

## European Committee on Antimicrobial Susceptibility Testing (EUCAST) Technical Notes on antimicrobial susceptibility testing

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### ABSTRACT

The main objectives of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are to harmonise breakpoints for antimicrobial agents in Europe, and to act as the breakpoint committee for the European Medicines Agency (EMA) during the registration of new antimicrobial agents. Detailed EUCAST procedures for harmonising and setting breakpoints for antimicrobial agents are available on the EUCAST website. Beginning with the current issue, a series of EUCAST Technical Notes will be published in *CMI*, based on the rationale documents produced by EUCAST for each of the antimicrobial agents studied, with the aim of highlighting important background information underlying decisions on breakpoints made by EUCAST.

**Keywords** Antimicrobial agents, breakpoints, EMA, EUCAST, MICs, susceptibility tests

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EUCAST is the European Committee on Antimicrobial Susceptibility Testing. The main objectives of EUCAST are to harmonise antimicrobial breakpoints in Europe [1,2] and to act as the breakpoint committee for the European Medicines Agency (EMA) during the registration of new antimicrobial agents, as defined in a Standard Operating Procedure agreed between the EMA, EUCAST and the pharmaceutical industry in 2005 [3]. An informal interchange of information exists between EUCAST and the CLSI (formerly NCCLS) in the USA. However, differences in structure, financing and relationships with regulatory authorities have precluded formal collaboration in the setting of breakpoints.

EUCAST is convened by the European Society of Clinical Microbiology and Infectious Diseases

(ESCMID) and the national antimicrobial breakpoint committees of France (Comité de l'Antibiogramme de la Société Française de Microbiologie; CA-SFM) [4], Germany (Deutsches Institut für Normung; DIN) [5], Norway (Norwegian Working Group on Antimicrobials; NWGA) [6], Sweden (Swedish Reference Group of Antibiotics; SRGA) [7], The Netherlands (Commissie Richtlijnen Gevoeligheidsbepalingen; CRG) [8] and the UK (British Society for Antimicrobial Chemotherapy; BSAC) [9]. EUCAST is financed by ESCMID, the national breakpoint committees and the 5th Directorate General (DG-Sanco) of the European Union.

EUCAST has a General Committee, with one representative from each European country, the International Society of Chemotherapy (ISC) and the Federation of European Societies of Chemotherapy and Infection (FESCI). EUCAST also has a Steering Committee, with a representative from each of the six national breakpoint committees

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listed above, two representatives from the EUCAST General Committee, and a Chairperson and Scientific Secretary. All appointments to the Steering Committee are made by the ESCMID Executive Committee. This structure was established in 2002 following a reorganisation of EUCAST. EUCAST has Sub-committees on Antifungal Susceptibility Testing (EUCAST AFST) and on Expert Rules for Antimicrobial Susceptibility Testing. The responsibility for development of harmonised breakpoints rests with the Steering Committee, in consultation with the national breakpoint committees, the EUCAST General Committee, the pharmaceutical industry and the manufacturers of susceptibility testing devices.

During 2004 and 2005, EUCAST harmonised breakpoints for several classes of antimicrobial agents (aminoglycosides, fluoroquinolones, glycopeptides, oxazolidinones) [10], and during 2005 has set breakpoints for two new antimicrobial agents, daptomycin and tigecycline, following the procedure agreed with EMEA. It is currently working on harmonisation of breakpoints for carbapenems, cephalosporins, monobactams and penicillins. The EUCAST AFST is currently working on European breakpoints for fluconazole.

EUCAST procedures for harmonising breakpoints for existing antimicrobial agents, and for setting breakpoints for new agents, are described on the EUCAST website [11]. EUCAST breakpoint

tables can also be found on the EUCAST website [10], with links to tables of wild-type MIC distributions and rationale documents produced for each of the antimicrobial agents addressed by EUCAST.

