EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Standard Operating Procedure

Review and revision of antimicrobial breakpoints

EUCAST SOP 3.3

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Foreword

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002.

The current remit of EUCAST is to maintain clinical breakpoints for existing antimicrobial agents in Europe, to determine clinical breakpoints for new agents, to set epidemiological cut-off values, to review and revise breakpoints as required, to develop and refine methodology for antimicrobial susceptibility testing, to maintain a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST, EUCAST breakpoints and all documents are freely available on the EUCAST website at http://www.eucast.org.

Citation of EUCAST documents

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EUCAST documents published on the EUCAST website should be cited in the following way: **European Committee on Antimicrobial Susceptibility Testing. Name of document, EUCAST version number, year. Website address**.

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Abbreviations

BSAC	British Society for Antimicrobial Chemotherapy (UK)
CA-SFM	Comité de l´Antibiogramme de la Société Francaise de Microbiologie
CRG	Commissie Richtlijnen Gevoeligheidsbepalingen (Netherlands)
DIN	Deutsches Institut für Normung eV. (Germany)
ECDC	European Centre for Disease Prevention and Control
ECOFF	Epidemiological cut-off value
EMA	European Medicines Agency
EUCAST	European Committee on Antimicrobial Susceptibility Testing
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
MIC	Minimum Inhibitory Concentration
NAC	National Antimicrobial Susceptibility Testing Committee
NWGA (AFA)	Norwegian Working Group for Antibiotics (Arbeidsgruppen for antibiotikaspørsmål) (Norway)
PD	Pharmacodynamics
PK	Pharmacokinetics
SOP	Standard Operating Procedure
SRGA	The Swedish Reference Group of Antibiotics (Sweden)

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1	Scope
1.1	This SOP describes how existing EUCAST breakpoints may be reviewed and revised. It is valid for both antibacterial and antifungal breakpoints

2	Introduction
2.1	Antimicrobial breakpoints may require review because of changes that have occurred since the breakpoints were originally set including: • New clinical indications • New target organisms • New clinical data • New resistance mechanisms • New formulation of an agent • New agent in the same class • New dosage regimens or modes of administration • New PK-PD data

3	Instigation of the review process
3.1	Any of the following groups with a formal interest in antimicrobial breakpoints may instigate the review process by sending a reasoned statement to the EUCAST Steering Committee.
3.2	**National Breakpoint Committees and National AST Committees (NACs)** There were originally six National Breakpoint Committees: BSAC (UK), CA-SFM (France), CRG (The Netherlands), DIN (Germany), NWGA (Norway) and SRGA (Sweden). The DIN breakpoint committee was later replaced by the German NAC. Each of these committees has had many years of experience in determining and revising breakpoints. In addition, NACs have been set up in many other countries more recently. Any of these groups can suggest that EUCAST should review breakpoints for an antimicrobial agent or class of agents.
3.3	**Medicines Agencies** Most countries have a regulatory medicines agency. In Europe, these agencies now collaborate through the EMA. It is the task of medicines agencies to limit and to allow extensions of indications of existing drugs and to safeguard the proper use of medicines. Any medicines agency can ask EUCAST to review existing breakpoints for an antimicrobial agent or class of agents.
3.4	**European Centre for Disease Prevention and Control**

	The ECDC has a responsibility for public health in Europe. It performs systematic surveillance of antimicrobial resistance development in many organisms of public health importance in Europe. This surveillance may provide information indicating the need to review breakpoints. ECDC can ask EUCAST to review existing breakpoints for an antimicrobial agent or a class of agents.
3.5	**Professional antimicrobial chemotherapy organisations** Individuals in professional organisations involved in antimicrobial chemotherapy have up-to-date and/or first-hand knowledge and experience in using antimicrobial agents. The professions have a responsibility to ensure that agents are used safely and efficiently. Professional organisations involved in antimicrobial chemotherapy can ask EUCAST to review existing breakpoints for an antimicrobial agent or a class of agents.
3.6	**Pharmaceutical companies** Pharmaceutical companies involved in the development, manufacturing and/or sale of antimicrobial agents have an obligation and an interest in making sure that the drugs are used in a safe, efficacious and proper manner. Companies responsible for an agent can ask EUCAST to review existing breakpoints.

4	**Relevant factors in review of breakpoints for antimicrobial agents**
4.1	A change in one or more of the factors (4.2-4.11) taken into consideration when setting breakpoints merits a review of the breakpoints.
4.2	**Available formulations** A formulation not previously available (oral, intravenous, etc.) may be marketed.
4.3	**Standard and maximum dosing and mode of administration** The standard dose or the maximum dose or both and/or the mode of administering the agent may have been changed. This will be expressed as the dosage and daily frequency in the form of dosage in g x the number of daily doses (e.g. 0.5 g x 4). For intravenous agents, when the dosage regimen requires an infusion time that exceeds 30 minutes, that time will be specified (e.g. 1 g x 3 over 4h)
4.4	**Clinical indications** It is common practice for companies to apply for an extension of indications a few years into the life of the agent.
4.5	**Target organisms**

