EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Standard Operating Procedure

Harmonisation of breakpoints for existing antimicrobial agents

EUCAST SOP 2.3

23 October 2019

SOP Number (number.version):	2.3
Date of issue:	23 October 2019
Review interval:	2 years
Authorised by:	EUCAST Steering Committee
Author:	EUCAST Steering Committee

Document amendment history	
Issue date	**Version number**
23 October 2019	2.3
21 November 2016	2.2
20 July 2013	2.1
26 October 2010	2.0

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 current remit of EUCAST is to harmonise clinical breakpoints for existing antimicrobial agents in Europe, to determine clinical breakpoints for new drugs, 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

The copyright of all documents and data published on the EUCAST website remains with EUCAST. All are freely available for re-use if reference to the EUCAST website is given and documents and data are not sold. Any secondary publication of the data must be referenced with the declaration that "These data have (or this document has) been produced in part under ECDC service contracts and made available at no cost by EUCAST and can be accessed freely on the EUCAST website www.eucast.org. EUCAST recommendations are frequently updated and the latest versions are available at www.eucast.org."

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.

This SOP should be cited as: “European Committee on Antimicrobial Susceptibility Testing. Revising breakpoints for existing antimicrobial agents, EUCAST SOP 2.3, 2019. http://www.eucast.org”.

Abbreviations	
BSAC	British Society for Antimicrobial Chemotherapy
CA-SFM	Comité de l´Antibiogramme de la Société Francaise de Microbiologie
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
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
MIC	Minimum Inhibitory Concentration
NAC	National Antimicrobial Susceptibility Testing Committee
NWGA (AFA)	Norwegian Working Group for Antibiotics (Arbeidsgruppen for antibiotikaspørsmål)
PD	Pharmacodynamic
PK	Pharmacokinetic
SOP	Standard Operating Procedure
SRGA	The Swedish Reference Group of Antibiotics
SWAB	Stichting Wertkgroep Antibioticabeleid

Contents

Section		Page
	Foreword	3
	Citation of EUCAST documents	3
	Abbreviations	4
	Contents	5
1	Scope	6
2	Introduction	6
3	Groups involved in breakpoint setting	7
4	Data collection	7
5	Relevant factors in setting breakpoints for antimicrobial agents	8
6	Data collation by the EUCAST secretariat	9
7	Presentation of data pharmaceutical companies to the EUCAST Steering Committee	10
8	Assessment of data in setting breakpoints for antimicrobial agents	10
9	Presentation of EUCAST breakpoints	12
10	Preliminary breakpoints	13
11	Consultation on preliminary breakpoints	13
12	Consultation on tentative breakpoints	13
13	Finalisation of breakpoints	14
14	Publication of breakpoints	14

1	Scope
1.1	This SOP describes how EUCAST harmonizes breakpoints for existing 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 existing agents is described.
1.3	In addition to clinical breakpoints, epidemiological cut-off values (ECOFFs) are defined.

2	Introduction
2.1	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. Many of the other countries, in the absence of a national system, claim to use breakpoints published by the CLSI (USA). The divergence in interpretation was 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 antimicrobial breakpoints in Europe. This was achieved in 2010 for all agents commonly used in Europe.
2.2	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 susceptible populations lacking acquired resistance to the antimicrobial agent in question. The ECOFF is defined for an agent and a species. It is essentially the highest MIC value for isolates lacking phenotypically expressed resistance mechanisms and thus also the highest acceptable MIC for the wild-type distribution (EUCAST SOP 10.1). ECOFFs are of value in the detection of phenotypic 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 be an indication of the gradual development of resistance that may in time increase to a clinically significant level. ECOFFs may also be useful in situations where clinical breakpoints have not been defined, such as with some topical agents, or in 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 European 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 European country and some non-European countries. Members are proposed by national antimicrobial susceptibility testing committees (NACs), national medical groups 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.
3.4	**EMA, national medicines agencies and ECDC representatives** EMA, national medicines agency and ECDC representatives may be present as observers at EUCAST Steering Committee meetings.
3.5	**Individual Pharmaceutical Companies** The individual company will be contacted if the agent is still under patent. For agents where the patent has expired, all companies will be included as part of the general consultation process.

