

European Committee on Antibiotic Susceptibility Testing (EUCAST)

Minutes of the Meeting of 10th November 1997 at The Ramada Hotel, London, UK

1. Present

See attached list.

2. Introduction

2.1 The Chairman, Prof. Ian Phillips, welcomed attendees and explained that the European Committee on Antibiotic Susceptibility Testing (EUCAST) of ESCMID is the reconstituted European Breakpoint Committee. The objective is to bring together a body which has the authority that the NCCLS exercises in the United States and to discuss common goals with NCCLS, possibly leading to common methods in the future. Agreement on details of reference MIC methods should be possible. Whatever technology is routinely used should produce accurate and reproducible results which are comparable, but the details of the methods may differ in different countries.

2.2 Dr Derek Brown agreed to be Scientific Secretary of the Committee.

3. Apologies for absence

3.1 Dr Auckenthaler (Switzerland). Prof. J. Acar (France) has retired from the committee and his place taken by Dr F. Goldstein. Dr P. Huovinen (Finland) was represented by Dr A. Nissinen. Prof. R. Wise (UK) was represented by Mrs J. Andrews.

3.2 Prof. Phillips reported that others had been invited. Dr Ferrero (USA NCCLS) had been invited but no representative was available at short notice. NCCLS representatives would be invited to future meetings. Prof. Hildebrandt (European Medicines Evaluations Agency) would wish to attend or send a representative but could not get to this meeting. Dr R. Williams (WHO) was invited but could not attend. If there are other representatives who should be invited write to the EUCAST Office.

4. Constitution

Prof. Phillips introduced a draft constitution, copies of which had been distributed prior to the meeting. The draft was the basis of extended discussion. Prof Phillips and Dr Brown will redraft the constitution in the light of these discussions.

[ACTION Ian Phillips & Derek Brown]

5. The main committee

- 5.1 The main committee would comprise:
 - 5.1.1 The Chairman.
 - 5.1.2 The Scientific Secretary.
 - 5.1.3 One member per country representing national societies, authorities or groups. If countries do not have national groups, a representative could be sought through soundings and contacts. Representatives would serve for 2-3 years.
 - 5.1.4 Representatives of the pharmaceutical industry and device manufacturers.
 - 5.1.5 Members of the original ESCMID committee not falling into the above categories will be included in order to ensure continuity.
- 5.2 It was agreed that there should be two representatives of the pharmaceutical industry and two of device manufacturers. The groups would nominate their own members. It was noted that not all companies were at this meeting and there would need to be a mechanism for communication among companies, both in seeking opinion and disseminating information. The industry members present at the meeting agreed that for one year their representatives on the main committee would be Dr Anne Harris (Glaxo-Welcome), Prof Andre Bryskier (HMR), Dr Margaret Harrison (Oxoid) and Dr Hilya Ibert (bioMérieux).
- 5.3 It was suggested that representatives of European Regulatory Authorities should be included, but Prof. Phillips reported that those contacted had no desire to be members although they might attend as observers. They would wish to be assured that the methods and breakpoints are sound but do not feel they can contribute to establishing methods and breakpoints.

6 Sub-committees

- 6.1 Sub-committees would be set up to work in particular areas and it is expected that this approach will produce more rapid progress than has been seen in the past. Sub-committee membership will be partly from EUCAST, partly from industry and, as required, additional co-opted experts who are not on the main committee. The sub-committees might comprise around 10 persons. The meetings will be open to observers.
- 6.2 There was discussion concerning the consultation process regarding any recommendations and how votes would be taken. It would not be practical for the main committee to meet much more frequently than once a year so many decisions will be taken by the sub-committee. It is the intention that all reports are published as consultation documents (blue inserts in CMI). The blue inserts should take no longer than three months to publish and could be sent directly to all members of the main committee in advance of publication. Any comments would be returned to the sub-committee within about three months of publication.

Following discussion the draft will be modified and published with a note that the document will be revised in 12 months. If there were contentious issues the matter could be referred to the main committee where there might be a vote. If there was failure to agree in a sub-committee, minority reports might be necessary.

- 6.3 The question of "voting rights" of, industrial members was raised. Agreed that company representatives should not vote on issues relating to another company. Interests should be declared in advance.
- 6.4 Dr Hohl asked that borderline decisions should not be accepted on important issues.
- 6.5 Circulation of all information relating to sub-committees to all members (as NCCLS) would be very expensive and probably beyond the resources of EUCAST at present. Dr Edwards asked if European bodies could be approached for funding. Prof. Phillips suggested that funding should be from a combination of industry (possibly through European Agencies) and European sources. Dr Harris suggested that any dossier submitted to the breakpoint sub-committee has a summary which could be distributed more widely.
- 6.6 Dr Harris felt that the breakpoint sub-committee should not recommend on prescribing and this was generally agreed.
- 6.7 Dr Livermore asked what the mechanism would be for revising breakpoints without delay. It was felt that this should be part of the remit of the sub-committee.
- 6.8 Dr Poupard asked what method the breakpoints would be based on as countries were not expected to change their routine methods. Prof. Phillips suggested that breakpoints would be related to a reference MIC method but that routine tests in individual countries would be done by whatever method is nationally recommended. These national methods should give the correct answer as indicated by the breakpoint applied to tests by a reference MIC method.
- 6.9 Prof. Williams asked for clear definitions of different categories of interpretation. Prof. Phillips indicated that such definitions will be included in the report on terminology which has recently been published as a tentative document.
- 6.10 It was emphasised that surveillance was not part of the EUCAST remit as this was being undertaken by other groups with whom EUCAST might liaise.
- 6.11 Dr Metodiev suggested that sub-committees should be geographically representative. It was noted that the first requirement was to ensure that the sub-committee had the required expertise but other considerations including geographical origin would be taken into account. There will be several sub-committees, the membership of which is likely to change over the years.

