**Written responses to open questions of the webinar 'Building better breakpoints: data and methods needed to determine breakpoints for new agents' by John Turnidge and Anouk Muller, originally broadcast on 21 October 2020. See webinar recording here: https://revive.gardp.org/building-better-breakpoints-data-and-methods-needed-to-determine-breakpoints-for-new-agents/**

| | **Question asked** | **Response from the speakers and moderator** |
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| 1 | When we have different replicas of MIC/MBC with different but proximal values (e.g. 4,4,8) which MIC/MBC value should we assume? | There is no hard and fast rule about this. It is conventional to choose the most common or median value<br><br>Agree, no rules. I am used to repeating about 5 times with the gold-standard method and subsequently work with the median.<br><br>Agree. So, with 4, 4 and 8 the final MIC would be 4. Depending on the situation, I prefer it when investigators report on the number of repeats and how the consensus MIC was reached. |
| 2 | Could you clarify again if there was any situation where non-neutropenic models are used? | No, non-neutropenic models are never used to assess PK/PD parameters or targets<br><br>In addition to the first speaker: it is important that mice develop an infection with the micro-organism injected. Mice does not develop infections in the same way as humans do. Therefore, it is essential to use neutropenic models. |
| 3 | In clinical trial, if high efficacy rates are observed that precludes E-R analyses, however, few high MIC strains are encountered that have MICs higher than proposed PK/PD breakpoint, will it be considered in awarding the breakpoint? | In general, the breakpoint (BP) would be PK/PD cut-off in this circumstance, but there is no hard-and-fast rule. A lot will depend on the types of infections being treated<br><br>The tradition in EUCAST is to require "proof" beyond the PK/PD – when there is no clinical data to support a "higher than the wild type MICs", EUCAST tends to favour the ECOFF as the breakpoint until further evidence is available. |
| 4 | What is the role of infection site-specific MIC breakpoints, and the scope of expanding beyond the examples already in use in the current EUCAST breakpoint tables? | Site-specific BPs should be considered for 'privileged' infection sites, i.e. where the antimicrobial exposure is very different from that of plasma and extracellular fluid, and are not dealt with using standard or high dosages<br>e.g. Uncomplicated UTI Meningitis |

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| 5 | If there is not an ISO MIC method for the organism you are studying, how do you suggest we proceed with MIC evaluations? | In the absence of an ISO standard, a reference method should be developed, with the agreement of both EUCAST and CLSI. For Haemophilus species both EUCAST and CLSI methods need to be run. |
| 6 | Would it be correct to say that if the ECOFF for a drug-bug combination is 8 mg/ml but the drug's dosing regimen does not achieve adequate concentrations required for achieving a PTA of >90% for its PD target, then that bug cannot be clinically treated with the drug? | As a general principle that would be true if the target cannot be achieve with high dosages. However, EUCAST has a few breakpoints that cut into the highest wild type MICs, simply because the percentage of wild type at that MIC is very low, and EUCAST prefers to have the agent recognised at being effective.<br>**Also, EUCAST uses a minimum percentage of 95% in its deliberations, not 90% (as used by CLSI)** |
| 7 | Thank you to both speakers for an excellent presentation. Is the choice of a 1 log kill as a bacteriocidal end point for in vivo studies a historic choice that is now accepted standard or is there a particular reason for that choice? Do you think the use of targets such as 2 log kill or maximum bacteriocidal concentration is more applicable in different populations (e.g. immunocompromised hosts). Would this kind of information support different / more aggressive dosing with certain antibiotics in those populations? | There is no hard-and-fast rule, but the choice of target depends on the seriousness of the infections at which the agent is aimed. For conditions with low morbidity/mortality, a bacteriostasis target is considered satisfactory. For example, bacteraemic UTI and complicated intra-abdominal infection are in this category. For more serious conditions like pneumonia or septicaemia, a 1-log kill is preferred. A 2-log kill target is rarely used at present; many agents cannot achieve that in the *in vivo* models. Even if they can, it is not used as it does not correlate any better than a 1-log target.<br>As far as immunocompromise is concerned, by itself it does not influence decisions. If we know that PK is altered in certain immunocompromised states then that is what it taken into account. |
| 8 | When do we have to check for the PK parameters in patients (obese!, in ICU!, When they don't improve)? | It is important to realise that breakpoints are based on PK models in healthy volunteers or patients with mild infections (e.g. pneumonia on the normal ward). So that would be your reference patient and you can compare the expected exposure in your current patient with this reference patient. In case the expected exposure is too high (most often for patients with an impaired renal function), doctors are used to lower the dose to reach a comparable exposure as the reference patient has. But in case the expected exposure will be low, it gets complicated. I prefer to immediately adjust the dose, since you may lose time, especially in critically ill. For many drugs (e.g. beta-lactams) it is safe to initially start with a higher dose and after the critical phase is over you can reduce again. I would suggest doing TDM where possible in more toxic drugs. |