4	Data collection
4.1	National breakpoint committees will provide: • National recommended dosages of the agent being assessed and the available formulations. • National recommended clinical indications and target organisms for the agent. • MIC distributions for relevant species. • Current national breakpoints for the agent.

5	**Relevant factors in setting breakpoints for antimicrobial agents**
5.1	**Available formulations** Whether oral, intravenous, 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). While there will be one standard dosing regimen and possibly an increased exposure dosing regimen clearly stated for new agents there may be national differences that have developed over the years for existing agents.
5.3	**Clinical indications and target organisms** For existing agents there may be different practices in different countries.
5.4	**MIC distributions for individual species** For existing agents more extensive data are likely to be available than for new agents. In addition to studies commissioned by the pharmaceutical company there will be data from comparative studies and resistance surveillance programmes. When the agent is a member of a group of related agents where resistance is established, the MICs of the agent for organisms with known resistance mechanisms affecting the group should be examined. Full (on-scale) MIC distributions for individual species are required. The test methods must be stated and data from different studies or different sources must not be combined at this stage. At least some of the data should have been 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. Extensive data are likely to be published in scientific journals or in presentations at scientific meetings (in which case the reference should be included). Additional unpublished data may be held by pharmaceutical companies. If unpublished data are used, they may be included in rationale documents and referred to as “data on file reviewed by EUCAST”.
5.6	**Pharmacodynamic (PD) data** Exposure-response relationships obtained in *in vitro* studies, animal studies

	and humans are desirable. For older existing agents, little or no pharmacodynamic data may be available as pharmacodynamic analysis is a relatively new process. If data are published, the reference should be included. If unpublished data are used, they may be included in rationale documents and referred to as “data on file reviewed by EUCAST”.
5.7	**Information from modelling processes** Information from modelling processes, such as Monte Carlo simulation, may be available to assess the likelihood of achieving proposed pharmacodynamic targets. Such information is used to assist the process of breakpoint setting. For older existing agents, data may be limited or no modelling data may be available as such analysis is a relatively new process. If data are published the reference should be included. If unpublished data are used, they may be included in rationale documents and referred to as “data on file reviewed by EUCAST”.
5.8	**Clinical data relating outcome to MIC values** These data may be from studies undertaken by or commissioned by pharmaceutical companies or they may be from independent studies. 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. If unpublished data are used, they may be included in rationale documents and 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 more likely to be available for existing agents, where resistance is likely to be more common and the effects of resistance on outcome of treatment more likely to be published, than for new agents. 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. If unpublished data are used, they may be included in rationale documents and referred to as “data on file reviewed by EUCAST”.

6	**Data collation by the EUCAST secretariat**
6.1	Information on national indications, dosages and current breakpoints will be collated and distributed to the national committee representatives on the Steering Committee for ratification.
6.2	MIC distributions will be entered into the EUCAST MIC distribution program, thereby making all MIC distributions available to all national committees on the internet.

	If MIC distributions pass quality checks to ensure that there are adequate numbers of organisms (EUCAST SOP 7), 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 distribution, as described in SOP 10.1s. For existing agents, the collated distributions may include data from many sources. Preliminary ECOFF values may be suggested for discussion by the Steering Committee members.

7	**Presentation of data by pharmaceutical companies to the EUCAST Steering Committee**
7.1	While this is less likely with existing agents than with new agents, it is possible that pharmaceutical companies may wish to present data directly to the Steering Committee and to discuss data with the Steering Committee. Any company wishing to present data may contact the EUCAST secretariat during the consultation process and a meeting with the Steering Committee will be arranged.