Breakpoints defined by EUCAST are MIC breakpoints. The International Standards Organization (ISO) is currently developing a worldwide standard to determine MICs by microdilution. The EUCAST [12] and the CLSI [13] microdilution methods are both compatible with the final version of the ISO method, which is currently being distributed for an international vote on acceptance. How laboratories will use and implement EUCAST breakpoints will depend on the methods used in individual laboratories. In order to facilitate the process, EUCAST participated in a workshop during November 2005 with pharmaceutical companies and manufacturers of susceptibility testing devices to discuss implementation of EUCAST breakpoints in Europe. The various routes by which implementation might be accomplished were clarified:

- The manufacturers of automated susceptibility testing systems can download EUCAST breakpoints from the EUCAST website. It was agreed that the time needed by the manufacturers to implement breakpoints in their systems would delay implementation in automated systems

**Table 1.** Format of data in EUCAST rationale documents and Technical Notes

Section title	Section contents
1. Dosages	Lists the known dosages used in European countries as 'most common dose', 'maximum dose' and 'administration forms available'.
2. MIC wild-type distributions	Extensive MIC distribution data have been collected in an internet-based database freely available to the public [15]. Excerpts from the database are listed in a table showing numbers of isolates with MIC values in the wild-type distribution for each species.
3. Breakpoints before harmonisation	For established agents, the existing breakpoints in each of the national systems are listed, together with the current CLSI breakpoints [16] where available. This table will be empty for new agents.
4. Pharmacokinetics	A summary of the pharmacokinetic (Pk) data.
5. Pharmacodynamics	A summary of the pharmacodynamic (Pd) data <i>in vitro</i> , in animal systems and clinical data obtained from trials in humans.
6. Monte Carlo simulations and Pk/Pd breakpoints	Using simulated population pharmacokinetics, known Pd properties and probabilities of target attainment, the theoretical Pk/Pd breakpoint or breakpoints are determined for various groups of microorganisms causing infection.
7. Clinical data	Available clinical data in relation to known MIC values and resistance mechanisms are evaluated.
8. Clinical breakpoints	Preliminary clinical breakpoints based on clinical data and Pk/Pd breakpoints are defined. Species considered targets for the agent are listed. The preliminary breakpoints are checked against MIC distributions for target species to ensure that wild-type distributions are not divided by the breakpoints. To avoid cutting the wild-type distribution, breakpoints may be adjusted one two-fold dilution step up or down.
9. Consultation process and breakpoint table	Following the EUCAST consultation process, through which the national breakpoint committees, the EUCAST General Committee members, the pharmaceutical industry and the susceptibility testing devices industry are given the opportunity to comment on the preliminary breakpoints, the final breakpoints are presented in a table.
10. Exceptions noted for individual national committees	It is possible for a national committee to require an exception from the EUCAST harmonised breakpoints (e.g., on the basis of different national dosages of the agent). The exception will be noted in the rationale document and the reason given.

until late 2006. The importance of informing the manufacturers of new breakpoints as early as possible was emphasised.

- EUCAST breakpoints will be implemented in the susceptibility testing systems of the national breakpoint committees in Europe. Disk-diffusion susceptibility testing methods that implement EUCAST breakpoints include the BSAC [14], CA-SFM [4] and SRGA [7] systems.
- Antimicrobial resistance surveillance systems in which MIC values are collected can start using EUCAST epidemiological cut-off values and clinical breakpoints as they become available. The effects of changing breakpoints can be assessed by retrospective comparison of data interpreted by previous breakpoints and by EUCAST breakpoints.

Beginning with the current issue, a series of EUCAST Technical Notes (ETNs) will be published in *CMI*. The ETN on daptomycin, recently approved by EMEA, is the first to appear [17]. ETNs on aminoglycosides, fluoroquinolones, glycopeptides and linezolid will follow in the near future. The ETNs are based on the rationale documents produced by EUCAST for each of the antimicrobial agents subjected to the processes of harmonising or setting breakpoints. The aim of the ETNs is to highlight important background information on which decisions concerning breakpoints are made by EUCAST. The antimicrobial agent-specific rationale documents will be available on the EUCAST website [10] and will be more detailed than the ETNs. Both follow the format and include the information outlined in Table 1. The rationale documents will be updated whenever breakpoints are reviewed. The publication of the ETNs in *CMI* will assist in the dissemination of harmonised European breakpoints, provide transparency to EUCAST decisions on breakpoints, and provide references to EUCAST breakpoints and the background to them.

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