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| 9 | For the example discussed, what is the proportion of patients for which the PK/PD target is attained if the MIC is 8? Said differently: at Breakpoint, 95% of patients are supposed to reach the PK/PD target, but what is the proportion for an MIC that is 2x breakpoint. | At the MIC of 8 97.5% of the (healthy)population reaches the lower limit of the target. And at an MIC of 16 mg/L around 5% will reach the lower limit of the target. |
| 11 | Can you tell us a bit about numbers diversity and "age" of epidemiological MIC data for a new EMA Market application | For EUCAST, the information can be found in SOP 10. Age of the isolates is not important because the evidence shows that the wild type of a species does not change over time<br><br>Agree. The diversity between distributions, apart from the fact that in older contributions the proportion of non-wild type isolates is greater, can always be ascribed to methodological issues. . |
| 12 | Could you comment on the use of PK/PD indices derived from immunocompetent vs. neutropenic mouse thigh infection model. What is the immunocompetent reflect better the clinical response? | There are few data on non-neutropenic mice or other animal models. What data exist suggests that PK/PD targets are lower<br><br>See also Q2. Immunocompetent mice will have less severe infections if they develop an infection at all. Therefore, the amount of antibiotics needed will be less. |
| 13 | Could you please comment on drug combinations in terms of estimating resistance suppression and predicted efficacy | This is a complex problem and beyond the scope of the webinar |
| 15 | What are your thoughts on determining PK/PD indices and exposure targets in an in vitro system (e.g. chemostat) to limit number of required animal studies? | There may well be value in generating data in vitro and using less animals. Unfortunately, the relationship between in vitro and in vivo model results has not been studied in any detail. Instead, strategies have been developed to minimise the number of animals and maximise the interpretation of results<br><br>In some cases both in vitro and animal models have been performed, and the results are not always similar. |
| 16 | Why is the MBC not used to set BPs? | A comparison of MBCs with MICs as a ‘denominator’ in PK/PD parameters has not been studied. However, an MBC would not work in a PK/PD parameter for bacteriostatic classes of agents<br>It has not been studied and realise that you then also should use the MBC in the studies for the PK/PD target. |

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| 17 | For a new drug for pneumonia will you estimate PK/PD targets in ELF the *in vitro* and *in vivo* models? | Yes, this is preferable, although not yet mandated by any organisation.<br><br>In case you would like to estimate the target attainment in ELF you first have to determine the PK/PD target in ELF. |
| 19 | Is the clinical application of MIC measurements, beyond a EUCAST susceptibility classification, and using it to guide antimicrobial dose-adjustments in clinical practice a valid use of a MIC value? | There are problems relying on a single MIC measurement in guiding patient therapy. If it is to be used, then please review the following reference for recommendations:<br>*MIC-based dose adjustment: facts and fables.*<br>*Mouton JW, Muller AE, Canton R, Giske CG, Kahlmeter G, Turnidge J. Journal of Antimicrobial Chemotherapy 2018 Mar 1;73(3):564-568. doi: 10.1093/jac/dkx427.*<br>The problem arises because a single MIC measurement is subject to assay variation |
| 20 | Is there any data that would help support grouping species for breakpoints (e.g. enterobacterales)? | Not as much as we would like. For example, there are a very large number of Enterobacterales species, and they would all have to be studied in models to confirm that their targets are the same.<br>Instead, for pragmatic reasons, we rely on the most commonly isolated and most obviously pathogenic members of groups having similar phenotypic and growth characteristics, and similar antimicrobial mechanism of action targets |
| 21 | My question is: when you are determining MICs and do several repeats for a certain isolate and the results are inconsistent, which result do you consider? The highest or the most consistent result? Let me add that the context for these tests in my case is to know the distribution of wild-type strains (using ECOFFINDER) and not directly for clinical purposes. | Same answer as Q1. Also, if EUCAST SOP 10 procedures are followed, then this form of variation is included in determining the wild type |
| 22 | Say the susceptibility report in a clinic indicates that 2 drugs (say ceftazidime and meropenem) are susceptible. The clinician starts empiric therapy with ceftazidime, however, the patient does not respond after 5 days of therapy. If the clinician is switching to Meropenem at that point, can he/she rely on the original MIC of Meropenem that was reported in the susceptibility report? | Yes. The administration of ceftazidime will not induce resistance to meropenem. But as the ceftazidime was reported susceptible, you should question yourself why the patients do not respond to therapy: selection of ceftazidime resistance, inadequate exposure due to altered PK, other infection etc.? |

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