EUCAST SOP 1.0

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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 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 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

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.

### Abbreviations

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BSAC</td>
<td>British Society for Antimicrobial Chemotherapy</td>
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<tr>
<td>CA-SFM</td>
<td>Comité de l’Antibiogramme de la Société Française de Microbiologie</td>
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<td>CHMP</td>
<td>EMA Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
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<tr>
<td>CRG</td>
<td>Commissie Richtlijnen Gevoeligheidsbepalingen</td>
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<tr>
<td>DIN</td>
<td>Deutsches Institute for Normung eV.</td>
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<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>ECOFF</td>
<td>Epidemiological cut-off</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency (formerly EMEA)</td>
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<td>EUCAST</td>
<td>European Committee on Antimicrobial Susceptibility Testing</td>
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<td>ESCMID</td>
<td>European Society for Clinical Microbiology and Infectious Diseases</td>
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<tr>
<td>FESCI</td>
<td>Federation of European Societies of Chemotherapy and Infection</td>
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<tr>
<td>ISC</td>
<td>International Society for Chemotherapy</td>
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<tr>
<td>ISO/CEN</td>
<td>International Organization for Standardization/European Committee for Standardization</td>
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<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
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<tr>
<td>NWGA (AFA)</td>
<td>Norwegian Working Group for Antibiotics (Arbeidsgruppen for antibiotikaspørsmål)</td>
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<tr>
<td>Pd</td>
<td>Pharmacodynamics</td>
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<td>Pk</td>
<td>Pharmacokinetics</td>
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<tr>
<td>S/I/R</td>
<td>Susceptible/Intermediate/Resistant</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>SRGA</td>
<td>The Swedish Reference Group of Antibiotics</td>
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<td>SWAB</td>
<td>Stichting Wertgroep Antibioticabeleid</td>
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Setting breakpoints for new antimicrobial agents
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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 Historically, at least seven different sets of clinical antimicrobial MIC breakpoints have been used in Europe. Recently, there have been six active European National Breakpoint Committees: BSAC (UK), CA-SFM (France), CRG (recently superseded by SWAB, The Netherlands), DIN (Germany), NWGA (Norway) and SRGA (Sweden). 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 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 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 an SOP (SOP /H/3043, 2005, revised 2007; http://www.eucast.org/fileadmin/src/media/PDFs/4ESCMID_Library/3Publications/EUCAST_Documents/Other_Documents/EMEA_CHMP_EUCAST_SOP_on_Harmonising_European_Breakpoints_2007.pdf).

The national committees (BSAC, CA-SFM, CRG (SWAB), DIN, NWGA, SRGA) 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 file, one presentation of the agent and a common European breakpoint.

2.3 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 of wild type susceptible organisms lacking acquired or mutational resistance to the antimicrobial agent in question. The ECOFF is essentially the upper MIC value of the wild type distribution. 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 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 and two country representatives from the EUCAST General Committee are appointed by the ESCMID Executive Board. Each of the six 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. Members may represent a national antibiotic 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 are representatives of the International Society for Chemotherapy (ISC) and the Federation of European Societies of Chemotherapy and Infection (FESCI). This group provides a Europe-wide 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 licensing 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 EUCAST email networks
EUCAST has email networks for:
- the pharmaceutical industry
- the susceptibility testing device and materials manufacturing industry
- expert individuals, specialist groups, and other interested parties

Any company, individual or organisation with an interest in antimicrobial susceptibility testing may, at the discretion of the EUCAST Chairman, be included in these networks. Confidential information provided in relation to the setting of breakpoints for new agents as part of the licensing process through EMA is not released to this group.

3.6 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 licensing 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 registration file. The company will provide:
- Proposed dosages of the agent being assessed and the available formulations
- Proposed indications for the agent
- Proposed target organisms
- MIC distributions of relevant species
- Pharmacological data
- Pharmacodynamic data
- Modelling data, such as Monte Carlo simulations
- Clinical trial data

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.
### Relevant factors in setting breakpoints for antimicrobial agents

#### 5.1 Available formulations
Whether oral, intravenous, infusion etc.

#### 5.2 Standard and maximum dosing
This will be expressed as the dosage and daily frequency in the form of dosage in mg x the number of daily doses (e.g. 500 mg x 4).

There will be one standard dose and possibly a maximum dose.

#### 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, 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, non-aggregated, 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. 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), 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
Dose-effect 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, may be available to assess the likelihood of achieving proposed pharmacodynamic targets and is used to assist 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 entered into the EUCAST MIC distribution program, thereby making all MIC distributions available to all National Committees via the internet.
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. For new agents the collated distributions may be based on very few studies.

Preliminary epidemiological cut-off 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 to EMA for licensing 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 licensing, 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 for licensing, 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 at these meetings.

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
The S/I breakpoint is normally based on the standard dose and the I/R breakpoint on the maximum dose.

8.3 Clinical indications and target organisms
These will be noted.

8.4 MIC distributions for individual species
Through the EUCAST MIC distribution database, full MIC distributions of 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.

### 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 for established agents.

The Pk data examined will, when available, include for each dosage the maximum serum concentration, minimum serum concentration, total body clearance rate, the serum 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 from *in vitro* studies, animal studies and humans are examined and, when possible, appropriate pharmacodynamic targets established (e.g. time above MIC, 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 “non-species related” or “Pk/Pd” breakpoints as part of the process of setting clinical breakpoints.

### 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 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 Enterobacteriaceae, *Pseudomonas* spp., *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*.
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 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 categorization.

9.4 Non-species related breakpoints determined mainly on the basis of Pk/Pd data and independent of specific species are presented. 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 the tables are posted on the EUCAST website.

   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 Preliminary 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 rapporteur and EMA representatives. The company is informed of the rationale for the decision.

### Consultation on preliminary breakpoints

11.1 The preliminary 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.

### Consultation on tentative breakpoints

12.1 The tentative breakpoints are sent to the pharmaceutical company for comment, together with any explanatory arguments related to proposals on preliminary breakpoints. The tentative breakpoints are also presented to National Breakpoint committees by Steering Committee national representatives.

12.2 The pharmaceutical company may send further comments or request a further meeting with the Steering Committee and EMA representatives. Any further comments from any of the National Committees will also be discussed and taken into account in further assessment of breakpoints.

### Finalisation of breakpoints

13.1 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 licensing process. The final decision on
### 13.2
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 with the breakpoints agreed on by the rest of the Steering Committee.

### 14 Publication of breakpoints

14.1 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.

14.2 As the breakpoints are incorporated into EUCAST National Committee methods they will be published on National Committee websites and in national guidelines.

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.

### 15 Revision of breakpoints

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