- 6.12 Dr Hohl suggested that sub-committees should meet during the ESCMID symposia and issues arising considered at the main committee meeting held at the same symposium.
- 6.13 A co-ordinator of each sub-committee will be needed and sub-committee membership established. All attendees were asked to write down in order of preference the three sub-committees they would wish to be involved with. It was agreed that Prof Phillips and Dr Brown would identify co-ordinators and some members. Additional expert members might be identified by co-ordinators. Members would serve on sub-committees for two years, after which membership could change or continue as appropriate. **[ACTION Ian Phillips & Derek Brown]**
- 6.14 Terms of reference
Terms of reference and timescales should be defined for each sub-committee.

7 Proposals for sub-committees

- 7.1 Prof Baquero suggested that the sub-committees should mirror the NCCLS committees. Following discussion it was agreed that the following sub-committees (7.2-7.13) could be established although some would be given higher priority than others:
- 7.2 Terminology
The discussion document has been published as a blue insert in the CMI Journal. It was suggested that common antibiotic acronyms should be accepted and these should be in line with WHO recommendations as far as published. Any further comments should be sent to the EUCAST office.
- 7.3 Breakpoints
The first requirement is for a document detailing the process for establishment of breakpoints. There are several models including NCCLS and DIN. The sub-committee will produce breakpoints as required for new agents.
- 7.4 MIC methods
A reference method is highly desirable (see paragraph 14).
- 7.5 Disc diffusion methods
- 7.6 Automation
It was suggested that device manufacturers are responsible for ensuring that devices produce the correct results and QA schemes will pick up failures. EUCAST is not responsible for calibrating machines.
- 7.7 Bactericidal testing methods.
- 7.8 Molecular methods

7.9 Quality assurance

Some studies may be needed to ensure that different methods give the same results. Comparability of methods is a priority. Something similar to the ICS study would be one approach but an EQA approach with distributed strains of known susceptibility would achieve the same result (and would give a better estimation of the routine performance of the methods than a research study in a small number of laboratories). A European QA scheme would establish the comparability of methods and might attract EC support. The importance of external quality assessment based on an extended set of control strains was agreed. Susceptibility of reference strains would be defined on the basis of tests with a reference MIC method. Any activity by EUCAST relating to QA should not compete with national QA schemes, but could be very useful in establishing comparability of methods used in different countries. The value of an internationally accepted set of routine quality control strains is clear but it was recognised that different methods may require different routine control strains.

Validation of individual national methods is largely a national responsibility.

7.10 Fungal testing

7.11 Mycobacteria

7.12 Anaerobes

7.13 Intracellular pathogens

8 Meetings

8.1 The main committee will meet at least annually, at ESCMID meetings when possible.

8.2 All sub-committees should have their first meeting within the next six months.

8.3 At previous meetings it was suggested that all meetings would be open with the exception of the breakpoint sub-committee, and there was debate about whether the breakpoint sub-committee should be confidential. There was considerable support for complete openness (Dr Byskier, Dr Edwards, Dr Hohl, Prof. Baquero, Dr Harris, Dr Goldstein) as data are openly presented to NCCLS and full disclosure is required. It is desirable to present the same data package in different parts of the world, and openness will help to avoid discrepancies between breakpoints for similar drugs from different companies. Dr Goldstein suggested that some companies who file drugs only in Europe might prefer meetings relating to their drugs to be confidential. Prof Baquero noted that companies might be advised on tentative breakpoints for early studies. Dr Livermore suggested that discussions of the final breakpoint should be open, although Dr Degener indicated that it is difficult to say when the final breakpoint

is reached and Prof Bryskier and Dr Hohl noted that "final" breakpoints must be given before the drug is registered. On an informal show of hands an overwhelming majority was in favour of complete openness, with two votes against. A formal vote would be taken when the full committee meets and the interim position is that there would be total openness unless it is otherwise decided by the breakpoint group.

