The working order between the pharmaceutical industry, EUCAST and EMA

As part of the Centralised Procedure for the assessment and approval of new antibacterial medicines in the European Union, a Standard Operating Procedure (SOP/H/3043) regarding the setting of antimicrobial susceptibility testing interpretive criteria (breakpoints) has been drawn up between the European Medicines Agency (EMA) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The SOP sets out the conditions under which applicants/companies, the Rapporteurs appointed by the Committee for Medicinal Products for Human Use (CHMP), the EMA and EUCAST will work together in confidence on the process of establishing susceptibility testing interpretive criteria (see SOP for details).

EUCAST Steering Committee members Conflicts of interest. The members of the EUCAST executive (Chair, Scientific Secretary and Clinical Data Coordinator) are under no circumstances employees of pharmaceutical companies or members of industrial advisory boards. Other members of the EUCAST Steering Committee cannot be employees of pharmaceutical or device manufacturing companies but may at times be temporarily engaged as advisors for industry on strategic matters during the development of new agents. When this occurs, they are not allowed to be part of deliberations or decisions related to the agent and will not receive any materials provided by companies for these discussions. This rule does not apply to situations where advice of a purely technical nature is given (e.g. susceptibility testing methodology, population modelling) as companies are encouraged to ask for such advice.

“Visiting” General Committee members may be present at discussions but will excuse themselves during confidential company presentations unless there is a formal agreement with the company and a confidentiality agreement has been signed.

During company presentations at EUCAST Steering Committee meetings, and during deliberations before and after presentations, any full Steering Committee member or “visiting” member who has a conflict of interests and/or is not party to confidentiality agreements with the presenting company must leave the meeting. They will not in any way take part in the discussion or decision process on breakpoints for the affected agent.

Subject to the agreement of the applicant to share data from the application dossier with EUCAST, the Steering Committee will review data relevant to the setting of appropriate susceptibility testing breakpoints before a final opinion regarding approval is reached by CHMP. Subject to the agreement of the CHMP for each product, the EUCAST breakpoints will be included in the EUCAST breakpoint table.

The EUCAST process for setting new breakpoints will adhere to the agreed timetable drawn up by the aforementioned bodies for each Centralised Procedure. The EUCAST Steering Committee plays a key role in the process and meets five times per year, usually in February, in conjunction with the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in March-April, in July, September and November.
This document has been developed by EUCAST to provide practical advice and information for companies regarding the breakpoint-setting process. In principle, pharmaceutical companies present their agent twice to EUCAST. The first presentation is informational and is to present plans and current data to EUCAST and for EUCAST to provide the company with advice and details about the continued process. The second presentation is more formal and is scheduled for a time immediately after filing with EMA.

1. Informational EUCAST presentation
EUCAST encourages pharmaceutical companies to be prepared to give a first presentation of the agent to the EUCAST Steering Committee before (typically 1–2 years before) the Centralised Procedure commences. In order to initiate this process, the EUCAST Chairman and/or Scientific Secretary should be contacted through the official EUCAST website (www.eucast.org). EUCAST will not propose breakpoints at or following this meeting.

The EUCAST Scientific Secretary will provide the contact details of the current Steering Committee members if this is needed for confidentiality agreements. Prior to the meeting the company should inform the EUCAST Scientific Secretary of the names and roles of the persons who will represent the company at the meeting.

The total time for the first meeting will be 60 minutes. A 30-minute presentation allows time for comment and discussion. The process is most productive if EUCAST members are allowed to ask questions and make comments during the presentation. Ideally, the first presentation should contain:

- Brief structure, mode of action, resistance mechanisms/selection of resistance
- Clinical indications and expected benefits over existing agents
- Microbiological activity (full species-related non-truncated MIC distributions, not MIC50/90)
  - submit non-aggregated MIC-distributions using the available MIC templates (found at http://www.eucast.org/mic_distributions_and_ecoffs/)
- Administration forms and dosages
- Pharmacokinetic data in healthy volunteers and patients
- Activity in animal models
- Pharmacodynamic studies
  - In vitro and/or animal model pharmacodynamic indices and target values
  - Monte Carlo simulations for Probability of Target Attainment
- Clinical studies, including
  - Relationships between dosing regimens, MICs and clinical and microbiological outcomes
- Company proposal for breakpoints
- Breakpoints already decided by other committees/medicines agencies
- Planned timescale for studies, regulatory approval
- EUCAST has published a guideline on Important considerations for breakpoint setting of antibiotic-inhibitor combinations. This is available at http://www.eucast.org/ast_of_bacteria/guidance_documents/
- Anything else that the company considers important/useful
It is very helpful if a copy of the presentation can be sent to EUCAST at least one week before the meeting. The company does not need to produce a "Company Rationale Document" at this early stage but companies have found it useful to bring their data together in this format before the formal process through EMA. No "dossier" is needed but if the company wishes to provide additional information it may do so. The minutes of the discussion with EUCAST are shared with the company following the meeting.