8	**Assessment of data in setting breakpoints for antimicrobial agents**
8.1	**Available formulations** Different breakpoints may be appropriate for different formulations.
8.2	**Standard and maximum dosing** Any national differences will be highlighted. Where there are “common doses” in the majority of countries these will be taken as the standard and increased exposure doses. If there are wide differences these will need to be accommodated in the final breakpoints. The susceptible breakpoint is normally based on the common standard dosing regimen and the resistant breakpoint on the increased exposure dosing regimen, if there is one.
8.3	**Clinical indications and target organisms** Different practices in different countries will be highlighted and any implications for breakpoints noted.
8.4	**MIC distributions for individual species** Through the EUCAST MIC distribution database, full MIC distributions of individual species are examined. Multiple MIC distributions are examined and any differences in the wild-type populations that may indicate technical problems are highlighted. For distributions meeting acceptance criteria described in SOP 10.1, multiple MIC distributions are combined in the

	database. Epidemiological cut-off values (ECOFFs) are defined for relevant species when sufficient distributions are available.
8.5	**Organisms with resistance mechanisms** If the agent is a member of a group of related agents where resistance is established, the MICs of the 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 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 concentration half-life, the area under the serum concentration curve, the fraction unbound and the 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 in *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. For established agents, such data may not have been formally collected or agents may have been widely used in combination therapy.

9	**Presentation of EUCAST breakpoints**
9.1	EUCAST breakpoints are presented in tables with a separate section for each major group of organisms.

	Current major groups are: *Enterobacterales* *Pseudomonas* spp. *Stenotrophomonas maltophilia* *Acinetobacter* spp. *Staphylococcus* spp. *Enterococcus* spp. Streptococcus groups A,B,C andG *Streptococcus pneumoniae* Viridans group streptococci *Haemophilus influenzae* *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 drug 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 (IE) that the species is a good target for the drug it is marked by "IE" in breakpoint tables. This indicates that the agent should normally not be considered for therapy and if included in the susceptibility report by giving an MIC value, with or without comment, it should not be given a susceptibility categorization.
9.4	The PK-PD breakpoints are determined mainly on the basis of PK-PD data. These breakpoints are generally independent of specific species. They 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 in the breakpoint tables, which are updated annually.

	The MIC distributions for the agent can be accessed by clicking on the MIC breakpoint of the agent in the breakpoint tables. The rationale document giving the rationale behind the EUCAST breakpoints can be accessed by clicking on the agent name in the breakpoint table.

10	**Preliminary breakpoints**
10.1	The Steering Committee will seek consensus breakpoints based on discussion of existing national breakpoints and reassessment 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 endure 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 drug or there is insufficient evidence that the species is a good target for the drug.

11	**Consultation on preliminary breakpoints**
11.1	The preliminary breakpoints are presented to National Breakpoint committees by Steering Committee national representatives.
11.2	Comments from any of the National Committees will be discussed and taken into account in any further discussions.
11.3	Following discussion of representations from the National Breakpoint Committees, the breakpoints will be reassessed and adjusted if appropriate.
11.4	At this stage breakpoints are considered tentative.

12	**Consultation on tentative breakpoints**
12.1	The tentative breakpoints are released for wide consultation with National Breakpoint committees, the EUCAST General Committee and more widely via the EUCAST website. A six to nine-week consultation period will normally be

	allowed.
12.2	Comments from any source will be discussed and taken into account in any further assessment of breakpoints.
12.3	If there are particular contentious issues, there may be further discussions and further rounds of consultation until consensus breakpoints are agreed by the Steering Committee.

13	**Finalisation of breakpoints**
13.1	When breakpoints are finally agreed by the Steering Committee, they will be published by EUCAST in the next version of the Breakpoint Tables.
13.2	If any National Committee cannot agree with the EUCAST breakpoints they will submit their reasoning in writing, and this will be published with the breakpoints agreed on by the rest of the Steering Committee.

14	**Publication of breakpoints**
14.1	Breakpoints will be published on the EUCAST website and included in the next version of the Breakpoint Tables.
14.2	The breakpoints are incorporated into National Committee guidelines and will be published on National Committee websites.
14.3	A rationale document giving a summary of the background information and reasoning behind the breakpoints will be published on the EUCAST website.
14.4	A technical note giving an outline of the reasoning behind the breakpoints will be published in Clinical Microbiology and Infection only if there are particular issues that the Steering Committee considers warrant publication in this format.