	With the accumulation of data and clinical experience it may be appropriate to extend the range of target organisms for an agent
4.6	**MIC distributions for individual species** Wild type distributions will not change but more data may enable refinement of ECOFFs (see current version of EUCAST SOP 10) and the MIC distribution for non-wild type isolates may require adjustment of breakpoints.
4.7	**Pharmacokinetic (PK) data in humans** For older agents, data may have been limited at the time of determining breakpoints. Several groups are now investigating the pharmacokinetics of older drugs and new data may merit review of existing breakpoints.
4.8	**Pharmacodynamic (PD) data** For older agents, data may have been limited at the time of determining breakpoints. Several groups are now investigating the pharmacodynamics of older drugs and new data may merit review of existing breakpoints.
4.9	**Information from modelling processes** For older agents, data may have been limited at the time of determining breakpoints. Several groups are now applying modelling techniques to older drugs and new data may merit review of existing breakpoints.
4.10	**Clinical data relating outcome to MIC values** Data may be scarce when breakpoints are set for a new agent. Accumulated data may provide evidence supporting review of existing breakpoints.
4.11	**Information on resistance mechanisms, the clinical significance of the resistance mechanisms and the MICs for organisms expressing the resistance mechanisms** When breakpoints were initially determined, resistance mechanisms may have been rare or not yet reported. When new resistance mechanisms appear, it is necessary that their relationship to breakpoints and clinical outcome is assessed.
4.12	**A new agent in an existing class** During the process of determining breakpoints for a new agent in an existing class of antimicrobial agents, it is good practice to review breakpoints of existing agents in the class. This is to ensure that breakpoints for older agents, possibly determined without modern methods, do not create an imbalance in perceived usefulness of the agents in the class.

5	Data collation by the EUCAST secretariat
5.1	New data will be added to the current EUCAST rationale document for discussion by the Steering Committee.
5.2	New MIC distributions will be entered into the EUCAST MIC distribution program, thereby making all MIC distributions available to all on the internet.

6	Presentation of data by pharmaceutical companies to the EUCAST Steering Committee
6.1	For an agent in patent, the company will be contacted when the Steering Committee has decided that there is a good case for changing the breakpoints. For agents out of patent, companies known to be major suppliers of the agent may be similarly consulted but there may be multiple suppliers worldwide and some of these may be unknown to EUCAST. EUCAST will not undertake searches to find all possible suppliers. Pharmaceutical companies informed that breakpoints for an existing agent are being reviewed may wish to present data directly to the Steering Committee and to discuss data with the Steering Committee. The process for this will be identical to the process used in the course of setting breakpoints for a new agent (see current version of EUCAST SOP 1).

7	Assessment of new data relevant to revision of breakpoints for antimicrobial agents
7.1	New data will be reviewed by the EUCAST Steering Committee and if data support modification of breakpoints, proposals for new breakpoints will be prepared.
7.2	The Steering committee will seek consensus-revised breakpoints based on discussion of new data as described above.
7.3	The Steering Committee may refrain from setting new breakpoints if the data are considered insufficient to support revision of breakpoints.

8	Discussion with National Breakpoint committees and NACs
8.1	Proposals for revised breakpoints, or the argument for retaining the *status quo* if no change is proposed following review, are presented to National Breakpoint committees and NACs by Steering Committee national representatives.
8.2	Comments from any of the national committees will be discussed and taken into account in any further discussions. If necessary, a second round of discussion with national committees will precede the next step.
8.3	When the EUCAST Steering Committee and the national committees agree on the proposed breakpoints and relevant footnotes, breakpoints are considered tentative and ready for wide consultation.

9	Consultation on tentative revised breakpoints
9.1	The tentative breakpoints are released for wide consultation with national breakpoint committees, the EUCAST General Committee, email networks and more widely via the EUCAST website. Generally, a 4-8-week consultation period is allowed. The consultation document with deadline for comments is posted on the EUCAST website.
9.2	Comments from any source will be discussed and taken into account in any further assessment of breakpoints.
9.3	If there are particular contentious issues, there may be further discussions and further rounds of consultation until consensus breakpoints are agreed between the EUCAST Steering Committee and the national breakpoint committees.

10	Finalisation of revised breakpoints
10.1	Agreed revised breakpoints are published on the EUCAST website.
10.2	A national committee which cannot agree with the EUCAST revised breakpoints may submit their reasoning in writing, and this will be published in the Rationale Document with the revised breakpoints agreed by the rest of the Steering Committee.

11	Publication of revised breakpoints

11.1	Revised breakpoints will be published on the EUCAST website (www.eucast.org).
11.2	As the revised breakpoints are incorporated into the methods of the national breakpoint committees, they will be published on national websites and in national guidelines.
11.3	A revised rationale document giving a summary of the background information and reasoning behind the revised breakpoints will be published on the EUCAST website.
11.4	If deemed necessary by the Steering Committee, a technical note giving an outline of the reasoning behind the revised breakpoints will be published in a peer-reviewed journal.