As early as possible in the process, the company should inform the EUCAST Development Laboratory about the need for developing disks contents (potency) and disk diffusion criteria to establish zone diameter correlates to MIC breakpoints. Disk diffusion criteria should not be included in submissions to EMA or the EUCAST Steering Committee and will not be included in the SmPC. However, if criteria have been established in time for the approval of the agent by the CHMP, these will be published by EUCAST together with MIC clinical breakpoints. Companies are therefore encouraged to contact the EUCAST Development Laboratory early in the process.

**Company rationale document.** We suggest that companies prepare a document in the style of the "EUCAST rationale document" (see documents and template at [http://www.eucast.org/documents/rd/](http://www.eucast.org/documents/rd/)) and submit to EUCAST as early as possible in the process, preferably before or at the latest when filing with EMA. The "Company Rationale Document" will be one of many of EUCAST’s sources of information in the breakpoint setting process. It will be treated with the same confidentiality as all other material which is part of the process. It will be available only to the Company, EUCAST and the EMA and the Rapporteurs. However, the existence of a Company Rationale Document will help highlight differences between the Company and EUCAST with respect to data and interpretation. The Company Rationale Document can be amended by the Company at any time during the process whereby the changed (added or deleted) section must be highlighted and a copy sent to EUCAST, EMA and the Rapporteurs.

### 2. Formal company presentation to EUCAST following filing

As soon as the company has filed for approval with EMA, the company should request a formal meeting between the company and EUCAST. This is to initiate the discussion on breakpoints. The EMA is informed and on a case by case basis, representatives of the Rapporteurs teams and of the EMA may participate in the meeting as observers. At this meeting the company will have the opportunity to formally present and discuss the agent and breakpoints. The process may have to be shortened if CHMP has granted the product an accelerated assessment process.

### 3. EUCAST proposed clinical breakpoints

Immediately following this meeting EUCAST will suggest preliminary clinical breakpoints and when possible, tentative epidemiological cut off values and prepare a EUCAST rationale document listing the data supporting the breakpoints proposed by EUCAST to the EMA and the company. The proposed breakpoints and the rationale for the these are sent by EUCAST to the EMA, the assessors of the Rapporteurs, National Breakpoint Committees (whose Chairholders constitute most of the EUCAST Steering Committee) and the company for comments and questions. **Comments should be given in writing.**
4. Formal decision on proposed breakpoints.
When there are no more questions on the EUCAST proposed breakpoints they will be finalised and transmitted to the EMA for consideration by the CHMP.

This will normally occur as part of the initial approval process. Following the approval of the medicine (if applicable), EUCAST will publish the breakpoints for the antibacterial agent on the EUCAST website, either as part of an existing table for existing classes of drugs, or as a separate table for a new class. From the breakpoint table the rationale document can be accessed.

5. Post-approval changes to breakpoints.
In the post-approval period companies may choose to bring new data to EUCAST to request a revision of the breakpoints. New data may support the setting of breakpoints for species which were not given breakpoints during the approval process. New data (clinical data, different dosing or modes of administration, resistance mechanisms) may also support a different breakpoint than given originally. Please note that EUCAST will only consider setting breakpoints for species relevant to the already approved clinical indications.

However, although there is no formal process set up by EMA/CHMP, EUCAST and Industry, EUCAST will consider revising breakpoints as a result of a request from any of the three involved parties (EMA/CHMP, EUCAST or Industry). In case EUCAST and companies agree to add or to change breakpoints relevant for the pharmacodynamic information in the SmPC for centrally approved medicinal products, a variation to the marketing authorisation of that product may be relevant.

Questions on any of these steps in the process can be addressed to EUCAST secretariat (emails available on www.eucast.org).

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