EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Standard Operating Procedure

Setting breakpoints for new antimicrobial agents

EUCAST SOP 1.3

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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, currently in France, Germany, Norway, Sweden, The Netherlands and The United Kingdom. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. Countries outside Europe are increasingly forming EUCAST-affiliated national antimicrobial susceptibility testing (AST) committees and implementing the EUCAST systems of testing methods and breakpoints.

The remit of EUCAST is to harmonise clinical breakpoints for existing antimicrobial agents in Europe, to determine clinical breakpoints for new agents, to set epidemiological (microbiological) breakpoints, to revise breakpoints as required, to harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms, to provide continuing education on AST 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
CA-SFM	Comité de l´Antibiogramme de la Société Francaise de Microbiologie
CHMP	EMA Committee for Medicinal Products for Human Use
CLSI	Clinical and Laboratory Standards Institute
CRG	Commissie Richtlijnen Gevoeligheidsbepalingen
DIN	Deutsches Institute for Normung eV.
ECDC	European Centre for Disease Prevention and Control
ECOFF	Epidemiological cut-off
EMA	European Medicines Agency (formerly EMEA)
EUCAST	European Committee on Antimicrobial Susceptibility Testing
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
FESCI	Federation of European Societies of Chemotherapy and Infection
ISC	International Society for Chemotherapy
MAA	Marketing Authorisation Application
MIC	Minimum Inhibitory Concentration
NAC	National Antimicrobial Susceptibility Testing Committee
NWGA (AFA)	Norwegian Working Group on Antibiotics (Arbeidsgruppen for antibiotikaspørsmål)
PD	Pharmacodynamics
PK	Pharmacokinetics
S/I/R	Susceptible-standard exposure/Susceptible-increased exposure/Resistant
SOP	Standard Operating Procedure
SRGA	The Swedish Reference Group of Antibiotics
SWAB	Stichting Wertkgroep Antibioticabeleid

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1	Scope
1.1	This SOP describes how EUCAST determines breakpoints for new antibacterial and antifungal agents.
1.2	A similar procedure is applied to setting breakpoints for both new and existing antimicrobial agents, the difference being that existing agents have established dosages and breakpoints in different countries. In this SOP the procedure for new agents is described.
1.3	In addition to clinical breakpoints, epidemiological cut-off values are defined.

2	Introduction
2.1	**Historical Background** Historically, at least seven different sets of clinical antimicrobial MIC breakpoints have been used in Europe. In 2002 there were six active European National Breakpoint Committees: BSAC (UK), CA-SFM (France), SWAB (superseding CRG, The Netherlands), DIN (Germany), NWGA (Norway) and SRGA (Sweden). The DIN committee ceased to have meetings in 2011 and was replaced by NAC Germany in 2013. Following completion of the EUCAST harmonization process for European breakpoints most European countries and several outside Europe have adopted EUCAST breakpoints or are in the process of adopting EUCAST breakpoints. Some other countries, in the absence of a national system, claim to use breakpoints published by the CLSI (USA). The divergence in interpretation between EUCAST and CLSI has been considerable, creating confusion for clinicians and making comparison of resistance rates from different countries misleading. One of the main objectives of EUCAST is to achieve harmonization of existing and new antimicrobial breakpoints.
2.2	**Regulatory Background** The procedure through which the European Medicines Agency (EMA), EUCAST and the pharmaceutical industry interact in setting clinical MIC breakpoints as part of the approval process for new antimicrobial agents is defined in The Working Order Between Industry, EMA and EUCAST (update 5 May 2019) (http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/The_working_order_between_EUCAST_and_industry_and_EMA_2019.pdf). The national committees (BSAC, CA-SFM, SWAB, NWGA, SRGA and NAC Germany) have agreed to notify each other when one or several are approached to set breakpoints for a new antimicrobial agent outside of the

