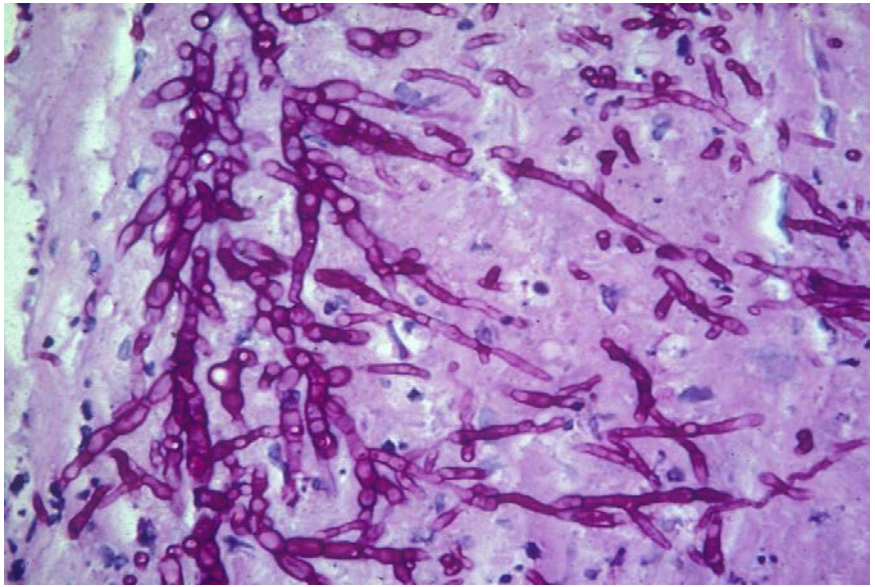
Primary endpoint of invasive aspergillosis/candidiasis

- EU-preferred primary endpoint is **global clinical response at test-of-cure**
- Pre-defined NI margins often based on mortality in datasets of variable proven vs. probable cases; relevance to studied population questionable; nevertheless, 10% NI margin has been accepted
- A pre-defined primary efficacy endpoint of all-cause mortality at day 42 or day 84 has been accepted provided that the global clinical response rates are supportive



Treatment of rare invasive fungal diseases (I)

- Some sponsors conducted/proposed non-randomised studies in patients with various rare fungal infections; some derived historical controls
- Some proposed initial approval for specific rare pathogens based on such studies ± PK-PD to support adequacy of dose
- CHMP advised that at least one RCT in IFD due to Candida or Aspergillus should be conducted before, or in parallel with, a rare fungal pathogen study
- Justify dose for rare fungal pathogens using the efficacy results vs. Candida and/or Aspergillus **plus** PK-PD analyses using patient PK data



Treatment of rare invasive fungal diseases (II)

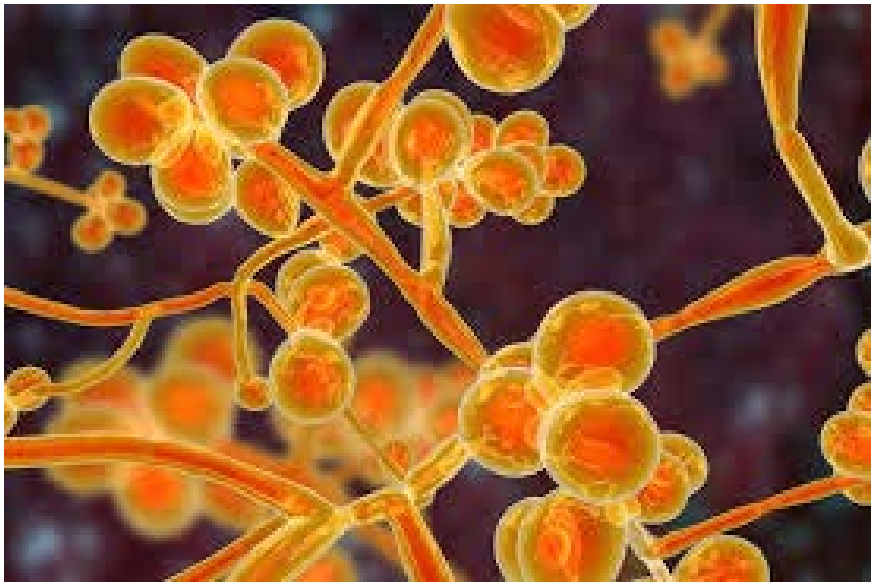
- at present, guidance does not foresee that approval for treatment of rare pathogens could be based only on pos. RCT(s) in Candida or Aspergillus plus PK-PD
- randomization step always preferred
- use unbalanced randomisation
- prefer separate studies by fungal type (e.g. mucormycosis)
- compare with licensed agent(s) or BAT
- if there is nothing approved or no treatment is considered adequate ->seek to demonstrate superiority of the test regimen vs. BAT

Treatment of refractory invasive fungal disease

- studies of clinical efficacy in refractory IFD →only after satisfactory efficacy has been shown for an antifungal agent in one or more specific types of IFD
- patients with proven IFD (except probable cases of invasive aspergillosis acceptable) that have persisted or progressed despite previous antifungal therapy; avoid those who discontinued prior therapy only due to intolerance
- primary objective needs discussion depending on whether an active controlled design is possible

Prophylaxis of invasive fungal disease

- Conduct studies in prophylaxis of IFD only **after** showing satisfactory **clinical efficacy in treatment** of IFD
- conduct RCT vs. comparative regimen
- discuss NI margin/power on case by case basis
- compare rates for proven/probable IFD during treatment and for a defined period after cessation of prophylaxis (depending on half-life and criteria for stopping)
- indication likely to reflect the evidence for prevention of IFD due to specific types



Unmet medical need

- **Conditional marketing authorisation (CMA)**
  - For products where the B/R balance is such that the immediate availability outweighs the limitations of less comprehensive data than normally required, i.e. medicines with an established potential to address an unmet medical need.
  - UMN=a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the EU or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected (art 4(2) of Regulation EC 507/2006)
- **Accelerated assessment (AA)**
  - Medicinal product of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation
  - Needs justification by the applicant (typically: arguments to support that the medicine addresses to a significant extent the UMN for maintaining and improving the health of the Community, e.g. by introducing new methods of therapy or by improving existing ones

Other areas where unmet medical need is considered

- Orphan designation
  - Art 3 of Regulation 141/2000 refers to life-threatening or chronically debilitating nature of the condition as requirement for orphan designation of a medicine
  - Unmet need implicit in significant benefit criteria for designation: responsibility of the sponsor to establish that there exists no satisfactory method of diagnostic, prevention or treatment of the condition in question, or if such a method exists that the medicinal product will be of significant benefit to those affected by that condition
- PRIME: UMN definition concept similar to that of CMA and applied in the context of fostering AA
- Paediatric Investigation Plans: can be waived if medicine does not represent a significant therapeutic benefit over existing treatments for children

Summary

- EMA guidance on antifungals was finalised 10 years ago and is still in force
- Few new approvals/new indications for antifungal agents since 2010 and relatively few requests for CHMP scientific advice for treatment/prevention of IFI
- Meanwhile, experience with applying PK-PD analyses to antifungals has accumulated/is accumulating
- CHMP has been flexible on primary endpoint in treatment of IA
- For rare pathogens, advice is to:
  - first establish efficacy in Candida or Aspergillus;
  - use data to support results of small RCTs in rare pathogen(s);
  - use PK-PD to support dose
- Prophylaxis should be investigated after treatment
- Regulatory tools exist for products addressing an unmet medical need

Thank you!

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