9 Funding

Prof. Phillips suggested that funding for the EUCAST meetings would be expected to come largely from pharmaceutical companies, possibly in the form of sustaining members . The European Union will be approached. WHO do not appear to have any available funds. Regulatory bodies such as EMEA might include support for EUCAST in their fees. It was suggested that some of the work will be very time-consuming and might require some payment. Prof. Phillips felt that for each piece of work there will be one person who leads and will be shoulder much of the work. For each breakpoint the cost is around , 20000 and this has largely been paid by the pharmaceutical company involved. It was suggested that national societies might fund representatives on some of the sub-committees and individuals should approach their own societies. Some funds might be raised by sale of documents. Short term funding is the main problem. Prof. Phillips will pursue funding alternatives with industry representatives.
[ACTION Ian Phillips]

10 Dissemination of information

In order to disseminate information from the sub-committees a series of documents would be produced. The importance of publishing documents was stressed to establish EUCAST as an influential group.

11 Advice to other agencies

As appropriate, advice on aspects of susceptibility testing would be given to other institutions such as the European Medicines Agency.

12 Collaboration

- 12.1 Collaboration with several international groups would be desirable. Established programmes include the WHO surveillance group, the EUUS task force on antibiotic resistance, Dr Spranger in the Netherlands is applying for EU funds for surveillance. Agreed that these groups should be aware of EUCAST activities.
- 12.2 Prof Phillips is meeting with the Chairman of the NCCLS Susceptibility Testing Sub-committee in January 1998. Dr Harris felt that the NCCLS MIC method should be accepted as a reference method. Dr Degener noted the problems with

agreement on breakpoints and the need to be involved in NCCLS decision making. Prof Bryskier reported that the NCCLS method is used because of the need for use of the method in producing data for registration in the USA. It would be very expensive if the work had to be repeated by a different method in Europe. Dr Edwards agreed but pointed out that as Europe grows the market will become at least as important as the USA. The committee would work with NCCLS to achieve consensus in susceptibility testing.

13 Educational aspects

- 13.1 Education and training in relation to the work of EUCAST would be an integral part of the work of the sub-committees.
- 13.2 Dr Ibert raised the question of recommendations on agents to test and interpretive reading in the laboratory. It was agreed that these are educational matters and could be applied to any method.

14 Reference MIC method

Agreed to look at the NCCLS agar dilution MIC method as the reference method, perhaps with some minor modifications. It would be necessary to establish what differences the modifications make, eg. medium used. The MIC methods sub-committee should look at this as a priority.

15 Terminology document

- 15.1 This was produced by the old working party. The blue discussion document was distributed in August 1997. A few reprints are available from the EUCAST office. Prof Phillips reported that he had received comments from 15 people/groups. Five said the document was acceptable as drafted. Additional comments received were:
 - 15.1.1 Antibiotics are defined only in terms of bacteria - all microbes should be included.
 - 15.1.2 There is confusion over microbiological and clinical breakpoints.
 - 15.1.3 Sections 6.3-6.6 on bactericidal definitions other than MBC are given too much prominence.
 - 15.1.4 Greek letters should not be used, eg mcg in place of µg.
 - 15.1.5 Combined effects should be explained in a clinical context.
 - 15.1.6 The use of acronyms should be included.

15.2 Further comments were noted in discussion

15.2.1 Use "Drug substance" in place of "Test substance" (Prof Bryskier)

15.2.2 Use "Antimicrobial agent" in place of "antibiotic" (Prof Bryskier, Dr Hohl, Dr Brown).

15.2.3 Is the disc content range of 90-120% practical? (Dr Hohl)

15.2.4 The definition of intermediate should include those strains between microbiological resistant and clinical resistant (Prof Williams). Strains should be defined as susceptible if fully susceptible and borderline susceptible if they have reduced susceptibility but are still clinically susceptible (Prof. Verbist). The intermediate category should be considered a buffer zone (Dr Goldstein). Strains may be microbiologically and clinically resistant even when the MIC is well below the pharmacological breakpoint eg *Klebsiella* with ceftazidime MIC 1mg/l (Dr Livermore). Dr Harris noted that tests may be done for clinical or epidemiological reasons. Dr Vatopoulos suggested that it is not always known whether a resistance mechanism conferring low level resistance is clinically important.

15.2.5 Definition of interpretive reading needed (Dr Livermore)

15.2.6 Indicate that the drug concentration in Fig 2 is a logarithmic scale (Dr Livermore)

15.3 Agreed that any more comments would be sent within the next 2 weeks to the EUCAST office. The document will be modified in sub-committee and published with a note of intention to revise it in 12 months time.

16 Any other business

16.1 Berlin ESCMID

Prof Phillips reported that he had been asked what contribution EUCAST would like to make to the meeting of March 1999. Agreed that we would suggest a plenary meeting relating to EUCAST describing the work that has been done.

16.2 Document archive

National documentation in its original form and translated into English was being collected at the EUCAST office as a central reference. Several contributions have already been received. Others would be welcome.

16.3 European Committee on Laboratory Medicine (CEN)

Prof Phillips explained that this is a group covering all pathology disciplines. The main agenda is European Standards. Neils Hoiby is the ESCMID representative

and we shall send copies of our minutes to him.

16.4 List of attendees

Agreed that a list of committee members with addresses will be distributed with the minutes.

17 Next meeting

The venue for the next meeting will be a major international meeting, yet to be decided.