	EMA procedure. The advantages of the agreed EMA procedure are that it results in common European clinical breakpoints for new antimicrobial agents, the procedure has a time limit, the expertise within the system is fully utilized and it is cost effective for European governmental agencies and for the pharmaceutical companies as there is only one dataset from the company, one presentation of the agent and a common European breakpoint.
2.3	**Epidemiological Cut-off Values** Epidemiological cut-off values (ECOFFs) have also been described as microbiological breakpoints, but the use of the term “breakpoint” leads to confusion with clinical breakpoints. ECOFFs are related to the distribution of MICs for wild-type organisms lacking acquired resistance to the antimicrobial agent in question. The ECOFF is essentially the highest acceptable MIC value of the wild-type distribution (EUCAST SOP 10.1). ECOFFs are of value in the phenotypic detection of resistance to antimicrobial agents as a biological phenomenon and may indicate the development of resistance at a level below the clinical breakpoint. This may or may not be clinically significant but may constitute an early warning of developing resistance. ECOFFs are also useful in situations where clinical breakpoints have not been defined, such as with some topical agents, or in some aspects of veterinary practice, where very different breakpoints may be appropriate for different genera or species.

3	**Groups involved in breakpoint setting**
3.1	**EUCAST Steering Committee** The Chairman, Scientific Secretary, Clinical Data Co-ordinator, Technical Data Coordinator and two country representatives from the EUCAST General Committee are appointed by the ESCMID Executive Board. Each of the National Breakpoint Committees is represented on the Steering Committee. This group is the centre of EUCAST activity in breakpoint setting.
3.2	**National Breakpoint Committees** Each consists of 10-20 experts within the fields of clinical microbiology, infectious diseases and pharmacology. Some have additional experts from other medical specialties and/or from veterinary medicine. These groups have a central role in providing expertise in relation to the setting of breakpoints and review of proposals from the Steering Committee.
3.3	**EUCAST General Committee** This group has a member from each country. Members may represent a national antimicrobial susceptibility testing committee (NAC) or be proposed by national societies of clinical microbiology and/or infectious diseases or, where such groups do not exist, by recommendation from prominent individuals. In addition, there is a representative of the International Society

	for Chemotherapy (ISC). This group provides a Europe-wide and international forum for review of proposals from the Steering Committee in relation to the setting of breakpoints. Confidential information provided in relation to the setting of breakpoints for new agents as part of the MAA process through EMA is not released to this group.
3.4	**EMA, national medicines agencies and ECDC representatives** EMA and ECDC representatives may be present as observers at EUCAST Steering Committee meetings. EMA representatives, including rapporteurs (the person/persons appointed to represent a national agency with primary responsibility for the approval process) may, at the discretion of EMA, take part as observers in the process of determining breakpoints for a new agent. ECDC observers do not take part in the process of determining breakpoints for a new agent.
3.5	**Individual pharmaceutical companies** For new antimicrobial agents the relevant pharmaceutical company will, if they agree to breakpoint setting by EUCAST as a confidential process as part of the MAA procedure through EMA, provide information and discuss breakpoints and associated issues with EUCAST.

4	**Data collection**
4.1	For agents submitted to EMA through the central registration procedure, the data will be the same for all European countries. With this procedure there is no pre-existing experience with the agent. The data will be provided by the pharmaceutical company as part of the MAA file. The company will provide: • Proposed indications for the agent • Proposed dosing regimens for the agent (by indication) and the available formulations • Proposed target organisms • MIC distributions for relevant species • Pharmacokinetic data • Pharmacodynamic data • Modelling data, such as Monte Carlo simulations • Clinical trial data, including outcome related to MIC where available
4.2	The company may suggest breakpoints as part of the file submitted to EMA. The company is encouraged to include the complete rationale for suggested breakpoints in a company “rationale document” prepared according to the format of the EUCAST rationale document. The final EUCAST versions of rationale documents are published on the EUCAST website and accompany EUCAST breakpoints for each agent.

