Standard Operating Procedure

Harmonization of breakpoints for existing antimicrobial agents

EUCAST SOP 2.1

20 July 2013
Harmonization of breakpoints for existing antimicrobial agents
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 drugs 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 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 resold. 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. Setting breakpoints for existing antimicrobial agents, EUCAST SOP 2.1, 2013. http://www.eucast.org".
**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSAC</td>
<td>British Society for Antimicrobial Chemotherapy</td>
</tr>
<tr>
<td>CA-SFM</td>
<td>Comité de l’Antibiogramme de la Société Francaise de Microbiologie</td>
</tr>
<tr>
<td>CLSI</td>
<td>Clinical and Laboratory Standards Institute</td>
</tr>
<tr>
<td>CRG</td>
<td>Commissie Richtlijnen Gevoeligheidsbepalingen</td>
</tr>
<tr>
<td>DIN</td>
<td>Deutsches Institute for Normung eV.</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>ECOFF</td>
<td>Epidemiological cut-off</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EUCAST</td>
<td>European Committee on Antimicrobial Susceptibility Testing</td>
</tr>
<tr>
<td>ESCMID</td>
<td>European Society for Clinical Microbiology and Infectious Diseases</td>
</tr>
<tr>
<td>FESCI</td>
<td>Federation of European Societies of Chemotherapy and Infection</td>
</tr>
<tr>
<td>ISC</td>
<td>International Society for Chemotherapy</td>
</tr>
<tr>
<td>ISO/CEN</td>
<td>International Organization for Standardization/European Committee for Standardization</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum Inhibitory Concentration</td>
</tr>
<tr>
<td>NAC</td>
<td>National Antimicrobial Susceptibility Testing Committee</td>
</tr>
<tr>
<td>NWGA (AFA)</td>
<td>Norwegian Working Group for Antibiotics (Arbeidsgruppen for antibiotikaspørsmål)</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>SRGA</td>
<td>The Swedish Reference Group of Antibiotics</td>
</tr>
<tr>
<td>SWAB</td>
<td>Stichting Wertgroep Antibioticabeleid</td>
</tr>
</tbody>
</table>

**Harmonization of breakpoints for existing antimicrobial agents**
Contents

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

Harmonization of breakpoints for existing antimicrobial agents
## 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. 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 of wild type susceptible populations lacking acquired or mutational resistance to the antimicrobial agent in question. The ECOFF is defined for an agent and a species. It is essentially the highest MIC value of isolates lacking phenotypically expressed resistance mechanisms and thus also the highest MIC of the wild type distribution. 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 and three 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 are representatives of the International Society for Chemotherapy (ISC) and the Federation of European Societies of Chemotherapy and Infection (FESCI). This group provides an 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 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. Individual members of these groups are responsible for ensuring that their email addresses are up to date. Emails rejecting correspondence on two successive occasions will be removed from network lists.

#### 3.6 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 contacted through the email network 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 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).

While there will be one standard dose and possibly a maximum dose 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 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.

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

Dose-effect 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”.

---

Harmonization of breakpoints for existing antimicrobial agents
<table>
<thead>
<tr>
<th>6</th>
<th>Data collation by the EUCAST secretariat</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.1</td>
<td>Information on national indications, dosages and current breakpoints will be collated and distributed to the National Committee representatives on the Steering Committee for ratification.</td>
</tr>
</tbody>
</table>
| 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, 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 existing agents the collated distributions may include data from many sources.  
Preliminary ECOFF values may be suggested for discussion by the Steering Committee members. |

<table>
<thead>
<tr>
<th>7</th>
<th>Presentation of data by pharmaceutical companies to the EUCAST Steering Committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1</td>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8</th>
<th>Assessment of data in setting breakpoints for antimicrobial agents</th>
</tr>
</thead>
</table>
| 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 maximum doses. If there are wide differences these will need to be accommodated in the final breakpoints. |
The susceptible breakpoint is normally based on the standard dose and the resistant breakpoint on the maximum dose.

### 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. If appropriate, multiple MIC distributions are combined in the database.

Epidemiological cut-off values (ECOFFs) are defined for relevant species.

### 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 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 in *in vitro* studies, animal studies and human studies 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 “PK/PD” (“non-species related”) 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:
- Enterobacteriaceae
- *Pseudomonas* spp.
- *Stenotrophomonas maltophilia*
- *Acinetobacter* spp.
- *Staphylococcus* spp.
- *Enterococcus* spp.
- Group A,B,C,G streptococci
- *Streptococcus pneumoniae*
- Viridans group streptococci
- *Haemophilus* spp.
- *Moraxella catarrhalis*
- *Neisseria gonorrhoeae*
- *Neisseria meningitidis*
- *Clostridium difficile*
- Gram-positive anaerobes
- Gram-negative anaerobes
- *Helicobacter pylori*
- *Listeria monocytogenes*
- *Pasteurella multocida*
- *Campylobacter jejuni and Campylobacter coli*

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 “non-species related 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 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 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 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 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, email networks and more widely via the EUCAST website. A twelve week consultation period will normally be allowed.

12.2 Comments from any of 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.

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.

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 only if there are particular issues that the Steering Committee considers warrant publication in this format.