5	**Relevant factors in setting breakpoints**
5.1	**Available formulations** Whether oral, intravenous, infusion etc.
5.2	**Standard and increased exposure dosing** This will be expressed as the dosage and dosing frequency in the form of dosage in mg x the number of doses per day (e.g. 500 mg x 4). There will be one standard dosing regimen and possibly an increased exposure ('higher') dosing regimen.
5.3	**Clinical indications and target organisms** These will be clearly stated.
5.4	**MIC distributions for individual species** These data are likely to be from studies undertaken by or commissioned by the pharmaceutical company. They may be published in scientific journals or in presentations at scientific meetings, held by national or international surveillance programs or may yet to be published and held by the company. When a new agent is a member of a group of related agents where resistance is established, the MICs of the new agent for organisms with known resistance mechanisms affecting the group should be examined. Full (on-scale) MIC distributions for individual species/species complexes are required. Distributions from different studies or MICs determined in different laboratories should be presented separately and should not be aggregated. The test methods for each study must be stated. At least some of the data should be generated using the ISO 20776-1 standard (v2, 2019) when applicable. Much published information is unacceptable as the MIC distributions are abbreviated to MIC_{50}, MIC_{90} or simply categorical reporting. However, the full MIC distributions underlying these data may be available to EUCAST.
5.5	**Pharmacokinetic (PK) data in humans** The characteristics of the population from which data are derived must be given. These data are likely to be from studies undertaken by or commissioned by the pharmaceutical company. They may be published in scientific journals or in presentations at scientific meetings (in which case the reference should be included), held by national or international surveillance programs or may yet to be published and held by the company. If unpublished data are used they may be included in rationale documents or referred to as "data on file reviewed by EUCAST".
5.6	**Pharmacodynamic (PD) data**

	Exposure-response relationships obtained from *in vitro* studies, animal studies and humans will be provided. These data are likely to be from studies undertaken by or commissioned by the pharmaceutical company. They may be published in scientific journals or in presentations at scientific meetings (in which case the reference should be included) or may yet to be published and held by the company. If unpublished data held by pharmaceutical companies are used, they may be included in rationale documents or referred to as “data on file reviewed by EUCAST”.
5.7	**Information from modelling processes** Information from modelling processes, such as Monte Carlo simulation, should be available to assess the likelihood of achieving proposed pharmacodynamic targets. Such data are a key part of the process of breakpoint setting. These data are likely to be from studies undertaken by or commissioned by the pharmaceutical company. They may be published in scientific journals or in presentations at scientific meetings in which case the reference should be included) or may yet to be published and held by the company. If unpublished data held by pharmaceutical companies are used, they may be included in rationale documents or referred to as “data on file reviewed by EUCAST”.
5.8	**Clinical data relating outcome to MIC values** These data are likely to be from studies undertaken by or commissioned by the pharmaceutical company. They may be published in scientific journals or in presentations at scientific meetings, in which case the reference should be included or may yet to be published and held by the company. If unpublished data held by pharmaceutical companies are used, they may be included in rationale documents or referred to as “data on file reviewed by EUCAST”.
5.9	**Information on resistance mechanisms, the clinical significance of the resistance mechanisms and the MICs for organisms expressing the resistance mechanisms** These data are likely to be from studies undertaken by or commissioned by the pharmaceutical company. They may be published in scientific journals or in presentations at scientific meetings, in which case the reference should be included or may yet to be published and held by the company. If unpublished data held by pharmaceutical companies are used, they may be included in rationale documents or referred to as “data on file reviewed by EUCAST”.

6	**Data collation by the EUCAST secretariat**
6.1	Information will be supplied as a package by the pharmaceutical company. This will normally be sent by the company to all Steering Committee members, with copies to the EMA.

6.2	MIC distributions will be provided to EUCAST using the standard spreadsheets (available on the webpage: http://www.eucast.org/mic_distributions_and_ecoffs/) and will be entered into the EUCAST MIC distribution program. If MIC distributions pass quality checks to ensure that there are adequate numbers of organisms, that MIC ranges are not truncated, that data for wild-type organisms are consistent with other data and that there are no obvious methodological concerns, they are also included in collated distributions, as described in SOP 10.1. For new agents the collated distributions may be based on very few studies. Tentative ECOFF values may be suggested for discussion by the Steering Committee members.

7	**Presentation of data by the pharmaceutical company to the EUCAST Steering Committee**
7.1	The pharmaceutical company may make an early preliminary presentation of data to the Steering Committee. This meeting would be in advance of submission of the MAA to EMA and gives the company the opportunity to meet the Steering Committee, to familiarise themselves with the requirements of the EUCAST process, and to be offered preliminary guidance on possible limitations of their data.
7.2	For new agents submitted to EMA for marketing authorisation, the pharmaceutical company may make a formal presentation of data directly to the Steering Committee and discuss data with the Steering Committee.
7.3	Following submission of the MAA, the EMA will be copied in on all correspondence between EUCAST and the company and will be invited to attend any meetings between EUCAST and the company.
7.4	Comment may be made by the Steering Committee members but no indication of proposed EUCAST breakpoints will be given during these meetings.

8	**Assessment of data in setting breakpoints for antimicrobial agents**
8.1	**Available formulations** Different breakpoints may be appropriate for different formulations and/or different dosing regimens.
8.2	**Standard and maximum dosing** The S/I breakpoint is normally based on the standard dosing regimen and the

	I/R breakpoint on the increased-exposure dosing regimen.
8.3	**Clinical indications and target organisms** These will be noted.
8.4	**MIC distributions for individual species** Through the EUCAST MIC distribution database (www.eucast.org), full MIC distributions of antimicrobial agents for individual species are available. Multiple MIC distributions are examined and differences in the wild-type populations that may indicate technical problems are highlighted. If appropriate, multiple MIC distributions are combined in the database. ECOFFs are defined for relevant species according to procedures detailed in in the introduction to the MIC and zone diameter distributions website and in detail in EUCAST SOP 10.1.
8.5	**Organisms with resistance mechanisms** For new agents there may be no resistant organisms, but if the agent is a member of a group of related agents where resistance is established, the MICs of the new agent for organisms with known resistance mechanisms affecting the group will be examined. The MICs for non-wild-type organisms will be noted.
8.6	**Pharmacokinetic (PK) data in humans** The population characteristics on which data are based will be assessed. This is commonly healthy volunteers for new agents but additional data based on relevant patient groups may be available, particularly for established agents. The PK data examined will, when available, include for each dosing regimen the maximum serum concentration, minimum serum concentration, total body clearance rate, the elimination half-life, the area under the serum concentration curve over 24 h, the fraction unbound and the steady state volume of distribution. References to the sources of the data are noted, together with any other relevant comments.
8.7	**Pharmacodynamic (PD) data** Exposure-response relationships obtained from *in vitro* studies, animal studies and human studies are examined and, when possible, appropriate pharmacodynamic targets established (e.g. percent free time above MIC, free AUC/MIC value).
8.8	**Information from modelling processes** Modelling processes, such as Monte Carlo simulation, will be applied when possible to assess the likelihood of achieving proposed pharmacodynamic targets. These data are used to establish “PK-PD” breakpoints as part of the process of setting clinical breakpoints, as described by Mouton *et al* (Clin Microbiol Infect 2012; 18:E37-45).

8.9	**Clinical data relating outcome to MIC values** For each target organism or group of organism clinical data relating MIC to outcome are assessed. It is understood that for new agents the data are often very sparse or absent for organisms other than wild-type isolates.

9	**Presentation of EUCAST breakpoints**
9.1	EUCAST breakpoints are presented in tables with major groups of organisms each having a breakpoint column. Current major groups are: *Enterobacterales* *Pseudomonas* spp. *Stenotrophomonas maltophilia* *Acinetobacter* spp. *Staphylococcus* spp. *Enterococcus* spp. *Streptococcus* group A,B,C andG *Streptococcus pneumoniae* Viridans group streptococci *Haemophilusinfluenzae* *Moraxella catarrhalis* *Neisseria gonorrhoeae* *Neisseria meningitidis* Gram-positive anaerobes *Clostridioides difficile* Gram-negative anaerobes *Helicobacter pylori* *Listeria monocytogenes* *Pasteurella multocida* *Campylobacter jejuni* and *coli* *Corynebacterium* spp. *Aerococcus sanguinicola* and *urinae* *Kingella kingae* *Aeromonas* spp. *Mycobacterium tuberculosis* Other organisms may, depending on the indications, be included.
9.2	If the species is considered a poor target for the agent it is marked by "—" in breakpoint tables. This indicates that the agent should not be considered for therapy and thus should not be included in susceptibility tests. If the agent is included in the susceptibility report it should be categorized as resistant without susceptibility testing.
9.3	If there is insufficient evidence that the species in question is a good target for therapy with the agent, yet the organism is considered a potential target for

	the agent, it is marked “IE” in the breakpoint tables. This indicates that the agent could be considered for therapy, but if included in the susceptibility report by giving an MIC value, with or without comment, it should not be given a susceptibility categorisation.
9.4	PK-PD breakpoints are determined on the basis of PK-PD data. These breakpoints are generally independent of specific species. These are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.
9.5	When breakpoints are finally released, they are posted on the EUCAST website and included the next annual breakpoint table update. The MIC distributions for the agent can be accessed by clicking on the MIC breakpoint of the agent in the breakpoint table. The rationale document giving the rationale behind the EUCAST breakpoints can be accessed by clicking on the agent name in the breakpoint table.

10	**Tentative breakpoints**
10.1	For new agents the Steering Committee will propose breakpoints based on assessment of data as described above.
10.2	Resulting breakpoints are tested against MIC distributions for each of the major target species. This is to ensure that the breakpoints do not divide the wild-type distributions of major target species, which would obviate a reproducible S, I and R categorisation in the laboratory. Breakpoints may also be adjusted to ensure that clinically significant resistance in particular species is not missed. Hence breakpoints may differ between species.
10.3	The Steering Committee may refrain from setting breakpoints if the species is considered a poor target for the agent or there is insufficient evidence that the species is a good target for the agent. This is done following discussions with the EMA rapporteur and EMA representatives. The company is informed of the rationale for all decisions by providing it with a copy of the relevant minutes.

11	**Consultation on tentative breakpoints**
11.1	The tentative breakpoints are sent to EMA and the pharmaceutical company for comment and are presented to National Breakpoint Committees by Steering Committee national representatives.

11.2	The pharmaceutical company may send comments or request a further meeting with the Steering Committee to present new data, to provide further argument or to seek clarification of the EUCAST rationale for the breakpoints. Comments from any of the National Committees will also be discussed and taken into account in any further discussions.
11.3	Following any further meeting with the pharmaceutical company and/or discussion of written representations from the company or from the National Breakpoint Committees, the breakpoints will be reassessed and adjusted if appropriate.
11.4	At this stage breakpoints are considered tentative.

12	**Finalisation of breakpoints**
12.1	If there are particular contentious issues there may be further discussion with the pharmaceutical company and National Breakpoint Committees, within the time limitations of the EMA MAA process. The final decision on breakpoints is made by the Steering Committee.
12.2	If any National Committee cannot agree with the EUCAST breakpoints they will submit their reasoning in writing, and this will be published as an exception, together with the breakpoints agreed on by the rest of the Steering Committee.

13	**Publication of breakpoints**
13.1	When the agent has been formally approved by EMA, i.e. the CHMP committee has made its final decision and the European Parliament has formally approved the decision, breakpoints will be published on the EUCAST website.
13.2	As the breakpoints are incorporated into EUCAST National Committee methods they will be published on National Committee websites and in national guidelines.
13.3	A rationale document giving a summary of the background information and reasoning behind the breakpoints will be published on the EUCAST website.
13.4	A technical note giving an outline of the reasoning behind the breakpoints may be published in Clinical Microbiology and Infection.

14	Revision of breakpoints
14.1	Established breakpoints can be reviewed on the initiative of EUCAST, EMA or the pharmaceutical company. See EUCAST SOP 3.